1,3,5(10)-Estratrien-17β-yl Enol Ethers and Acetals. New Classes of Orally and Parenterally Active Estrogenic Derivatives

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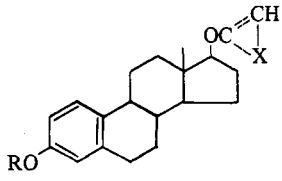
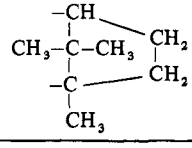
A series of 70 labile 17-ethers of estradiol has been synthesized and tested for uterotrophic activity. Most of the compounds proved to be more active orally than estradiol and some of them comparable with ethinylestradiol. Particularly high oral activity was displayed by enol ethers of 3-pentanone and of five- to nine-membered cyclanones and by mixed ketals. The cycloalkenyl ethers, mainly those deriving from 8–15-membered cyclanones, displayed also extremely prolonged parenteral uterotrophic activity.

In 1962 we briefly reported the activity of labile ethers of 17β-hydroxy steroids in the androstane and estratriene series.[1,2]

Further extension of this approach in the androanabolic series by us[3,4] and others[5,6] gave rise to many compounds at least as active orally as the corresponding 17α-alkylated de-

Table I



No.	R	X	Method[a]	Yield,[b] %	Mp, °C[c]	[α]D	Formula	Analyses
1	CH_3CO	$(CH_2)_3$	B	55	126–128	+65	$C_{25}H_{32}O_3$	C, H
2	C_2H_5CO	$(CH_2)_3$	B	63	91–93	+61.5	$C_{26}H_{34}O_3$	C, H
3	C_6H_5CO	$(CH_2)_3$	A_1	89	138–142	+53	$C_{30}H_{34}O_3$	C, H
4	*n*-C_3H_7	$(CH_2)_3$	A_1	80	81–82	+51	$C_{26}H_{36}O_2$	C, H
5	*n*-C_4H_9	$(CH_2)_3$	A_1	73	81–82.5	+64	$C_{27}H_{38}O_2$	C, H
6	C_5H_9[d]	$(CH_2)_3$	B	47	80–82	+63	$C_{28}H_{38}O_2$	C, H
7	H	$(CH_2)_4$	C	75	87–90	+75.5	$C_{24}H_{32}O_2$	C, H
8	CH_3CO	$(CH_2)_4$	B	60	116–118	+75	$C_{26}H_{34}O_3$	C, H
9	C_2H_5CO	$(CH_2)_4$	D	65	94–96	+71	$C_{27}H_{36}O_3$	C, H
10	$(CH_3)_2CHCO$	$(CH_2)_4$	D	79	73–76	+67	$C_{28}H_{38}O_3$	C, H
11	C_6H_5CO	$(CH_2)_4$	B	71	152–155	+61	$C_{31}H_{36}O_3$	C, H
12	H	$(CH_2)_5$	C	56	78–81	+72	$C_{25}H_{34}O_2$	C, H
13	C_6H_5CO	$(CH_2)_5$	B	86	149–151	+57	$C_{32}H_{38}O_3$	C, H
14	*p*-ClC_6H_4CO	$(CH_2)_5$	A	80	156–158	+53	$C_{32}H_{37}ClO_3$	C, Cl[e]
15	H	$(CH_2)_6$	C	89	117–120	+68	$C_{26}H_{36}O_2$	C, H
16	CH_3CO	$(CH_2)_6$	D	62	118–120	+64	$C_{28}H_{38}O_3$	C, H
17	C_2H_5CO	$(CH_2)_6$	A	43	80–82	+61	$C_{29}H_{40}O_3$	C, H
18	$(CH_3)_2CHCO$	$(CH_2)_6$	D	64	131–133	+57	$C_{30}H_{42}O_3$	C, H
19	$(CH_3)_3CCO$	$(CH_2)_6$	A	60	155–157	+56	$C_{31}H_{44}O_3$	C, H
20	$C_2H_5CH(C_6H_5)CO$[f]	$(CH_2)_6$	B	39	Oil	+48	$C_{30}H_{46}O_3$	C, H
21	C_6H_5CO	$(CH_2)_6$	B	82	174–176	+52	$C_{33}H_{40}O_3$	C, H
22	*p*-$CH_3C_6H_4CO$	$(CH_2)_6$	A	40	164–166	+51.5	$C_{34}H_{42}O_3$	C, H
23	*p*-FC_6H_4CO	$(CH_2)_6$	A	67	141–144	+48	$C_{33}H_{39}FO_3$	C, H
24	*o*-ClC_6H_4CO	$(CH_2)_6$	A	60	151–153	+51	$C_{33}H_{39}ClO_3$	C, H, Cl
25	*m*-ClC_6H_4CO	$(CH_2)_6$	A	64	150–152	+50	$C_{33}H_{39}ClO_3$	C, H, Cl
26	*p*-ClC_6H_4CO	$(CH_2)_6$	A	82	172–174	+47	$C_{33}H_{39}ClO_3$	C, H, Cl
27	*p*-$NO_2C_6H_4CO$	$(CH_2)_6$	A	93	220–222	+44	$C_{33}H_{39}NO_5$	C, H, N
28	*p*-$CH_3OC_6H_4CO$	$(CH_2)_6$	A	60	149–151	+48	$C_{34}H_{42}O_4$	C, H
29	*p*-$C_5H_9OC_6H_4CO$[d]	$(CH_2)_6$	A	80	200–202	+44	$C_{38}H_{48}O_4$	C, H
30	C_5H_9[d]	$(CH_2)_6$	A	79	94–96	+58.5	$C_{31}H_{44}O_2$	C, H
31	C_6H_5CO	$(CH_2)_7$	B_1	88	152–154	+52.5	$C_{34}H_{42}O_3$	C, H
32	C_6H_5CO	$(CH_2)_8$	A	63	149–151	+57	$C_{35}H_{44}O_3$	C, H
33	*p*-FC_6H_4CO	$(CH_2)_8$	A	74	164–166	+55	$C_{35}H_{43}FO_3$	C, H
34	C_2H_5CO	$(CH_2)_{10}$	A	41	117–119	+56.5	$C_{33}H_{48}O_3$	C, H
35	C_6H_5CO	$(CH_2)_{10}$	A	54	163–166	+51	$C_{37}H_{48}O_3$	C, H
36	*p*-$CH_3C_6H_4CO$	$(CH_2)_{10}$	A	89	139–142	+46.5	$C_{38}H_{50}O_3$	C, H
37	*p*-FC_6H_4CO	$(CH_2)_{10}$	A	75	152–154	+48.5	$C_{37}H_{47}FO_3$	C, H
38	*p*-ClC_6H_4CO	$(CH_2)_{10}$	A	67	145–147	+43	$C_{37}H_{47}ClO_3$	C, H, Cl
39	*p*-$CH_3OC_6H_4CO$	$(CH_2)_{12}$	A	83	119–121	+47	$C_{38}H_{50}O_3$	C, H
40	C_6H_5CO	$(CH_2)_{13}$	B_1	50	136–139	+40.5	$C_{40}H_{54}O_3$	C, H
41	C_6H_5CO		B_1	20	158–162	+39	$C_{35}H_{42}O_3$	C, H

[a] See the Experimental Section for the letter that corresponds to each synthetic method. [b] Yield is of analytically pure material. [c] All compounds were recrystallized from CH_2Cl_2–MeOH, except **20**, purified by chromatography on aluminum oxide. [d] C_5H_9 denotes cyclopentyl. [e] H: calcd, 7.38; found, 7.83. [f] Diastereoisomeric mixture.

rivatives but potentially nonhepatotoxic. The lack of hepatotoxicity[7,8] as well as their reversibility *in vivo*[9,10] was actually proved for some terms of these classes.

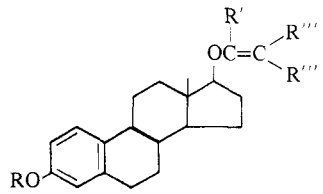
In this paper we wish to report *in extenso* the synthesis and the oral and parenteral activity of several alkenyl ethers and mixed acetals deriving from estradiol.

Orally effective 17-labile ethers of estradiol have been also reported by Cross, *et al.*,[11,12] and Agresta, *et al.*[13]

The potential interest of these non-17-alkylated derivatives is evident since ethinylestradiol and its 3-ethers are the sole estrogens contained in the estro-progestinic contraceptive combinations. The main risks associated with the steroid contraception, *i.e.*, thromboembolic phenomena, liver disturbances, and impairment of carbohydrate metabolism, are admittedly attributed to the estrogenic component. Although also the natural estrogens may induce abnormalities in liver function, the ethinyl group at C-17 has an additional effect on the hepatotoxicity.[14,15] Moreover, the ethinylated estrogens may affect some factors possibly related to thrombotic phenomena more than the natural ones.[16]

Chemistry. The title compounds were prepared by minor modifications of procedures already described for related derivatives in the androstane series.[3,4] The enol ethers (Tables I and II) were prepared from the parent 17β-hydroxyestratrienes by acid-catalyzed exchange etherification with alkyl enol ethers or acetals of the appropriate aldehyde or ketone in $PhCH_3$ (method A), PhH (method A_1), or in DMF (method B). In a modification of the last procedure, the intermediate dimethyl ketals were prepared *in situ* (method B_1). The acetals (Table III) were prepared by acid-catalyzed addition of the 17β-hydroxy steroid to the suitable methyl or ethyl enol ethers (method E) or by method A_1, in the case of nonenolizable aldehydes. Compounds of both classes were converted to related derivatives by alka-

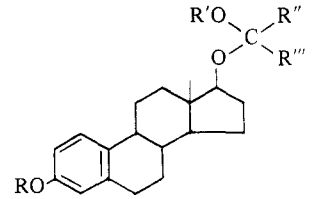
Table II



No.	R	R'	R''	R'''	Method[a]	Yield,[b] %	Mp, °C[c]	[α]D	Formula	Analyses
42	C_6H_5CO	H	H	n-C_4H_9	B	50	68–72	+64	$C_{31}H_{38}O_3$	C, H
43	C_6H_5CO	C_2H_5	H	CH_3	B	47	128–132	+61.5	$C_{30}H_{36}O_3$	C, H
44	C_6H_5CO	n-C_3H_7	H	C_2H_5	B	78	116–119	+57	$C_{32}H_{40}O_3$	C, H
45	C_6H_5CO	C_6H_5	H	CH_3	B	47	120–123	+16.5	$C_{34}H_{36}O_3$	C, H
46	CH_3CO	n-C_3H_7	H	C_6H_5	C + D	76	129–131	+59.5	$C_{31}H_{38}O_3$	C, H
47	C_6H_5CO	n-C_3H_7	H	C_6H_5	B	79	137–139	+51.5	$C_{36}H_{40}O_3$	C, H
48	C_6H_5CO	H	CH_3	CH_3	A	93	125–127	+68.5	$C_{29}H_{34}O_3$	C, H
49	C_6H_5CO	H	$(CH_2)_4$		A	70	168–172	+77	$C_{31}H_{36}O_3$	C, H

[a–c] See footnotes *a–c*, respectively, in Table I.

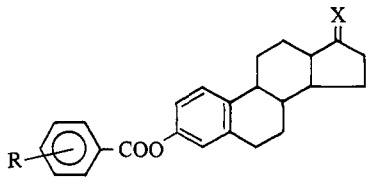
Table III



No.	R	R'	R''	R'''	Method[a]	Yield,[b] %	Mp, °C[c]	[α]D	Formula	Analyses
50	C_6H_5CO	C_2H_5	H	CH_3	E	35	122–125	+30	$C_{29}H_{36}O_4$	C, H
51	C_6H_5	CH_3	H	C_6H_5	A_1	80	143–146	+36	$C_{34}H_{36}O_4$	C, H
52	C_6H_5CO	CH_3	H		A_1	29	115–117	+35	$C_{32}H_{34}O_5$	C, H
53	CH_3CO	C_2H_5	CH_3	CH_3	C + D	30	83–87	+65	$C_{25}H_{36}O_4$	C, H
54	C_2H_5CO	C_2H_5	CH_3	CH_3	C + D	32	70–73	+55.5	$C_{26}H_{38}O_4$	C, H
55	C_6H_5CO	C_2H_5	CH_3	CH_3	E	71	137–139	+53	$C_{30}H_{38}O_4$	C, H
56	CH_3CO	CH_3	CH_3	C_2H_5	C + D	60	53–57	+64	$C_{25}H_{36}O_4$	C, H
57	C_2H_5CO	CH_3	CH_3	C_2H_5	C + D	43	64–68	+62	$C_{26}H_{38}O_4$	C, H
58	C_6H_5CO	CH_3	CH_3	C_2H_5	E	71	135–137	+58	$C_{30}H_{38}O_4$	C, H
59	CH_3CO	CH_3	C_2H_5	C_2H_5	C + D	68	105–107	+50.5	$C_{26}H_{38}O_4$	C, H
60	C_2H_5CO	CH_3	C_2H_5	C_2H_5	C + D	44	85–87	+48.5	$C_{27}H_{40}O_4$	C, H
61	C_6H_5CO	CH_3	C_2H_5	C_2H_5	E	73	136–138	+42.5	$C_{31}H_{40}O_4$	C, H
62	H	CH_3	$(CH_2)_4$		C	91	127–129	+50	$C_{24}H_{34}O_3$	H[e]
63	CH_3CO	CH_3	$(CH_2)_4$		D	63	89–91	+49.5	$C_{26}H_{36}O_4$	C, H
64	C_2H_5CO	CH_3	$(CH_2)_4$		D	73	81–83	+44.5	$C_{27}H_{38}O_4$	C, H
65	C_6H_5CO	CH_3	$(CH_2)_4$		E	42	128–130	+37	$C_{31}H_{38}O_4$	C, H
66	H	CH_3	$(CH_2)_5$		C	78	108–110	+53.5	$C_{25}H_{36}O_3 \cdot 0.5H_2O$	C, H, CH_3O
67	CH_3CO	CH_3	$(CH_2)_5$		D	73	79–82	+51.5	$C_{27}H_{38}O_4$	C, H
68	C_2H_5CO	CH_3	$(CH_2)_5$		D	81	68–70	+47	$C_{28}H_{40}O_4$	C, H
69	C_6H_5CO	CH_3	$(CH_2)_5$		E	72	153–155	+39	$C_{32}H_{40}O_4$	C, H
70	C_5H_9[d]	CH_3	$(CH_2)_5$		E	68	101–104	+47	$C_{30}H_{44}O_3$	C, H

[a–d] See footnotes *a–d*, respectively, in Table I. [e] C: calcd, 77.80; found, 77.32.

Table IV



No.	R	X	Mp, °C[a]	[α]D	Formula	Analyses
71	*p*-CH_3	O	252–256	+115	$C_{26}H_{28}O_3$	C, H
72	*p*-F	O	210–212	+114.5	$C_{25}H_{25}FO_3$	H[b]
73	*o*-Cl	O	214–216	+110.5	$C_{25}H_{25}ClO_3$	C, H, Cl
74	*m*-Cl	O	212–214	+111.5	$C_{25}H_{25}O_3Cl$	C, H[c]
75	*p*-Cl	O	215–217	+108	$C_{25}H_{25}ClO_3$	C, H, Cl
76	*p*-NO_2	O	231–234	+105.5	$C_{25}H_{25}NO_5$	H, N[d]
77	*p*-CH_3O	O	229–231	+110	$C_{26}H_{28}O_4$	H[e]
78	*p*-C_5H_9O[f]	O	217–220	+98	$C_{30}H_{34}O_4$	C, H
79	*p*-CH_3	<OH H	208–211	+57	$C_{26}H_{30}O_3$	C, H
80	*p*-F	<OH H	210–212	+56	$C_{25}H_{27}FO_3$	C, H
81	*o*-Cl	<OH H	168–172	+55.5	$C_{25}H_{27}ClO_3$	C, H, Cl
82	*m*-Cl	<OH H	166–169	+53.5	$C_{25}H_{27}ClO_3$	C, H, Cl
83	*p*-Cl	<OH H	183–185	+52	$C_{25}H_{27}ClO_3$	C, H, Cl
84	*p*-NO_2	<OH H	210–213	+52.1	$C_{25}H_{27}NO_5$	C, H, N
85	*p*-CH_3O	<OH H	195–197	+53	$C_{26}H_{30}O_4$	C, H
86	*p*-C_5H_9O[f]	<OH H	199–202	+47	$C_{30}H_{36}O_4$	C, H

[a] See footnote *c* in Table I. [b] C: calcd, 76.51; found, 76.07. [c] Cl: calcd, 8.67; found, 9.11. [d] C: calcd, 71.58; found, 71.08. [e] C: calcd, 77.20; found, 77.62. [f] See footnote *d* in Table I.

line deacylation (method C) or acylation (method D). The new estrone and estradiol esters (Table IV) required as intermediates were prepared according to conventional procedures.

Biology and Discussion

The compounds have been tested for the oral and parenteral uterotrophic activity. The oral activity was assayed at two dose levels in the 3-day test in immature mice, according to Rubin, *et al.*[17] The results are given in Table V. The long-lasting parenteral activity was assayed in spayed rats autopsied 4, 8, or 12 weeks after a single subcutaneous treatment. The results are given in Table VI.

In the class of the cycloalkenyl ethers, a very high oral activity was displayed by the compounds at five- to nine-membered rings. A further ring enlargement or the introduction of a bicyclic structure as in **41** decreased the effectiveness. The nature of the ester group at C-3 did not affect the oral activity significantly.

The open-chain alkenyl ethers were less active than the cyclanone enol ethers. Some activity was displayed by derivatives of less bulky ketones, like **44**. The hexanal derivative **42** was poorly active, while derivatives of α-substituted aldehydes, *i.e.*, **48** and **49**, were somewhat more active.

In the class of the mixed acetals, the aldehyde derivatives **50**, **51**, and **52** were about as active as estradiol, but all the ketone derivatives, except for 3-cyclopentyl ether **70**, were significantly more active, some of them being among the most active oral estrogens reported in this paper.

Most of the cycloalkenyl ethers assayed showed also a parenteral uterotrophic activity clearly higher and more long lasting than estradiol 17-valerate[18,19] and estradiol 17-enanthate.[19] The highest activity and protraction was exhibited by the compounds at 8–15-membered rings, which gave rise to extremely high uterus weights even 12 weeks after a single injection. Bornenyl derivative **41** showed high but poorly prolonged activity. The nature of the ester at C-3 did not give any significant contribution to the activity of the molecule, while a 3-cyclopentyl ether, *i.e.*, **30**, did not display any activity. The assayed mixed acetals did not display prolonged parenteral activity.

Many factors may be responsible for the structure-activity relationships discussed above, particularly the ether linkage lability and the partition properties.

The lability of the ether linkage plays an important role, since very likely the title derivatives are inactive *per se* and should be converted *in vivo* to estradiol. A slow release of the active compound may be responsible for the depot activity. Moreover, the ether linkage should be stable enough to survive the acidic gastric medium and suitably delay the hepatic inactivation after oral administration.

As to the partition properties, all the ethers discussed in this paper are highly lipophilic and also this factor may account for their long-lasting parenteral activity. However, as observed in some classes of esters,[20] an extremely lipophilic compound could be released too slowly from the injection site or irreversibly absorbed and stored in a near lipoid area. This may be the case of bisether **30**, which was found to be poorly active although the etherification at C-3 with cyclopentanol is known to endow most of the estrogens with a higher and long-lasting activity.[21–23]

Like other lipophilic compounds,[24] the labile estradiol 17-ethers are significantly absorbed and highly active after oral treatment mainly when given in oil solution. However, a too high lipophilicity may reduce the biological availability of the compound also after oral administration, as observed in the bisethers **6** and **70**.

Table V. Oral Uterotrophic Activity in Mice

Compd[a]	Uterus wt[b] 0.3 nmol/day	0.9 nmol/day
Estradiol	9.2 ± 0.9	15.1 ± 1.6
Ethinylestradiol	23.6 ± 1.3	26.6 ± 2.1
1	16.7 ± 1.0	28.1 ± 1.6
2	15.4 ± 0.6	35.2 ± 1.8
6	12.2 ± 0.9	18.6 ± 2.2
7	13.0 ± 0.2	20.3 ± 1.3
8	14.9 ± 1.6	25.0 ± 1.2
9	15.5 ± 1.4	28.3 ± 1.3
12	13.9 ± 0.8	24.1 ± 2.3
13	21.2 ± 1.2	29.1 ± 1.4
15	13.7 ± 0.5	22.0 ± 2.6
16	15.1 ± 0.8	26.1 ± 1.4
17	14.5 ± 0.9	25.0 ± 2.9
18	14.7 ± 1.2	30.1 ± 1.8
19	18.0 ± 0.6	24.9 ± 0.8
21	19.4 ± 1.4	29.2 ± 1.2
31	16.2 ± 1.2	28.6 ± 1.7
32	11.5 ± 0.6	19.8 ± 1.2
35	6.8 ± 0.4	10.3 ± 1.0
40	7.9 ± 0.6	10.5 ± 0.6
41	9.4 ± 0.9	10.2 ± 0.7
42	7.5 ± 0.5	8.7 ± 0.5
44	8.9 ± 0.4	21.9 ± 1.4
45	7.8 ± 0.4	12.5 ± 0.9
46	5.3 ± 0.5	5.7 ± 0.2
47	5.5 ± 0.3	8.3 ± 0.4
48	14.3 ± 0.6	17.0 ± 0.9
49	12.4 ± 1.0	13.7 ± 0.9
50	13.8 ± 2.7	13.5 ± 0.7
51	8.4 ± 0.3	14.3 ± 1.6
52	10.3 ± 1.5	15.1 ± 1.3
54	15.9 ± 1.4	26.7 ± 1.7
56	17.7 ± 1.6	28.9 ± 2.3
57	18.5 ± 1.5	26.2 ± 1.4
59	18.5 ± 1.7	28.6 ± 0.6
60	17.5 ± 1.4	24.4 ± 1.7
62	23.8 ± 1.4	31.4 ± 1.7
63	16.4 ± 1.2	23.7 ± 2.6
64	18.0 ± 1.3	25.3 ± 1.4
66	14.5 ± 1.8	29.8 ± 1.8
67	12.0 ± 2.0	21.1 ± 0.5
68	15.7 ± 1.2	28.6 ± 1.1
69	10.2 ± 0.7	22.9 ± 2.6
70	9.0 ± 1.1	16.2 ± 2.2

[a] Administered in sesame oil solution. [b] In milligrams, average ± S.E. from at least ten mice per dose.

Table VI. Parenteral Long-Lasting Uterotrophic Activity in Rats

Treatment[a]	Uterus wt,[b] weeks 4	8	12
Estradiol 17-valerate	58.3 ± 3.9	47.6 ± 1.5	48.0 ± 2.0
Estradiol 17-enanthate	128.5 ± 5.3	104.4 ± 10.5	71 3 ± 3.8
1	112.6 ± 16.0	94.1 ± 8.8	53.8 ± 2.9
7	126.8 ± 9.9	97.7 ± 6.1	54.1 ± 4.4
9	110.2 ± 17.6	71.9 ± 2.8	68.0 ± 3.7
12	160.1 ± 15.6	131.0 ± 14.1	50.0 ± 3.1
13	209.3 ± 15.7	154.1 ± 11.9	71.1 ± 4.9
16	299.3 ± 9.4	121.0 ± 10.6	76.6 ± 5.4
18	163.1 ± 11.3	172.2 ± 7.5	128.8 ± 6.0
19	181.2 ± 27.1	166.8 ± 15.9	83.8 ± 6.1
21	163.9 ± 17.8	159.5 ± 14.6	115.9 ± 11.9
23	194.3 ± 7.4	180.5 ± 9.5	124.7 ± 9.0
24	146.0 ± 15.3	158.8 ± 12.9	157.7 ± 19.9
25	163.2 ± 5.2	165.0 ± 6.8	187.6 ± 8.1
26	195.2 ± 9.6	164.4 ± 13.4	142.1 ± 8.2
28	207.9 ± 7.2	174.9 ± 16.1	118.4 ± 10.3
30	24.4 ± 1.4	26.2 ± 1.1	25.1 ± 0.8
31	164.2 ± 7.2	172.8 ± 10.7	139.6 ± 11.0
32	132.7 ± 13.8	153.1 ± 9.5	132.8 ± 6.6
35	142.4 ± 11.0	200.2 ± 7.6	157.7 ± 10.2
40	171.5 ± 12.4	194.8 ± 9.8	170.4 ± 15.2
41	137.3 ± 14.7	42.9 ± 1.2	34.2 ± 3.7
57	117.1 ± 15.6	71.8 ± 10.3	79.2 ± 5.1
60	80.6 ± 11.6	75.2 ± 16.0	73.1 ± 4.8
64	88.7 ± 5.6	66.5 ± 3.4	54.1 ± 2.8
68	57.9 ± 18.6	47.7 ± 4.3	50.0 ± 3.0

[a] Single subcutaneous injection of 0.05 μmol in sesame oil. [b] In milligrams, average ± S.E. from ten rats per group.

The above quoted factors will be better discussed after a wider investigation of the pharmacodynamic and pharmacokinetic properties of these compounds. The results will be published in forthcoming papers.

Experimental Section

All temperatures are uncorrected. Optical rotations were measured in dioxane at 24° at a concentration of about 0.5%. Uv spectra were determined in 95% EtOH with an Optica CF_4 spectrometer; ir spectra were measured on a Perkin-Elmer 21 or a Perkin-Elmer 457 instrument. Absorption bands of these spectra were in agreement with the assigned structure. All analytical samples moved as a single spot on tlc with aluminium oxide (E. Merck AG Darmstadt), visualization with H_2SO_4–EtOH (1:1). Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

General Methods of Preparation. A. 17β-(Cyclododec-1-enyloxy)estra-1,3,5(10)-trien-3-ol *p*-Fluorobenzoate (38). To a solution of **80** (1.5 g) and TsOH (15 mg) in PhMe anhydrous (700 ml), cyclododecanone diethyl ketal (2 ml) was added. After refluxing for 15 min and concentrating to 100 ml by distillation over 40 min, Py (0.2 ml) was added and the solvent was removed *in vacuo*. The residue was taken up in MeOH, filtered, and recrystallized from CH_2Cl_2–MeOH.

A_1. PhH was used as the solvent in method A.

B. 17β-(4′-Hept-3′-enyloxy)estra-1,3,5(10)-trien-3-ol Benzoate (44). Estradiol 3-benzoate (2 g), 4,4-diethoxyheptane (4 ml), and TsOH (10 mg) in DMF (5 ml) were heated at 160° for 1 hr under a gentle stream of N_2. After addition of Py (0.2 ml), the solvent was evaporated and the residue worked up in the usual way.

B_1. 17β-(Cyclopentadec-1′-enyloxy)estra-1,3,5(10)-trien-3-ol Benzoate (41). Cyclopentadecanone (1.5 g), MeOH (2 ml), trimethylorthoformate (1.5 ml), and TsOH (15 mg) were heated at 60° for 30 min. After diluting with DMF (5 ml), estradiol 3-benzoate (2.2 g) was added and then the reaction was pursued as in method B.

C. 17β-(Cyclooct-1′-enyloxy)estra-1,3,5(10)-trien-3-ol (15). A suspension of **21** (11.2 g) in MeOH (400 ml) was treated with 10% K_2CO_3 aqueous solution (100 ml) and heated under reflux for 2.5 hr. After concentrating under reduced pressure, the residue was diluted with H_2O and the precipitate was filtered and recrystallized.

D. The corresponding 3-hydroxy derivative was conventionally acylated in Py at room temperature by treatment with the proper acid chloride or anhydride.

E. 17β-(1′-Methoxycyclohexyloxy)estra-1,3,5(10)-trien-3-ol Benzoate (69). To a suspension of estradiol 3-benzoate (10 g) in *tert*-BuOH (40 ml) cyclohexanone methyl enol ether (10 ml) and Py–TsOH (100 ml) were added. The mixture was kept under stirring while heating with a bath at 40° until complete solution occurred (about 20 min). Stirring was continued at room temperature overnight and then the precipitated crystals were slurried with MeOH (100 ml), filtered, and recrystallized.

Intermediates. The physical constants of new steroid intermediates **71–86** are listed in Table IV. Estrone esters **71–77** were prepared from estrone by acylation with the appropriate acid chloride. Estradiol 3-esters **78–86** were prepared by $NaBH_4$ (THF) reduction of the corresponding estrone esters. Ethyl vinyl ether was supplied by C. Erba, Milano. 1-(Dimethoxymethyl)cyclopentane[25] was prepared by reaction of cyclopentylmagnesium bromide with trimethyl orthoformate. All other alkyl acetals, ketals, and enol ethers required for preparation of compounds in Table I–III were obtained according to known procedures detailed in ref 3. Among these, only 3-methoxypent-2-ene, mp 94–96° [*Anal.* ($C_6H_{12}O$) C, H], appeared not yet described.

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Aminobenzoic Acid Diuretics. 4.[1] 4-Benzyl-5-sulfamylanthranilic Acid Derivatives and Related 1,2-Benzisothiazole 1,1-Dioxides

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A series of *N*-substituted 4-benzyl-5-sulfamylanthranilic acids and a series of 5-substituted amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides have been synthesized and screened for their diuretic properties. The results for some of the compounds are summarized and compared with those of selected anthranilic acid diuretics and bumetanide. The most potent diuretic compound in both series had the *N*-2-furylmethyl side chain and showed a diuretic profile almost similar to that of bumetanide. The existence of an equilibrium between the benzisothiazole dioxides and the corresponding benzoylsulfamylanthranilic acids has been investigated. The structure–activity relationship is discussed in these terms.

Previous studies in this laboratory have revealed that certain 4-substituted 3-amino-5-sulfamylbenzoic acid[2] and 5-sulfamylanthranilic acid[1] derivatives exhibit high ceiling diuretic activity superior in potency to the corresponding 4-Cl compounds. In continuation of our studies on the structural requirements for this activity, we report the synthesis and diuretic screening results of *N*-alkylated 4-benzyl-5-sulfamylanthranilic acids (**21–30**). In connection with this search we prepared a series of *N*-alkylated 5-amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides (**9–20**). As cyclodehydration products of the corresponding 4-benzoyl-5-sulfamylanthranilic acid derivatives, these compounds represent a structure modification of considerable interest.

Chemistry. The synthesis of the *N*-alkylated 4-benzyl-5-sulfamylanthranilic acids (**21–31**) and the related *N*-alkylated 5-amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides (**10–20**) is outlined in Scheme I and detailed in the Experimental Section. The sequence resulting in the key intermediate **5** involved cyclodehydration subsequent to the amidation of the sulfochloride **3**. This type of cyclization has previously been described by Wright[3] and is supported by spectroscopic evidence in the present case.

Replacement of the Cl in **5** with different amines resulted in the 5-substituted aminobenzisothiazoles (**10–19**) (Table II). For the reaction with benzylamine the corresponding benzisothiazoline **7** was formed as by-product. It was therefore convenient to prepare 5-amino-6-carboxy-3-phenyl-1,2-benzisothiazoline 1,1-dioxide (**6**) from the crude mixture by catalytic hydrogenation and simultaneous debenzylation. Benzylation and reductive alkylation provided the benzisothiazolines **7** and **8** (Table I) which could as well as **6** be dehydrogenated to the benzisothiazoles **9**, **10**, and **20**, respectively. The anthranilic acid derivatives **21–29** (Table III) were obtained from **10–20** by Wolff-Kishner reduction, except for **22** which was conveniently achieved by benzylation of the anthranilic acid **21**. The Wolff-Kishner reaction was probably made possible by hydrolytic ring cleavage to the corresponding benzophenones prior to the reduction due to the alkaline reaction conditions. **30** and **31** (Table III) were provided from the corresponding 2-chlorobenzoic acid derivative **32** by replacement reaction.

Diuretic Effect and Structure–Activity Relationship. **6**, **7**, and **8** (Table I), the 5-substituted amino-6-carboxy-3-phenyl-1,2-benzisothiazole 1,1-dioxides (Table II), and the *N*-alkylated 4-benzyl-5-sulfamylanthranilic acids (Table III) prepared in this study were screened for their diuretic properties in dogs. The urinary volume and electrolyte excretion following iv administration (solution in NaOH) were determined hourly. The urinary volume and the electrolyte excretion from the 3-hr test period for those compounds resulting in a Na^+ excretion >1.0 mequiv after iv administration of 1 mg/kg or less are summarized in Table IV and compared with relevant anthranilic acid diuretics, including furosemide, and with 3-*n*-butylamino-4-phenoxy-5-sulfamylbenzoic acid (bumetanide). In relation to diuretic profile, high potency, and the advantage of the *N*-2-furylmethyl substitution over the benzyl and alkyl substitution, the data