

**Reduction of (3RS,4RS)-4-Methyl-1,5-dioxaspiro[2.5]octane (19).** Following the procedure for 12, 31 mg (0.24 mmol) of 19 was reduced with 15 mg (0.4 mmol) of  $\text{LiAlH}_4$ . Work-up gave 25 mg (80%) of the alcohol 24 as a colorless liquid: ir (neat)  $3450\text{ cm}^{-1}$  ( $-\text{OH}$ ); NMR ( $\text{CDCl}_3$ )  $\delta$  4.07–3.45 (2 H, m, methylene at  $\text{C}_6$ ), 3.28 (1 H, q, methine at  $\text{C}_3$ ,  $J = 13\text{ Hz}$ ), 1.70 (4 H, m, methylene at  $\text{C}_4$  and  $\text{C}_5$ ), 1.21 (3 H, s, methyl at  $\text{C}_3$ ), 1.17 (3 H, d, methyl at  $\text{C}_2$ ,  $J = 5.5\text{ Hz}$ ). GLC analysis (5% FFAP,  $80^\circ\text{C}$ ) showed one peak at the retention time of 6.2 min.

**Reduction of (3SR,4SR)-4-Methyl-1,5-dioxaspiro[2.5]octane (20).** Following the procedure for 12, 30 mg (0.24 mmol) of 20 was reduced with 15 mg (0.4 mmol) of  $\text{LiAlH}_4$ . Work-up gave 20 mg (76%) of the alcohol 23 as a colorless liquid: ir (neat)  $3450\text{ cm}^{-1}$  ( $-\text{OH}$ ); NMR ( $\text{CDCl}_3$ )  $\delta$  4.15–3.43 (2 H, m, methylene at  $\text{C}_6$ ), 6.72 (1 H, q, methine at  $\text{C}_2$ ,  $J = 13\text{ Hz}$ ), 2.20 (1 H, broad,  $-\text{OH}$ ), 1.17 (3 H, d, methyl at  $\text{C}_2$ ,  $J = 5.5\text{ Hz}$ ), 1.11 (3 H, s, methyl at  $\text{C}_3$ ). GLC (5% FFAP,  $80^\circ\text{C}$ ) showed the presence of one component at the retention time of 2.7 min, identical with the major product of methylolithium addition to 18.

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## Steroidal 3,5-Dienes

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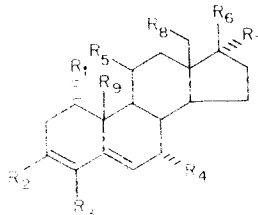
A series of  $\Delta^{3,5}$ -androstadienes, estradienes, and gonadienes was prepared and evaluated as claudogenic agents. Claudogenic activity was limited to relatively few members of the series, but three compounds—12, 14, and 15—were very potent.

The function of the carbonyl moiety at C-3 of steroid hormones in eliciting biological responses has been the subject of some study in this<sup>1</sup> and other laboratories.<sup>2,3</sup> In the course of our search for claudogenic steroids, we needed to prepare estr-4-ene-3 $\alpha$ ,17 $\beta$ -diol by reduction of 19-nortestosterone with  $\text{LiAlH}_4$ . Purification of the crude product gave estr-4-ene-3 $\beta$ ,17 $\beta$ -diol and estra-3,5-dien-

17 $\beta$ -ol (1). Routine screening of the latter compound, which presumably comes from dehydration of the 3 $\alpha$ -alcohol, showed marked claudogenic activity.

Searching the literature, we were impressed by a related family of steroidal 3-aryl- $\Delta^{3,5}$ -dienes 2 which were purported to "... share with estrone the capacity to inhibit uterine response to progesterone."<sup>4</sup> Based on the reported

Table I. Steroidal 3,5-Dienes



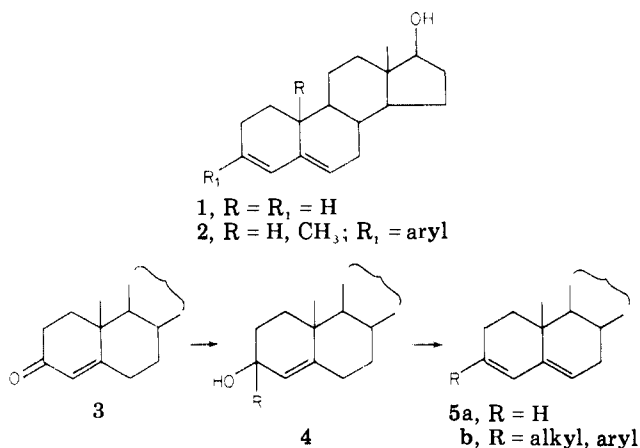
No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	R <sub>6</sub>	R <sub>7</sub>	R <sub>8</sub>	R <sub>9</sub>	Mp, °C	Lit. mp, °C	Yield, %	Formula	Analyses
1	H	H	H	H	H	OH	H	H	H	106-109	112-113 <sup>a,b</sup>	29.1		
6	H	H	H	H	H	OCOCH <sub>3</sub>	H	H	H	109-112	107-108 <sup>c</sup>	13.3		
7	H	H	H	H	H	O	H	H	H	214-218		47.8	C <sub>18</sub> H <sub>24</sub> O	H; C <sup>t</sup>
8	H	CH <sub>3</sub>	H	H	H	OCOCH <sub>3</sub>	H	H	H	157-164		37.3	C <sub>21</sub> H <sub>30</sub> O	C, H
9	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	OH	H	H	H	145-150	128-132 <sup>d</sup>	44.5		
10	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	OCOCH <sub>3</sub>	H	H	H	152-154	158-159 <sup>d</sup>			
11	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	O	H	H	H	190-193		27.1	C <sub>24</sub> H <sub>28</sub> O	C, H
12	H	H	H	CH <sub>3</sub>	H	OH	H	H	H	102-106			C <sub>19</sub> H <sub>28</sub> O·0.25H <sub>2</sub> O	C, H
13	H	H	H	CH <sub>3</sub>	H	OCOCH <sub>3</sub>	H	H	H	80-81			C <sub>21</sub> H <sub>30</sub> O <sub>2</sub>	C, H
14	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	OH	H	H	H	82-91			C <sub>20</sub> H <sub>30</sub> O	C, H
15	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	OCOCH <sub>3</sub>	H	H	H	114-115		30.1	C <sub>22</sub> H <sub>32</sub> O <sub>2</sub>	C, H
16	H	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	H	OH	H	H	H	145-148		59.2	C <sub>25</sub> H <sub>32</sub> O	C, H
17	H	H	H	H	H	OCOCH <sub>3</sub>	H	CH <sub>3</sub>	H	124-127		74	C <sub>21</sub> H <sub>30</sub> O <sub>2</sub>	C, H
18	H	CH <sub>3</sub>	H	H	H	OCOCH <sub>3</sub>	H	CH <sub>3</sub>	H	130-134		61	C <sub>22</sub> H <sub>32</sub> O <sub>2</sub>	C, H
19	H	H	H	CH <sub>3</sub>	H	OCOCH <sub>3</sub>	H	CH <sub>3</sub>	H	124-127		34	C <sub>22</sub> H <sub>32</sub> O <sub>2</sub>	C, H
20	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	OCOCH <sub>3</sub>	H	CH <sub>3</sub>	H	104-107		82	C <sub>23</sub> H <sub>34</sub> O <sub>2</sub>	C, H
21	H	H	H	H	H	OH	H	H	CH <sub>3</sub>	153-155	98-100 <sup>e</sup>	47.8	C <sub>19</sub> H <sub>28</sub> O	C, H
22	H	CH <sub>3</sub>	H	H	H	OH	H	H	CH <sub>3</sub>	128-131	134-136 <sup>f,h</sup>	43.7		
23	H	H	CH <sub>3</sub>	H	H	OH	H	H	CH <sub>3</sub>	146-150		31.7	C <sub>20</sub> H <sub>30</sub> O	C, H
24	H	H	H	CH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	142-144		77	C <sub>20</sub> H <sub>30</sub> O	C, H
25	H	H	H	CH <sub>3</sub> <sup>k</sup>	H	OH	H	H	CH <sub>3</sub>	159-162		52.5	C <sub>20</sub> H <sub>30</sub> O	C, H
26	CH <sub>3</sub>	H	H	CH <sub>3</sub> <sup>g</sup>	H	OH	H	H	CH <sub>3</sub>	148-150		56.2	C <sub>20</sub> H <sub>32</sub> O	C, H
27	H	CH <sub>3</sub>	CH <sub>3</sub>	H	H	OH	H	H	CH <sub>3</sub>	186-190		40.2	C <sub>21</sub> H <sub>32</sub> O	C, H
28	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	170-172		68.4	C <sub>21</sub> H <sub>32</sub> O	C, H
29	H	CH <sub>3</sub>	H	CH <sub>3</sub> <sup>g</sup>	H	OH	H	H	CH <sub>3</sub>	132-134		49	C <sub>20</sub> H <sub>32</sub> O	C, H
30	CH <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	161-165		47.3	C <sub>22</sub> H <sub>34</sub> O	C, H
31	H	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	155-160		53.3	C <sub>22</sub> H <sub>34</sub> O	H; C <sup>u</sup>
32	H	C <sub>4</sub> H <sub>9</sub>	H	H	H	OH	H	H	CH <sub>3</sub>	94-97			C <sub>23</sub> H <sub>36</sub> O·0.5H <sub>2</sub> O	H; C <sup>v</sup>
33	H	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	121-124		37.9	C <sub>24</sub> H <sub>38</sub> O	C, H
34	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	OH	H	H	CH <sub>3</sub>	162-164	154-156 <sup>h,u</sup>	45.8	C <sub>25</sub> H <sub>32</sub> O	C, H
35	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	OCOCH <sub>3</sub>	H	H	CH <sub>3</sub>	170-173			C <sub>27</sub> H <sub>34</sub> O <sub>2</sub>	C, H
36	H	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	161-162		57.8	C <sub>26</sub> H <sub>34</sub> O	C, H
37	H	H	H	H	OH	OH	H	H	CH <sub>3</sub>	178-180 <sup>r</sup>	150-151 <sup>i</sup>		C <sub>19</sub> H <sub>28</sub> O <sub>2</sub> ·0.5H <sub>2</sub> O	C, H
38	H	CH <sub>3</sub>	H	H	OH	O	H	H	CH <sub>3</sub>	164-166		4.1	C <sub>20</sub> H <sub>28</sub> O <sub>2</sub>	C, H

39	H	CH <sub>3</sub>	H	H	OH	OH	H	H	CH <sub>3</sub>	149-152	43.2	C <sub>20</sub> H <sub>30</sub> O <sub>2</sub> ·0.25H <sub>2</sub> O	C, H	
40	H	CH <sub>3</sub>	H	H	OH	OH	CH <sub>3</sub>	H	CH <sub>3</sub>	202-208	32.9	C <sub>21</sub> H <sub>32</sub> O <sub>2</sub> ·0.25H <sub>2</sub> O	C, H	
41	H	H	H	CH <sub>3</sub>	OH	OH	H	H	CH <sub>3</sub>	178-180	13.1	C <sub>20</sub> H <sub>32</sub> O <sub>2</sub> ·0.25H <sub>2</sub> O	C, H	
42	H	H	H	CH <sub>3</sub> <sup>g</sup>	OH	OH	H	H	CH <sub>3</sub>	134-145	30.6	C <sub>20</sub> H <sub>30</sub> O <sub>2</sub>	H; C <sup>u</sup>	
43	H	CH <sub>3</sub>	H	CH <sub>3</sub>	OH	OH	H	H	CH <sub>3</sub>	199-203	29.4	C <sub>21</sub> H <sub>32</sub> O <sub>2</sub>	C, H	
44	H	H	H	H	H	OH	H	H	CH <sub>2</sub> OH	143-147	25.5	C <sub>19</sub> H <sub>28</sub> O <sub>2</sub>	C, H	
45	H	H	H	H	H	OCOCH <sub>3</sub>	H	H	CH <sub>2</sub> OCOCH <sub>3</sub>	97-98	60.2	C <sub>23</sub> H <sub>32</sub> O <sub>4</sub>	C, H	
46	H	CH <sub>3</sub>	H	H	H	O	H	H	CH <sub>3</sub>	127-131	55	C <sub>20</sub> H <sub>28</sub> O	C, H	
47	H	C <sub>4</sub> H <sub>9</sub>	H	H	H	O	H	H	CH <sub>3</sub>	91-93	44.3	C <sub>23</sub> H <sub>34</sub> O	C, H	
48	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	G	H	H	CH <sub>3</sub>	207-209	206-207 <sup>h</sup>	35.9		
49	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	O	H	H	CH <sub>3</sub>	149-152	62.8	C <sub>21</sub> H <sub>30</sub> O	C, H	
50	H	H	H	H	H	OH	CH <sub>3</sub>	H	H	143-145	140-141 <sup>a,b</sup>	53.5		
51	H	C <sub>6</sub> H <sub>5</sub>	H	H	H	OH	CH <sub>3</sub>	H	H	168-170	36.2	C <sub>25</sub> H <sub>32</sub> O	C, H	
52	H	H	H	H	H	OH	CH <sub>3</sub>	H	CH <sub>3</sub>	136-140	160-162 <sup>j</sup>	22		
53	H	CH <sub>3</sub>	H	H	H	OH	CH <sub>3</sub>	H	CH <sub>3</sub>	151-153	153-154 <sup>k,s</sup>	34		
54	H	H	H	CH <sub>3</sub>	H	OH	CH <sub>3</sub>	H	CH <sub>3</sub>	145-147	30	C <sub>21</sub> H <sub>32</sub> O	C, H	
55	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	OH	CH <sub>3</sub>	H	CH <sub>3</sub>	118-121	54.2	C <sub>22</sub> H <sub>34</sub> O	C, H	
56	H	H	H	O	H	OH	H	H	CH <sub>3</sub>	170-172 <sup>l</sup>	65.3			
57	H <sup>w</sup>	H	H	O	H	OCOCH <sub>3</sub>	H	H	CH <sub>3</sub>	168-170	171-173 <sup>m</sup>	54.3		
58	H	H	H	O	H	O	H	H	CH <sub>3</sub>	164-166	164 <sup>n</sup>	77.5		
59	H	CH <sub>3</sub>	H	CH <sub>2</sub> OH	H	OH	H	H	CH <sub>3</sub>	171-175	63.7	C <sub>20</sub> H <sub>30</sub> O <sub>2</sub>	C, H	
60	H	CH <sub>3</sub>	H	COCH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	224-227	17.4	C <sub>22</sub> H <sub>32</sub> O <sub>2</sub>	C, H	
61	H	CH <sub>3</sub>	H	C(NH)CH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	150-152	4.3	C <sub>22</sub> H <sub>33</sub> NO	C, H, N	
62	H	Cl	H	H	H	OH	H	H	CH <sub>3</sub>	140-142	146-148 <sup>o</sup>	66.2		
63	H	Br	H	H	H	OH	H	H	CH <sub>3</sub>	143-145	55.9	C <sub>19</sub> H <sub>27</sub> BrO	C, H, Br	
64	H	Br	H	H	H	OCOCH <sub>3</sub>	H	H	CH <sub>3</sub>	175-177	162-168 <sup>p</sup>	64.8		
65	H	Cl	H	H	H	OCOCH <sub>3</sub>	H	H	H	115-117	34	C <sub>20</sub> H <sub>27</sub> ClO <sub>2</sub>	C, H, Cl	
66	H	Cl	H	CH <sub>3</sub>	H	OH	H	H	CH <sub>3</sub>	178-180	45.2	C <sub>20</sub> H <sub>29</sub> ClO	C, H, Cl	
67	H	Cl	H	CH <sub>3</sub>	H	OCOCH <sub>3</sub>	H	H	CH <sub>3</sub>	178-180	21.6	C <sub>22</sub> H <sub>31</sub> ClO <sub>2</sub>	C, H, Cl	
68	H	HOCH <sub>2</sub> CH <sub>2</sub> O	H	O	H	OCOCH <sub>3</sub>	H	H	CH <sub>3</sub>	178-180	22.5	C <sub>23</sub> H <sub>32</sub> O <sub>5</sub>	C, H	
69	H	CH <sub>3</sub> O	H	CH <sub>3</sub>	H	OCOCH <sub>3</sub>	H	H	CH <sub>3</sub>	174-179	71.9	C <sub>23</sub> H <sub>34</sub> O <sub>3</sub>	C, H	
70	H	CH <sub>3</sub> O	H	CH <sub>3</sub>	O	O	H	H	CH <sub>3</sub>	207-210	75.4	C <sub>21</sub> H <sub>28</sub> O <sub>3</sub>	C, H	
71	H	CH <sub>3</sub> O	H	CH <sub>3</sub> <sup>g</sup>	O	O	H	H	CH <sub>3</sub>	160-169	9.2	C <sub>21</sub> H <sub>28</sub> O <sub>3</sub>	C, H	
72	H	(C <sub>2</sub> H <sub>5</sub> O)PO <sub>2</sub>	H	H	H	OH	H	H	H	121-127		C <sub>22</sub> H <sub>35</sub> O <sub>3</sub> P	C, H	
73	H	(C <sub>2</sub> H <sub>5</sub> O) <sub>2</sub> PO <sub>2</sub>	H	H	H	OH	H	H	CH <sub>3</sub>	102-114		C <sub>23</sub> H <sub>37</sub> O <sub>5</sub> P	C, H	

<sup>a</sup> J. A. Szpilfogel, Dutch Patent 90 744 (1959); *Chem. Abstr.*, 54, 13178 (1960). <sup>b</sup> Organon Laboratories Ltd., British Patent 841 411 (1960); *Chem. Abstr.*, 55, 9475 (1961).  
<sup>c</sup> Isolated from preparation of 1: P. N. Rao and H. R. Gollberg, *Chem. Ind. (London)*, 1317 (1961). <sup>d</sup> L. J. Chinn, U.S. Patent 3 246 022 (1966); *Chem. Abstr.*, 64, 19726 (1966). <sup>e</sup> R. I. Dorfman, E. Caspi, and P. K. Grover, *Proc. Soc. Exp. Biol. Med.*, 110, 750 (1962); E. Caspi, P. K. Grover, N. Grover, E. J. Lynde, and T. Nussbaumer, *J. Chem. Soc.*, 1710 (1962). <sup>f</sup> F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, 79, 5029 (1957). <sup>g</sup>  $\beta$  isomer. <sup>h</sup> M. Douek and G. Just, *Can. J. Chem.*, 44, 2233 (1966). <sup>i</sup> W. R. Slaunwhite, Jr., L. Neely, and A. A. Sandberg, *Steroids*, 3, 391 (1964). <sup>j</sup> B. Pelc, *Collect. Czech. Chem. Commun.*, 25, 309 (1960). <sup>k</sup> B. Pelc, *ibid.*, 25, 1624 (1960). <sup>l</sup> A. Butenandt, E. Hausmann, and J. Paland, *Chem. Ber.*, 71, 1316 (1938). <sup>m</sup> H. J. Siemann, W. Pohnert, and S. Schwarz, East German Patent 39 210 (1965); *Chem. Abstr.*, 63, 18222 (1965). <sup>n</sup> J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, 31, 629 (1948). <sup>o</sup> G. W. Moresch and W. A. Neuklis, *Can. J. Chem.*, 41, 1627 (1963); F. Galinovsky, E. Kerschbaum, and H. Janisch, *Monatsh. Chem.*, 84, 193 (1953). <sup>p</sup> J. A. Ross and M. D. Martz, *J. Org. Chem.*, 29, 2784 (1964); mp 178-179.5 °C in an evacuated capillary.  
<sup>q</sup> Compound 35 is mentioned in this paper; however, the melting point and analytical data given for it correspond instead for the 17 $\beta$ -ol 34. <sup>r</sup> This material is the hemihydrate while the previously reported material is anhydrous. <sup>s</sup> B. Pelc, Czech Patent 96 125 (1960); *Chem. Abstr.*, 55, 15551 (1961). <sup>t</sup> C: calcd, 84.32; found, 83.72. <sup>u</sup> C: calcd, 84.02; found, 83.45. <sup>v</sup> C: calcd, 79.42; found, 78.93. <sup>w</sup> 6-Chloro. <sup>x</sup> C: calcd, 82.01; found, 81.48.

biological profile of 2 and the claudogenic activity of 1, we prepared and studied a number of estra-3,5-dienes, androsta-3,5-dienes, and gona-3,5-dienes hoping to find an effective claudogen preferably having an antiprogesterational mechanism of action.

**Chemistry.** Two convenient methods for preparation of  $\Delta^{3,5}$ -dienes were available from readily obtained  $\Delta^4$ -3-ketones 3. The first method was to reduce 3 to the corresponding alcohol 4a, followed by dehydration. The second method was to add an organometallic reagent to 3, followed by dehydration of the resulting alcohol. A



representative number of androsta-3,5-dienes were prepared as shown in Table I. The estra-3,5-dienes listed in Table I were also prepared by these methods; however, some difficulty was encountered in purifying 3-alkyl-estra-3,5-dien-17 $\beta$ -ols. These products were sensitive to air oxidation as evidenced by continually changing elemental analyses. Surprisingly, this problem was solved with 3,7 $\alpha$ -dimethylestra-3,5-dien-17 $\beta$ -ol by purification of its acetate derivative.

Preparation of a small number of  $\Delta^{3,5}$ -dienes with substituents other than alkyl or aryl at C-3 was accomplished by standard methods. Thus, the 3-methoxy- $\Delta^{3,5}$ -dienes were prepared from the corresponding  $\Delta^4$ -3-ketones and trimethyl orthoformate. The 3-halides were also prepared from the corresponding  $\Delta^4$ -3-ketones using POCl<sub>3</sub> or POBr<sub>3</sub>.

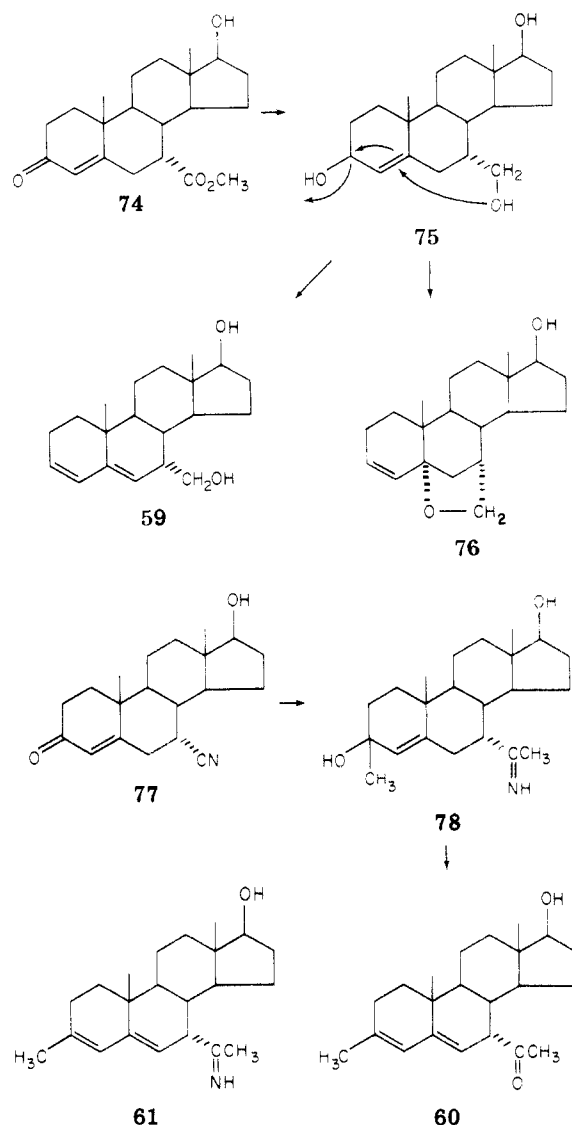
Reduction of methyl 17 $\beta$ -hydroxy-3-oxoandrost-4-ene-7 $\alpha$ -carboxylate (74) with lithium aluminum hydride, followed by acid-catalyzed dehydration of the resulting triol 75, gave the 7 $\alpha$ -hydroxymethyl derivative 59. The sample of 59 is most likely a mixture of 59 and the isomeric ether 76 since the uv extinction value of 8290 found for 59 is less than half that expected for the *trans*-diene system. The ether 76 could arise from the allylic alcohol 75 as shown by the arrows.

Reaction of 7 $\alpha$ -cyanotestosterone (77) with an excess of methyllithium gave, after the usual acidic work-up, the 7 $\alpha$ -acetyl compound 60 and a second compound 61. Elemental analyses for 61 correspond to the formula C<sub>22</sub>H<sub>33</sub>NO. The NMR spectrum of 61 showed clearly the C-18 and C-19 methyl groups at 0.79 and 0.97 ppm, respectively. The C-3 methyl appeared at 1.73 ppm, while a sharp singlet at 2.00 ppm is attributed to a C-methyl-imine [-C(CH<sub>3</sub>)=N-]. The NMR is similar to the NMR spectrum of 60. The uv spectrum has maxima at 232 nm ( $\epsilon$  14 800), 237 sh (14 300), and 251 (12 600) which are similar to the  $\Delta^{3,5}$ -diene's absorption, but the shape of the curve is different and also different from 60. The ir shows absorption at 3400, 3240, 1650, and 1625 cm<sup>-1</sup>. Overall, the spectral and analytical data indicate 61 is the iminodiene shown below.

Table II. Claudogenic Activity

No.	ED <sub>50</sub> , mg/kg	No.	ED <sub>50</sub> , mg/kg
1	10	21	10
6	30	24	10
7	30	28	30
12	3	30	30
14	3	40	30
15	10 <sup>a</sup>		

<sup>a</sup> ED<sub>100</sub>.



**Biological Results.** Primary claudogenic screening of the compounds listed in Table I, using a hamster model, showed a fairly restricted SAR. Only the compounds listed in Table II showed an ED<sub>50</sub> of 30 mg/kg or less, which we arbitrarily set as the minimum value for activity. The estradienes possessed the highest order of activity. Acetylation (6) of the parent 1 or oxidation of the 17-hydroxy (7) gave compounds of diminished activity. Introduction of a 7 $\alpha$ -methyl group (12) greatly enhanced activity. Surprisingly, acetylation of this compound led to loss of activity. Introduction of a 3-methyl group alone gave no activity but introduction of both a 3- and a 7 $\alpha$ -methyl group (14) gave high activity. In this case, acetylation (15) did not diminish the activity. The ED<sub>100</sub> of the latter compound was 10 mg/kg.

In the androstadiene series, the parent 21 was about as

active as 1. Introduction of a 7 $\alpha$ -methyl group (24) did not change the activity. Introduction of methyl groups at 3,7 $\alpha$  (28), 3,17 $\beta$  (30), and 1,3,7 $\alpha$  (30) gave active compounds but with diminished activity.

None of the gonadienes tested showed activity.

In summary, 7 $\alpha$ -methyl- and 3,7 $\alpha$ -dimethyl-17 $\beta$ -hydroxy-3,5-estradienes possess potent claudogenic activity with ED<sub>50</sub>'s of 3 mg/kg, while the corresponding androstadienes are less active. The SAR shows a rather restricted substitution pattern for activity. A more detailed biological study of selected compounds in this series is being made to determine the mode of action and will be reported when completed.

### Experimental Section

All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer using potassium bromide pellets. Ultraviolet spectra were recorded on a Perkin-Elmer 350 spectrophotometer in ethanol. Proton magnetic resonance spectra were run on a Varian A-60A with tetramethylsilane as an internal standard and were run in CDCl<sub>3</sub> unless specified otherwise. The standard drying agent used was magnesium sulfate and the solvents were removed in vacuo on a rotary evaporator. The use of Kieselgel and silica gel was used for chromatography.

**Biological Testing. Hamster Postcoital Antifertility Assay.** Virgin female Golden Syrian hamsters (Engle Laboratory Animal, Inc., Farmersburg, Ind., 90–120 g) were mated with proven males. Animals with sperm present in their postestrus vaginal lavages (day 1 of pregnancy) were randomly assigned to treatment groups. Test compound was given on days 3–8 of pregnancy. At necropsy on day 15 of gestation, animals were classified as (i) pregnant with live fetuses, (ii) as nonpregnant, showing no evidence of prior pregnancy, or (iii) as resorbing with uteri containing degenerative embryos and/or implantation sites. The contragestative effects were evaluated by the number of total live fetuses (TLF) per group of eight impregnated hamsters. The ED<sub>100</sub> as used is the test dose at which TLF is equal to 0, while ED<sub>50</sub> is 21–40 TLF per treatment group.

**General Procedure for Preparation of  $\Delta^{3,5}$ -Dienes.** A solution of 7 $\alpha$ -methyltestosterone (5.5 g, 18.2 mmol) in THF (150 ml) was added under N<sub>2</sub> to a stirred suspension of LiAlH<sub>4</sub> (1.1 g) in THF (150 ml). After 18 h, the excess hydride was decomposed by cautious addition of H<sub>2</sub>O. MgSO<sub>4</sub> was added and the inorganic salts were removed by filtration. The ether was concentrated and the residue crystallized or used directly in the next step. The alcohol was dissolved in acetone (0.5 l.), diluted with 10% aqueous HCl (50 ml), and heated at reflux for 0.5 h. The solution was concentrated and the residue diluted with H<sub>2</sub>O and filtered. The resulting solid was crystallized from aqueous acetone to give 24 (4.0 g, 77%).

**General Procedure for Preparation of 3-Substituted  $\Delta^{3,5}$ -Dienes.** A solution of 7 $\alpha$ -methyltestosterone (6.04 g, 20 mmol) in THF (150 ml) and ether (200 ml) was treated with 1.6 M ethereal methyllithium<sup>5</sup> (70 ml). After 0.5 h, the mixture was poured into saturated aqueous NH<sub>4</sub>Cl and the organic layer separated, dried, and concentrated. The residue was dissolved in acetone (0.5 l.), diluted with 10% aqueous HCl, and heated at reflux for 1 h. The solution was concentrated; the residue was diluted with H<sub>2</sub>O and filtered. The resulting solid was dried and chromatographed on silica gel eluting with C<sub>6</sub>H<sub>6</sub>–5% acetone. The product was crystallized from aqueous acetone to give 28 (4.1 g, 68.4%).

**General Preparation of 3-Halo- $\Delta^{3,5}$ -dienes.** 7 $\alpha$ -Methyltestosterone acetate (4.4 g, 12.7 mmol) in acetic acid (25 ml) was treated with POCl<sub>3</sub> (2 ml). After 18 h, the solid was filtered off and crystallized from acetone to give 67 (1.0 g, 21.6%).

Saponification of the 17-acetoxy was done as follows. The above acetate (3 g, 8.29 mmol) in methanol (100 ml)–10% aqueous NaOH (10 ml) was heated at reflux for 4 h, then concentrated to ca. one-third its volume, and cooled and the solid filtered off and

crystallized from aqueous acetone to give 66 (1.2 g, 45.2%).

**General Preparation of 3-Alkoxy- $\Delta^{3,5}$ -dienes.** A suspension of 7 $\beta$ -methylandrosta-4-ene-3,11,17-trione (6.5 g, 20.7 mmol), *p*-toluenesulfonic acid (0.4 g), and trimethyl orthoformate (7 ml) in dioxane (75 ml) was stirred at room temperature for 1 h. The solution was treated with pyridine (3 ml), followed by H<sub>2</sub>O (100 ml). The solid was filtered off, washed with H<sub>2</sub>O, dried, and crystallized from methanol to give 71.

**General Procedure for Oxidation of 17 $\beta$ -Hydroxyl.** A solution of 3,7 $\alpha$ -dimethylandrosta-3,5-dien-17 $\beta$ -ol (4.0 g, 13.3 mmol) in Me<sub>2</sub>SO (20 ml)–C<sub>6</sub>H<sub>6</sub> (20 ml) containing pyridine (1.0 ml), trifluoroacetic acid (0.5 ml), and dicyclohexylcarbodiimide (8.35 g) was stirred for 3 h. The mixture was diluted with ethyl acetate and treated with oxalic acid (4.5 g) in methanol (20 ml). After 20 min longer, the solid was filtered off. The filtrate was washed with H<sub>2</sub>O and with aqueous NaHCO<sub>3</sub>, dried, and concentrated. The residue was chromatographed on silica gel eluting with C<sub>6</sub>H<sub>6</sub>–5% acetone. The product was crystallized from aqueous acetone to give 49 (2.5 g, 62.8%).

**7 $\alpha$ -(Hydroxymethyl)androsta-3,5-dien-17 $\beta$ -ol (59).** Methyl 17 $\beta$ -hydroxy-3-oxoandrosta-4-ene-7 $\alpha$ -carboxylate<sup>6</sup> (0.9 g, 2.6 mmol) was added to a stirred suspension of LiAlH<sub>4</sub> (1.0 g) in THF (200 ml). After 18 h, the reaction mixture was worked up in typical fashion and the resulting triol was dehydrated in the usual manner with acetone–10% aqueous HCl. The crude material was crystallized from acetone to give 59 (0.5 g, 63.7%).

**7 $\alpha$ -Acetyl-3-methylandrosta-3,5-dien-17 $\beta$ -ol (60) and 7 $\alpha$ -Acetimidoyl-3-methylandrosta-3,5-dien-17 $\beta$ -ol (61).** A mixture of 7 $\alpha$ -cyanotestosterone (4.4 g, 14 mmol) in THF (150 ml) was treated with ethereal 1.85 M methyllithium<sup>5</sup> (100 ml). After 1 h, the reaction mixture was worked up in typical fashion and the resulting imino diol was dehydrated in the usual manner with acetone (500 ml)–10% aqueous HCl (50 ml). The crude material was purified by chromatography on Kieselgel (200 g), eluting with C<sub>6</sub>H<sub>6</sub> (0.5 l.), C<sub>6</sub>H<sub>6</sub>–10% acetone (1 l.), C<sub>6</sub>H<sub>6</sub>–30% acetone, (0.1 l.), and C<sub>6</sub>H<sub>5</sub>–10% methanol. The first product off the column was crystallized from acetone to give 60 (0.8 g, 17.4%). The material coming off the column with the 10% methanol was crystallized from acetone to give 61 (0.2 g, 4.3%), mp 150–152 °C.

**17 $\beta$ -Hydroxy-3-[(2-hydroxy)ethoxy]androsta-3,5-dien-7-one 17-Acetate (68).** This compound was prepared inadvertently during an attempted Wittig-type reaction. Thus, sodium hydride (0.6 g, 25 mmol) was added under N<sub>2</sub> at ambient temperature with stirring to Me<sub>2</sub>SO (50 ml). After 20 min, a solution of triethyl phosphonoacetate (5.6 g, 25 mmol) in THF (70 ml) was added dropwise. After 30 min, a solution of 17 $\beta$ -hydroxyandrosta-6-ene-3,7-dione 17-acetate 3-cyclic ethylene ketal (4.0 g, 10.3 mmol) in THF (60 ml)–Me<sub>2</sub>SO (60 ml) was added over 10 min. The mixture was stirred 20 h, then poured into cold H<sub>2</sub>O, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was separated, washed with H<sub>2</sub>O, dried, and concentrated. The oily residue was chromatographed on Kieselgel to give 68 (0.9 g) after two recrystallizations from acetone–hexane.

**Diethyl 17-Hydroxyandrosta-3,5-dien-3-yl Phosphorate (73).** A solution of testosterone (5.78 g, 20 mmol) and sodium methylate (3.24 g, 60 mmol) in Me<sub>2</sub>SO (50 ml) was stirred under N<sub>2</sub> for 1 h. This was poured into benzene (100 ml) and diethyl chlorophosphate (5 ml) and stirred for 2 min before adding ice–H<sub>2</sub>O. The organic layer was separated, washed with H<sub>2</sub>O, dried, and concentrated. The solid residue was triturated with hexane and then crystallized from ether–hexane to give 73.

### References and Notes

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