spectra showed the exocyclic methylene absorption at 6.0 μ was completely removed while the carbonyl was shifted slightly to 5.70 μ.

Carbamoylcarbamate (**IB**).—A mixture of 0.5 g. of 17α-ethynyl-4-androsten-17β-ol-3-one, 12 ml. of *n*-propyl isocyanate, and 0.05 g. of Dabco was heated at reflux using a magnetic stirrer for 94 hr. After 24 hr. an additional 2 ml. of isocyanate was added. The solvent was evaporated, and the residue was chromatographed on 30 g. of neutral alumina using 1:1 benzene–petroleum ether (b.p. 30–60°) as the initial solvent. The carbamoylcarbamate (IB) was eluted with benzene and recrystallized from ethyl ether to give 0.31 g., m.p. 132–133°.

Anal. Calcd. for $C_{29}H_{42}N_2O_4$: C, 72.16; H, 8.77; N, 5.80. Found: C, 72.15; H, 8.84; N, 5.83.

Carbamate (**IIB**).—While being agitated with a magnetic stirrer, a mixture of 0.5 g. of 17α-ethynyl-Δ^4-androsten-17β-ol-3-one, 10 ml. of *n*-propyl isocyanate, and 0.05 g. of Dabco was heated at reflux for 114 hr. The solvent was evaporated and the residue was chromatographed on 25 g. of neutral alumina using 2:1 benzene–petroleum ether (b.p. 30–60°) as solvent. Elution with benzene and recrystallization from ethyl ether–petroleum ether gave 0.33 g. of IIB, m.p. 184–185°.

Anal. Calcd. for $C_{25}H_{35}NO_3$: C, 75.52; H, 8.87; N, 3.52. Found: C, 75.94; H, 8.68; N, 3.32.

Carbamic Acid Lactone (IIC).—A solution of 0.2 g. of carbamate (IIB), 20 ml. of methanol, and 4 ml. of sodium methoxide solution (0.1 g. of sodium in 10 ml. of methanol) was heated at reflux for 12 hr. Most of the solvent was removed under vacuum, and the residue was poured into excess water. The mixture was extracted thoroughly with methylene chloride, and this latter combined solution was washed with sodium chloride solution. After drying (Na_2SO_4) the solution was concentrated and recrystallized from ethyl ether to give 0.11 g. of IIC, m.p. 197–199°.

Anal. Calcd. for $C_{25}H_{35}NO_3$: C, 75.52; H, 8.87; N, 3.52. Found: C, 75.43; H, 8.90; N, 3.28.

17α-Ethynyl Carbamate (IIC).—A mixture of 1.0 g. of 17α-ethynyl-19-nor-Δ^4-androsten-17β-ol-3-one, 35 ml. of methyl isocyanate, and 0.066 g. of Dabco was heated at reflux for 42 hr. while being agitated with a magnetic stirrer. At this time, solution had resulted. The solvent was evaporated, and the residue was taken up in 4:3 chloroform–ethyl ether and chromatographed on 40 g. of neutral alumina. Fractions 2 through 4 using the above solvent mixture were combined and recrystallized from ethyl ether to give 0.41 g., m.p. 130–132°.

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.21; H, 8.33; N, 4.22.

Carbamic Acid Lactone (IIIC).—A solution of 0.3 g. of carbamate IIC, 4 ml. of sodium methoxide solution (0.1 g. of sodium in 10 ml. of methanol), and 25 ml. of methanol was heated at reflux overnight. Some of the solvent was evaporated, and the solution was poured into excess water. The mixture was extracted thoroughly with ethyl ether, and the combined solution was washed with bicarbonate and sodium chloride solutions. After drying (Na_2SO_4) the solution was concentrated and recrystallized from methanol–water to give 0.11 g., m.p. 189–190°.

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.29; H, 8.34; N, 3.93.

Ethyl Carbamic Acid Lactone (IIIC).—A solution of 0.5 g. of 17α-ethynyl-19-nor-Δ^4-androsten-17β-ol-3-one, 20 ml. of ethyl isocyanate, and 0.04 g. of Dabco was heated at reflux for 87 hr. The solvent was evaporated, and the residue was taken up in 2:1 benzene–petroleum ether (b.p. 30–60°) and chromatographed on 30 g. of neutral alumina. The carbamate was eluted with 25% ethyl ether in benzene, and since it would not crystallize under a variety of conditions the oil was used directly for ring closure.

The residue was dissolved in 50 ml. of methanol and 10 ml. of the sodium methoxide solution was added. After heating at reflux overnight, some of the solvent was evaporated, and the solution was poured into an excess of water. The mixture was extracted thoroughly with methylene chloride–ethyl ether and after the usual washings was dried. The solvent was evaporated, and the residue was recrystallized from ethyl ether to give 0.15 g., m.p. 187–190°.

Anal. Calcd. for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.45; N, 3.79. Found: C, 74.78; H, 8.51; N, 3.88.

Acknowledgment.—We wish to express our thanks to our colleagues in microanalysis, physical chemistry, and pharmacology who contributed the data referred to in this paper. We particularly acknowledge the assistance of Dr. H. Boaz in interpreting the n.m.r. spectra.

The Synthesis and Myotrophic Activity of 1-Halo-4-methylestra-1,3,5(10)-trienes

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A large series of variously substituted 1-halo-4-methylestra-1,3,5(10)-trienes was prepared. Some of these compounds possessed oral myotrophic activity with little or no accompanying androgenicity.

We have previously reported two different syntheses of 17-substituted 1-halo-4-methylestra-1,3,5(10)-trienes.[1,2] Some of these compounds were found to possess oral myotrophic activity, and the present paper describes certain related compounds which were prepared (see Table I) together with a record of their pharmacological activities.

The parent compound of this series, 1-chloro-4-methylestra-1,3,5(10)-trien-17-one (**11**), was prepared in 87% yield from the reaction of androsta-1,4-diene-3,17-dione with oxalyl chloride and oxalic acid in benzene at room temperature.[1] Fifteen related compounds (**14**, **22**, **25**, **28**, **31**, **43**, **48–51**, **53–55**, **57**, and **58**) were prepared by the same reaction on the corresponding substituted 1,4-dienones (Ia → II).[3] Seven of these androsta-1,4-dien-3-ones (**4–10**) were new compounds, synthesized from the Δ^4-3-ketones by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone.[4] The yields of the 1-chloro-4-methylestra-1,3,5(10)-trienes prepared in this manner were generally good, ranging from 30 to 90%.

The addition of ethinylmagnesium bromide to the 17-ketone of **11** gave the 17α-ethinyl compound (**39**), and subsequent partial catalytic reduction of the

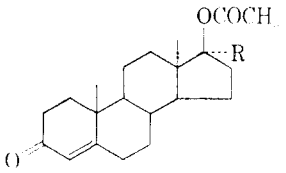
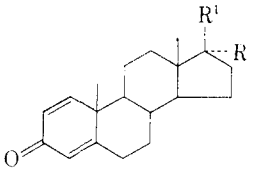
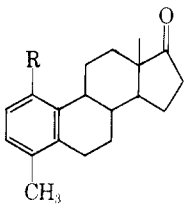
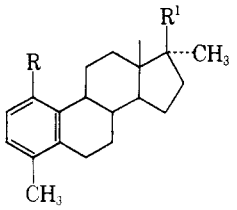
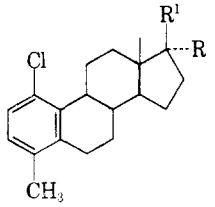
(1) G. W. Moersch, W. A. Neuklis, T. P. Culbertson, D. F. Morrow, and M. E. Butler, *J. Org. Chem.*, **29**, 2495 (1964).

(2) D. F. Morrow and M. E. Butler, *ibid.*, **29**, 1893 (1964).

(3) Professor A. S. Dreiding of the University of Zürich has indicated in his presentation at the Anniversary Meetings of the Chemical Society (London), Birmingham, April 9, 1964, the synthesis of compounds **11**, **12**, **23**, and **24** by an analogous rearrangement of the dienones with acetyl halides.

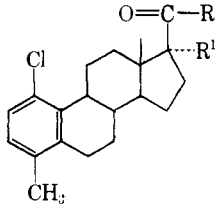
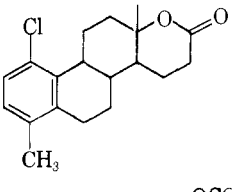
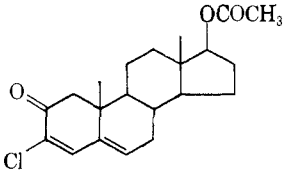
(4) D. Burn, D. N. Kirk, and Z. Petrow, *Proc. Chem. Soc.*, 14 (1960).

TABLE I

Compd.	R	R¹	Other	Prepn.[a]	Yield, %[b]	M.p., °C. (solvent[c])
			Substituted 17β-Acetoxyandrost-4-en-3-ones			
1	CH_3		1α,2β-Cl_2	A[e]	89	168–169 (Et)
2	H		7α-Me	B[f]	73	151–153 (Me)
3	CH_2CH_3			B[g]	57	152–153 (Me)
			Substituted Androsta-1,4-dien-3-ones			
4	-keto-		16β-Me	C[h]	52	188–189 (Me–W)
5	CH_3	$OCOCH_3$	2-Cl	D	63	215–218 (Et)
6	H	$OCOCH_3$	7α-Me	C	38	113–114 (He)
7	CH_2CH_3	$OCOCH_3$		C	25	139–140 (He)
8	$COCH_3$	$OCOCH_3$		C[i]	47	164–165 (E)
9	COOH	OH		E[j,k]	75	250–256 (Me–W)
10	$COOCH_3$	OH		F	75	177–178 (Me–W)
			1-Substituted 4-Methylestra-1,3,5(10)-trien-17-ones			
11	Cl			...[e]		
12	Br			...[l]		
13	F			...[l]		
14	Cl		16β-Me	G	36	137–138 (Me–W)
15	Cl		7α-Me	H	35	141–143 (Me)
16	NH_2			...[l]		
17	OCH_3			...[m]		
			Substituted 1-Halo-4,17α-dimethylestra-1,3,5(10)-trienes			
18	Br	OH		I[l]	55	159–160 (E–PE)
19	Br	$OCOCH_3$		B	87	147–148 (He)
20	F	OH		I[l]	68	177–178 (Me)
21	F	$OCOCH_3$		B	80	138–139 (Me)
22	Cl	$OCOCH_3$	2-Cl	G	62	219–222 (Me)
			Substituted 1-Chloro-4-methylestra-1,3,5(10)-trienes			
23	H	OH		J[e]	74	69–70 (Me–W)
24	H	$OCOCH_3$		B	75	121–122 (He)

$[\alpha]^{24}D$, deg.[d]	Formula	Calcd., % C	Calcd., % H	Calcd., % Cl	Found, % C	Found, % H	Found, % Cl
+13	$C_{22}H_{30}Cl_2O_3$	63.92	7.32	17.15	63.99	7.17	17.04
	$C_{22}H_{32}O_3$	76.70	9.37		76.55	9.39	
	$C_{23}H_{34}O_3$	77.05	9.56		76.95	9.72	
	$C_{20}H_{26}O_2$	80.50	8.78		80.41	8.52	
−17	$C_{22}H_{29}ClO_3$	70.10	7.76	9.41	70.05	7.70	9.47
+15	$C_{22}H_{30}O_3$						
	$C_{23}H_{32}O_3$	77.49	9.05		77.49	8.95	
+30	$C_{23}H_{30}O_4$	74.58	8.16		74.54	8.02	
+38 (Et)	$C_{20}H_{26}O_4$	72.71	7.93		72.38	7.72	
+48	$C_{21}H_{28}O_4$	73.23	8.19		73.52	8.35	
	$C_{20}H_{25}ClO$	75.81	7.96	11.19	75.88	8.06	11.25
	$C_{20}H_{25}ClO$	75.81	7.96	11.19	75.99	8.09	11.28
+200 (Me)	$C_{20}H_{27}BrO$	66.11	7.49	21.99[n]	66.37	7.69	22.15[n]
+187	$C_{22}H_{29}BrO_2$	65.18	7.21	19.71[n]	65.35	7.17	19.50[n]
+100 (Me)	$C_{20}H_{27}FO$	79.43	9.00	6.28[n]	79.52	9.10	6.12[n]
+96	$C_{22}H_{29}FO_2$	76.71	8.49	5.52[n]	76.64	8.62	5.74[n]
+214	$C_{22}H_{28}Cl_2O_2$	66.83	7.14	17.94	67.00	7.13	17.77
	$C_{19}H_{25}ClO \cdot CH_3OH$	71.30	8.67	10.52	71.51	8.50	10.81
+180	$C_{21}H_{27}ClO_2$	72.71	7.85	10.22	72.58	8.00	10.41

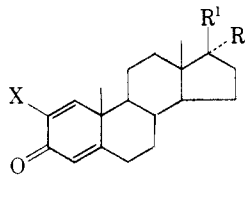
TABLE I (*Continued*)

Compd.	R	R¹	Other	Prepn.[a]	Yield, %[b]	M.p., °C. (solvent[c])
25	H	$OCOCH_2CH_3$				
26	H	$OCOCH_2CH_2C_6H_5$		K	47	120–121 (Ac–Me)
27	H	$OCOCH_3$	16β-Me	L, B	60	119–120 (Me)
28	H	$OCOCH_3$	7α-Me	G	52	119–121 (Me)
29	H	H		M[e]	81	107–108 (Ac–Me)
30	CH_3	OH		...[e]		
31	CH_3	$OCOCH_3$		...[e]		
32	CH_3	$OCOCH_2CH_3$		N[e]	54	100–102 (Me)
33	CH_3	$OCOCH_2CH_2COOH$		N[e]	30	142–143 (Ac–He)
34	CH_3	$OCOCH_2CH_2C_6H_5$		N[e]	33	105–106 (Ac–Me)
35	CH_3	OCH_2CH		O[e]	43	90–92 (Me)
36	CH_3	$OCH_2CH_2CH_3$		O[e]	50	70–72 (Me)
37	CH_3	OH	7α-Me	J	62	101–102 (Et–W)
38	CH_3	$OCOCH_3$	7α-Me	B	59	176–177 (Me)
39	C≡CH	OH		I[e]	72	167–168 (Bz–PE)
40	C≡CH	$OCOCH_3$		B	61	200–201 (Et)
41	$CH=CH_2$	OH		P	71	160–161 (Bz–PE)
42	$CH=CH_2$	$OCOCH_3$		B	83	170–171 (Et–W)
43	CH_2CH_3	$OCOCH_3$		G	30	165–167 (Et–W)
44	$CH_2CH=CH_2$	OH		I[e]	66	151–152 (Me–W)
45	$CH_2CH=CH_2$	$OCOCH_3$		B	73	134–135 (Me)
46	$CH_2CH_2CH_2OH$	OH		Q	91	200–202 (Et–W)
47	$-CH_2CH_2COO-$			R	58	204–211 (Et–W)
48	$COCH_3$	$OCOCH_3$		G	61	166–167 (Me)
		Substituted 1-Chloro-4-methyl-19-norpregna-1,3,5(10)-trienes				
49	CH_3	H		G[j,a]	87	192–194 (Et)
50	CH_3	OH		G[p,q]	37	192–194 (E–PE)
51	CH_3	$OCOCH_3$		G[r]	52	242–246 (Me)
52	CH_2OH	H		S	60	154–155 (Et)
53	CH_2OCOCH_3	H		G[j,s]	78	194–196 (Me)
54	CH_2OCOCH_3	OH		G[j,q]	74	219–221 (Et)
55	C_6H_5	H		G[t]	51	184–185 (Me)
56	OH	H		E	48	209–212 (Me)
57	OCH_3	H		G[u]	47	138–139 (Me)
58	OCH_3	OH		G	73	114–115 (He)
59				T[v]	78	150–152 (Me–W)
60				G[v]	82	238–240 (Me)

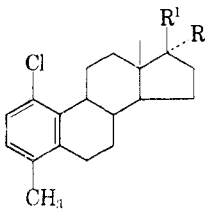
[a] The letters refer to the sections listed in Experimental. A footnote after the letter refers to the literature reference giving those starting materials which are not originally reported in this paper. [b] The per cent yields reported are based upon purified products having the melting points reported in the next column. [c] Me = methanol, Et = ethanol, E = ether, PE = petroleum ether, He = hexane, Ac = acetone, Bz = benzene, W = water. [d] Run as an approximately 1% solution in chloroform unless otherwise noted. [e] See ref. 1. [f] J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.*, **81**, 4069 (1959). [g] E. B. Hershberg, E. P. Oliveto, C. Gerold, and L. Johnson, *ibid.*, **73**, 5073 (1951). [h] F. Neumann, O. Mancera, G. Rosenkranz, and F. Sondheimer, *ibid.*, **77**, 5676 (1955). [i] I. Salamon and T. Reichstein, *Helv. Chim. Acta*, **30**, 1616 (1947). [j] E. Vischer, C. Meystre, and A. Wettstein, *ibid.*, **38**, 835 (1955). [k] A. Nobile, W. Charney, P. L. Perlman, H. L. Herzog, C. C. Payne, M. E. Tully, M. A. Jevnik, and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 4184

$[\alpha]^{24}D$, deg.[d]	Formula	Calcd., % C	Calcd., % H	Calcd., % Cl	Found, % C	Found, % H	Found, % Cl
+157	$C_{28}H_{33}ClO_2$	76.95	7.61	8.11	77.13	7.81	8.23
	$C_{22}H_{29}ClO_2$	73.22	8.10	9.82	73.21	8.01	9.88
+125	$C_{22}H_{29}ClO_2$	73.22	8.10	9.82	72.88	8.11	10.03
+200	$C_{19}H_{25}Cl$	79.00	8.72	12.27	79.14	8.98	12.07
	$C_{23}H_{31}ClO_2$	73.68	8.33	9.46	73.65	8.08	9.49
	$C_{24}H_{31}ClO_4$	68.81	7.46	8.46	68.64	7.57	8.65
	$C_{29}H_{35}ClO_2$	77.20	7.82	7.86	77.23	7.82	8.11
+182	$C_{22}H_{31}ClO$	76.16	9.01		75.98	9.10	
+180	$C_{23}H_{33}ClO$	76.53	9.21		76.06	9.01	
	$C_{21}H_{29}ClO$						
+136	$C_{23}H_{31}ClO_2$	73.67	8.34	9.46	73.82	8.55	9.46
	$C_{21}H_{25}ClO$	76.68	7.66	10.78	76.59	7.62	10.79
+99	$C_{23}H_{27}ClO_2$	74.48	7.34	9.56	74.53	7.44	9.55
+182	$C_{21}H_{27}ClO$	76.23	8.23	10.72	76.26	8.27	10.77
+194	$C_{23}H_{29}ClO_2$	74.06	7.84	9.51	74.16	7.95	9.70
	$C_{23}H_{31}ClO_2$	73.68	8.33	9.46	73.51	8.34	9.47
+190	$C_{22}H_{29}ClO$	76.61	8.47	10.28	76.52	8.42	10.40
+172	$C_{24}H_{31}ClO_2$	74.50	8.07	9.16	74.35	7.96	9.17
+165	$C_{22}H_{31}ClO_2$	72.80	8.61	9.77	72.70	8.76	10.04
+141	$C_{22}H_{27}ClO_2$	73.62	7.58	9.88	73.35	7.54	9.94
+163	$C_{23}H_{29}ClO_3$	71.01	7.51	9.11	71.00	7.68	9.18
+309	$C_{21}H_{27}ClO$	76.23	8.22	10.72	76.32	8.25	10.74
+189	$C_{21}H_{27}ClO_2$	72.72	7.84	10.22	72.64	7.99	10.26
+170	$C_{23}H_{29}ClO_3$	71.01	7.52	9.11	70.78	7.72	9.13
+279	$C_{21}H_{27}ClO_2$	72.72	7.84	10.22	72.43	7.82	10.50
+272	$C_{23}H_{29}ClO_3$	71.01	7.52	9.11	70.84	7.69	9.17
	$C_{23}H_{29}ClO_4$	68.22	7.21	8.76	68.07	7.02	9.07
+178	$C_{26}H_{29}ClO$	79.51	7.40	9.01	79.36	7.58	9.14
+250	$C_{20}H_{25}ClO_2$	72.16	7.57	10.64	71.85	7.69	10.34
+254	$C_{21}H_{27}ClO_2$	72.72	7.84	10.22	72.47	7.79	10.31
+185	$C_{21}H_{27}ClO_3$	69.50	7.50	9.77	69.22	7.27	9.73
+190	$C_{19}H_{23}ClO_2$	71.55	7.27	11.12	71.53	7.48	11.19
−163	$C_{21}H_{27}ClO_3$	69.50	7.50	9.77	69.20	7.60	9.90

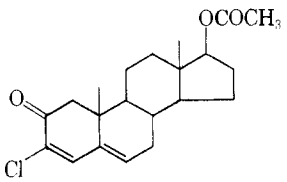
(1955). [l] See ref. 2. [m] C. Djerassi and C. R. Scholz, *J. Org. Chem.*, **13**, 697 (1948). [n] These analytical figures are for bromine and fluorine, respectively, rather than for chlorine. [o] F. Sondheimer, M. Velasco, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 5673 (1955). [p] G. Rosenkranz, S. Kaufmann, J. Pataki, and C. Djerassi, *ibid.*, **72**, 1046 (1950). [q] G. Rosenkranz, J. Pataki, S. Kaufmann, J. Berlin, and C. Djerassi, *ibid.*, **72**, 4081 (1950). [r] S. Wada, *Yakugaku Zasshi*, **79**, 120 (1959); *Chem. Abstr.*, **53**, 10296*b* (1959). [s] R. L. Clarke, K. Dobriner, A. Mooradian, and C. M. Martini, *J. Am. Chem. Soc.*, **77**, 661 (1955). [t] D. F. Morrow, T. P. Culbertson, E. L. Wittle, M. E. Butler, and M. M. Creger, *J. Med. Chem.*, **7**, 537 (1964). [u] C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947). [v] See ref. 8.



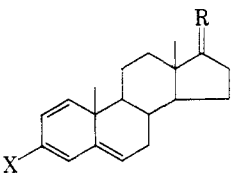
Ia, X = H
b, X = $OCOCH_3$
c, X = OCH_3

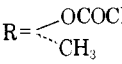


II



60



61, X = Cl; R = O
62, X = Cl; R = 
63, X = Br; R = O

ethinyl group afforded the 17α-vinyl derivative (**41**). The 17α-methyl compounds (**18**, **20**, **30**, and **37**) were synthesized by the addition of methylmagnesium bromide to the corresponding 1-halo-4-methylestra-1,3,5(10)-trien-17-ones (**11**,[1] **12**,[2] **13**,[2] and **15**). Acetate esters of these tertiary alcohols (**19**, **21**, **24**, **27**, **31**, **38**, **40**, **42**, and **45**) were easily prepared in high yield by treatment with acetic anhydride at reflux temperature. Esters other than acetates (**32–34**) were synthesized by the procedure of Evans, *et al.*,[5] in which the halomagnesium salt of the tertiary alcohol, prepared by treatment of the alcohol with 1 equiv. of methylmagnesium bromide, was allowed to react with the appropriate acid chloride.

The 17β-ethers (**35** and **36**) were prepared by reduction of the corresponding esters (**31** and **32**) with diborane. The procedure followed was essentially that of Pettit and Piatak,[6] although the generalized reaction conditions described by these authors were modified slightly. The slow addition of diglyme to a mixture of the steroid ester, sodium borohydride, and boron trifluoride etherate in tetrahydrofuran apparently helped regulate the rate of the reduction of the ester to the ether.

The addition of allylmagnesium bromide to the 17-ketone of **11** afforded the 17α-allyl derivative (**44**). Hydroboration of this yielded 1-chloro-4-methyl-17α-(3-hydroxypropyl)estra-1,3,5(10)-trien-17β-ol (**46**), which was oxidized with chromic acid in acetic acid to give the spirolactone **47**.

A Baeyer–Villiger oxidation of the 17-ketone **11** afforded the estrololactone analog **59**, and a Wolff–Kishner reduction of this ketone gave the 17-desoxy derivative **29**. A periodate cleavage of the ketol side chain of **52** yielded the 17β-carboxylic acid **56**.

Although the reaction of 2-chloro-17α-methylandrosta-1,4-dien-3-on-17β-ol acetate (**5**)[7] with oxalyl chloride and oxalic acid in benzene proceeded normally to give 1,2-dichloro-4,17α-dimethylestra-1,3,5(10)-trien-17β-ol acetate (**22**) in good yield, no ring A aromatic product could be isolated from similar treatment of either 2-acetoxy- (Ib)[8] or 2-methoxyandrosta-1,4-dien-3-on-17β-ol acetate (Ic).[8] The sole product isolated from these reactions was 3-chloroandrosta-3,5-dien-2-on-17β-ol acetate (**60**). The structure of **60** was assigned on the basis of its microanalysis and spectral data. The infrared (3040, 1739, 1687, 1628, and 1577 cm.$^{-1}$) and ultraviolet (306 mμ, ϵ 14,000) spectra were indicative of an α,β–γ,δ diunsaturated ketone. A peak at 7.11 p.p.m. in the n.m.r. spectrum of **60** indicated a vinyl proton β to the carbonyl group.[9] The absence of any α- or γ-vinylic protons was demonstrated by the fact that the peak at 7.11 p.p.m. was a singlet. The peak produced by the δ-proton was a multiplet, split by the allylic protons on C-7, at 6.07 p.p.m. The only reasonable structure consistent with these data is **60**. This compound was extremely resistant to aromatization and was recovered unchanged after being refluxed for 1 hr. in acetic anhydride in the presence of *p*-toluenesulfonic acid.

The myotrophic and androgenic activities of this series of compounds were determined by a modified Hershberger assay.[10] Daily oral doses of 2.0 mg./animal were given to immature castrate male rats for 14 days, and the increase in weight of the levator ani muscle, the seminal vesicles, and the ventral prostate were determined and compared with the corresponding increases of both vehicle-injected controls and rats receiving 2.0 mg. of oxymetholone[11] daily. The results are shown in Table II. The 3-haloandrosta-1,3,5-trienes (**61–63**) which were isolated as intermediates in the reaction of oxalyl halides with androsta-1,4-dien-3-ones[1] also possessed myotrophic activity. These results are included in Table II.

The complete lack of androgenicity in some of these myotrophic compounds is unusual. The tertiary acetate **31** gave no indication of androgenic effects at doses as high as 20 mg./rat/day for 14 days. Nitrogen balance studies[12] in rats were performed on compounds **31**, **40**, and **49** and again compared with oxymetholone[11] as a standard (Table III).

The tertiary acetate **31** was inactive orally as an inhibitor of the pituitary gland, as either a progestational or an antiprogestational agent, as an estrogen, as an ovulation inhibitor, and as a serum cholesterol lowering agent. Compound **49** likewise was inactive as either a progestational or serum cholesterol lowering agent, and compound **40** was ineffective as an ovulation inhibitor. In addition, compounds **23**, **35**, and **54** possessed no serum cholesterol lowering activity in rats, and the spirolactone **47** did not alter the renal electrolyte response to aldosterone in adrenalectomized rats. The tertiary acetate **31** was devoid of toxic manifestations in rats at a dosage of 35 mg./kg./day for 35 days and caused no loss in weight.

(5) D. D. Evans, D. E. Evans, G. S. Lewis, P. J. Palmer, and D. J. Weyell, *J. Chem. Soc.*, 3578 (1963).

(6) G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **27**, 2127 (1962).

(7) Prepared from 17α-methylandrosta-1,4-dien-3-on-17β-ol acetate[1] by the procedure of D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 1334 (1958).

(8) J. S. Baron, *J. Am. Chem. Soc.*, **80**, 1687 (1958).

(9) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, 1963.

(10) D. A. McGinty and C. Djerassi, *Ann. N. Y. Acad. Sci.*, **71**, 500 (1958).

(11) 2-Hydroxymethylene-17β-hydroxy-17α-methyl-5α-androstan-3-one.

(12) The procedure of C. D. Kochakian, *Am. J. Physiol.*, **160**, 53 (1950), was used with some slight modifications.

TABLE II

ORAL ANDROGENIC AND MYOTROPHIC ACTIVITY IN RATS[a]

No.	Andro-genicity	Myotro-phic activity	No.	Andro-genicity	Myotro-phic activity
11	+	++	40	0	++
12	+	+	41	0	0
16	+	++	43	+	++
17	0	0	45	0	++
19	+	++	47	0	+
21	+	++	48	0	0
22	0	0	49	+	++
23	0	0	50	0	0
24	0	++	51	+	0
25	0	++	52	0	+
27	++	0	53	0	++
28	0	++	54	0	0
29	0	+	55	0	0
30	0	0	56	0	0
31	0	++	57	+	+
32	+	++	58	0	+
33	+	++	59	0	0
34	0	++	60	0	++
35	+	0	61	+	+
36	0	0	62	0	++
38	+	0	63	0	++
39	+	+			

[a] Dose, 2 mg./rat; + = <25% oxymetholone,[11] ++ = 25–50% oxymetholone.[11]

TABLE III

ORAL NITROGEN-RETAINING ACTIVITY IN RATS

No.	No. of assays run	Design[a]	Potency (oxymetholone[b] = 1.0)
31	3	4:4	0.45 (mean)
40	1	2:1	0.29
49	1	4:4	0.29

[a] Number of doses of standard:number of doses of test compound. [b] See footnote 11.

Experimental[13]

A. 1α,2β-Dichloro-17α-methylandrost-4-en-3-on-17β-ol Acetate (1).—A solution of 2.0 g. of 17α-methylandrosta-1,4-dien-3-on-17β-ol acetate[1] in 80 ml. of ether was cooled to −28° and treated with 5.20 ml. of a 1.2 *M* solution of chlorine in propionic acid. The solution was left overnight at −28° and then filtered, affording the pure dichloro compound.

B. 17β-Acetates (2, 3, 19, 21, 24, 27, 38, 40, 42, and 45).—A solution of the appropriate 17α-substituted 1-halo-4-methylestra-1,3,5(10)-trien-17β-ol (3.2 mmoles) in 30 ml. of acetic anhydride was refluxed for 1 hr., cooled to room temperature, treated with 30 ml. of methanol, and refluxed an additional 0.5 hr. The solvents were removed under reduced pressure to give the crude acetate ester.

C. Androsta-1,4-dien-3-ones (4, 6–8).—A solution of the appropriate androst-4-en-3-one (11.2 mmoles) and 2,3-dichloro-5,6-dicyanobenzoquinone (14.1 mmoles) in 50 ml. of benzene was refluxed 9.5 hr. The solution was cooled to room temperature, diluted with an equal volume of ether, and filtered. The filtrate was extracted several times with 2 *N* NaOH solution and with water, and was then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded the crude product.

D. 2-Chloro-17α-methylandrosta-1,4-dien-3-on-17β-ol Acetate (5).—A suspension of 3.0 g. of 1α,2β-dichloro-17α-methylandrost-4-en-3-on-17β-ol acetate (1) in 50 ml. of pyridine was stirred at room temperature for 1 hr. The solution was then diluted with ether, washed well with dilute HCl and with water. The solution was dried over magnesium sulfate and concentrated to dryness, yielding the crude androstadiene.

E. Periodate Cleavage of the Ketol Side Chain (9 and 56).—A solution of the 21-hydroxy-20-keto steroid (2.21 mmoles) in 70 ml. of dioxane was treated with a solution of 1.2 g. (5.25 mmoles) of periodic acid in 30 ml. of water and allowed to stand overnight at room temperature. The solution was poured into water, and the crude acid was separated by filtration.

F. Methyl 17α-Hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate (10).—A solution of 3.20 g. of 17α-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid (9) in 200 ml. of tetrahydrofuran was treated with an excess of diazomethane. The solution was allowed to stand at room temperature for 5 min., and the excess diazomethane was then decomposed with acetic acid. Evaporation to dryness under reduced pressure afforded the crude ester.

G. Reaction of Oxalyl Chloride with Androsta-1,4-dien-3-ones (14, 22, 28, 43, 48–51, 53–55, 57, 58, and 60).—A solution of the androsta-1,4-dien-3-one (2.30 mmoles) in 30 ml. of benzene was treated with 4.5 ml. (53 mmoles) of oxalyl chloride and 0.30 g. (2.40 mmoles) of powdered oxalic acid dihydrate. The mixture was stirred at room temperature overnight and then evaporated under reduced pressure. The oily residue was triturated with ether or dilute sodium bicarbonate solution to induce crystallization.

H. 1-Chloro-4,7α-dimethylestra-1,3,5(10)-trien-17-one (15).—A cold solution of 1.7 g. of crude 1-chloro-4,7α-dimethylestra-1,3,5(10)-trien-17β-ol, obtained from the acetate ester (28) by procedure J, in 60 ml. of acetic acid was treated with a solution of 1.45 g. of chromium trioxide in 20 ml. of acetic acid and 1 ml. of water and allowed to stand 1 hr. at 0°. The solution was then poured into water and filtered. The product was chromatographed on Florisil. Elution with 1:1 benzene–hexane afforded the ketonic product.

I. Introduction of 17α-Alkyl Substituents (18, 20, 37, 39, and 44).—A solution of the appropriate 1-halo-4-methylestra-1,3,5(10)-trien-17-one (5.25 mmoles) in 80 ml. of ether and 20 ml. of benzene was treated with 15 mmoles of methyl(or allyl or ethinyl)magnesium bromide in ether (or tetrahydrofuran). The mixture was stirred and refluxed 1 hr., cooled, and treated with 20% aqueous ammonium chloride solution. The organic layer was separated, washed with water, dried over magnesium sulfate, and concentrated to dryness on a steam bath, affording the crude product.

J. 1-Chloro-4-methylestra-1,3,5(10)-trien-17β-ol (23).—A solution of 2.5 g. of 1-chloro-4-methylestra-1,3,5(10)-trien-17β-ol propionate (25)[1] in 90 ml. of 5% ethanolic KOH solution was refluxed for 1 hr. The solution was cooled in ice and diluted with water. The precipitate was filtered and dissolved in benzene. The solution was dried over magnesium sulfate and concentrated to dryness, yielding the crude alcohol.

K. 1-Chloro-4-methylestra-1,3,5(10)-trien-17β-ol β-Phenylpropionate (26).—A cold solution of 1.7 g. of 1-chloro-4-methylestra-1,3,5(10)-trien-17β-ol (23) in 40 ml. of ether was treated with 9 ml. of triethylamine and 3 ml. of β-phenylpropionyl chloride. The mixture was kept at room temperature for 3 days and then filtered. The filtrate was washed with 3 *N* HCl, saturated sodium bicarbonate solution, and water. The solution was then dried over magnesium sulfate and concentrated to dryness, affording the crude ester.

L. 1-Chloro-4,16β-dimethylestra-1,3,5(10)-trien-17β-ol (27).—A solution of 0.50 g. of 1-chloro-4,16β-dimethylestra-1,3,5(10)-trien-17-one (14) in 60 ml. of ethanol was treated with 0.50 g. of sodium borohydride. The solution was stirred overnight at room temperature and poured into water. The product was extracted with ether, washed with water, and dried over magnesium sulfate. Evaporation of the ether gave the crude alcohol.

M. 1-Chloro-4-methylestra-1,3,5(10)-triene (29).—A suspension of 575 mg. of 1-chloro-4-methylestra-1,3,5(10)-trien-17-one (11)[1] in 50 ml. of diethylene glycol was treated with 5.0 g. of KOH and 6 ml. of 95% hydrazine. The resulting mixture was refluxed for 1 hr., distilled until the vapor temperature reached 175°, and then refluxed an additional 2.5 hr. The solution was cooled to room temperature, poured into water, and filtered to give the crude desoxy compound.

N. 17β-Esters (32–34).—A stirred solution of 1.75 g. (5.50 mmoles) of 1-chloro-4,17α-dimethylestra-1,3,5(10)-trien-17β-ol (30)[1] in 160 ml. of ether was treated with 2.0 ml. (6.00 mmoles)

(13) The melting points were determined on a Fisher-Johns block and are corrected. The n.m.r. spectrum was run on a Varian A-60 instrument in deuteriochloroform solution; resonances are expressed as parts per million downfield from tetramethylsilane, used as an internal reference. The crude materials obtained from the generalized procedures were purified by recrystallization from the appropriate solvent noted in Table I.

of 3 *M* methylmagnesium bromide. The resulting mixture then was treated with 8.25 mmoles of the appropriate acid chloride in 20 ml. of ether and stirred at room temperature for 60 hr. Cold concentrated sodium bicarbonate solution was then added. The ether layer was separated, washed well with sodium bicarbonate solution and with water, dried over magnesium sulfate, and concentrated to dryness to yield the crude ester.

O. 17β-Ethers (35 and 36).—To a stirred mixture of 1.0 g. of sodium borohydride in 100 ml. of ether cooled in an ice bath was added a solution of 5.55 mmoles of the appropriate ester of 1-chloro-4,17α-dimethylestra-1,3,5(10)-trien-17β-ol (**31** and **32**) in 50 ml. of ether and 50 ml. of tetrahydrofuran. Freshly distilled boron trifluoride etherate (20 ml.) was then added and the resulting mixture was cooled to 0°. To this cold solution was then slowly added 50 ml. of distilled diglyme, and the mixture was stirred and allowed to warm to room temperature over a 2-hr. period. It was then heated to distil 50 ml. of ether and refluxed for 1 hr. The solution was cooled, diluted with 200 ml. of ether, and treated with 5 ml. of 12 *N* HCl. The ether layer was separated, washed with water, dried over magnesium sulfate, and evaporated to an oil. The oil was dissolved in 100 ml. of petroleum ether (b.p. 35–60°) and chromatographed on 15 g. of alumina. Elution with petroleum ether gave the pure 17β-ether.

P. 1-Chloro-4-methyl-17α-vinylestra-1,3,5(10)-trien-17β-ol (41).—A solution of 2.00 g. of 1-chloro-4-methyl-17α-ethinylestra-1,3,5(10)-trien-17β-ol (**39**) in 120 ml. of pyridine was treated with 0.20 g. of 5% palladium on calcium carbonate and hydrogenated at atmospheric pressure until 1.0 equiv. of hydrogen had been absorbed. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure, giving the crude vinyl compound.

Q. 1-Chloro-4-methyl-17α-(3-hydroxypropyl)estra-1,3,5(10)-trien-17β-ol (46).—A solution of diborane in tetrahydrofuran was prepared by adding 14.2 g. of boron trifluoride etherate in 40 ml. of tetrahydrofuran to a stirred mixture of 3.1 g. of powdered sodium borohydride in 60 ml. of tetrahydrofuran cooled in an ice bath. The mixture was allowed to stand overnight at room temperature.

A solution of 1.35 g. of 1-chloro-4-methyl-17α-allylestra-1,3,5(10)-trien-17β-ol (**44**) in 50 ml. of tetrahydrofuran was treated with 15 ml. of the above diborane solution. After 2 hr. at room temperature, the solution was cooled to 0° and treated with 16 ml. of 30% hydrogen peroxide and 16 ml. of 10% aqueous sodium hydroxide solution. This mixture was stirred for 0.5 hr. and then refluxed for 1.5 hr. The solvent was removed under reduced pressure and the residue was poured into water. The aqueous suspension was extracted with ether. The ether solution was dried over magnesium sulfate and concentrated to dryness, yielding the crude oil.

R. 1-Chloro-4-methylestra-1,3,5(10)-trien-17β-ol-17α-propionic Acid, Lactone (47).—A solution of 1.27 g. of 1-chloro-4-methyl-17α-(3-hydroxypropyl)estra-1,3,5(10)-trien-17β-ol (**46**) in 120 ml. of acetic acid and 40 ml. of propionic acid was cooled to 0°, covered with an atmosphere of nitrogen, and treated with 1.90 ml. of a solution of chromium trioxide (prepared by dissolving 26.72 g. of chromium trioxide in 23 ml. of 36 *N* sulfuric acid and diluting to 100 ml. with water) over a period of 30 min. The reaction was stirred for an additional 15 min., poured into water, and filtered. The precipitate was dissolved in benzene and chromatographed on 20 g. of Florisil. Elution with 4:1 benzene–ether afforded the pure lactone.

S. 1-Chloro-4-methyl-19-norpregna-1,3,5(10)-trien-21-ol-20-one (52).—A solution of 1.50 g. of 1-chloro-4-methyl-19-norpregna-1,3,5(10)-trien-21-ol-20-one 21-acetate (**53**) in 450 ml. of methanol was treated with a solution of 1.60 g. of potassium bicarbonate in 32 ml. of water and refluxed for 1 hr. under an atmosphere of nitrogen. The solution was then concentrated under reduced pressure to about 150 ml. and poured into water. The precipitated crude 21-alcohol was filtered and recrystallized.

T. 1-Chloro-4-methyl-17a-oxa-D-homoestra-1,3,5(10)-trien-17-one (59).—A solution of 1.00 g. of 1-chloro-4-methylestra-1,3,5(10)-trien-17-one (**11**) and 0.05 g. of *p*-toluenesulfonic acid monohydrate in 10 ml. of acetic acid and 3 ml. of 40% peracetic acid was allowed to stand at 4° for 7 days. The solution was poured into water and filtered to give the crude lactone.

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6α-Fluoro- and 6α-Methyl-16α-fluoroprednisolones[1]

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The preparation of 6α-fluoro- and 6α-methyl-16α-fluoroprednisolones is described.

Recently we described the synthesis of 16α-fluoroprednisolone acetate and showed that the 16α-fluoro group strongly enhanced the antiinflammatory property of prednisolone acetate.[2] The 16α-fluoro substituent has now been introduced into suitable 6α-fluoro[3] and 6α-methyl[4] intermediates and the corresponding 6α-fluoro- and 6α-methyl-16α-fluoroprednisolones have been prepared and evaluated biologically.

The method of synthesis for the 6-substituted 16α-fluorocorticoids was essentially that previously described.[2] The processes are outlined in Chart I.

Preliminary endocrine data for the 16α-fluorocorticoids are summarized in Table I.

Experimental[5]

6α-Fluoro-11β,16α,21-trihydroxy-4,17(20)-*cis*-pregnadien-3-one 21-Acetate (2).—A mixture of 40 g. of 11β,21-dihydroxy-6α-fluoro-4,17(20)-*cis*-pregnadien-3-one 21-acetate (1),[6] 18.5 g. of selenium dioxide, 150 ml. of water, and 960 ml. of dioxane was heated under reflux for 1 hr. The dioxane was distilled *in vacuo*. The residue was partitioned between methylene chloride and water. After drying, the organic phase was percolated through 4 kg. of Florisil (synthetic magnesia–silica gel). The fraction eluted with 20:80 acetone–Skellysolve B (saturated hydrocarbon fraction, b.p. 60–71°) weighed 49 g. This product when recrystallized from ethyl acetate weighed 22 g. (52.8% yield) and

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(2) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Am. Chem. Soc.*, **82**, 1252 (1960); B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, in press.

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(5) Melting points were taken in capillary tubes and are corrected. Rotations were observed at 26°.

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