2.05, 2.09 (6-, 7-, and 17-$OCOCH_3$). *Anal.* ($C_{28}H_{36}O_8$) *m/e* 500.

General Procedure for the Preparation of 17-Esters of 6-Chloro-16-methylene-4,6-pregnadiene-17α-ol-3,20-dione (1, X = Cl). A soln, or suspension, of 1.0 g of 6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione## and 100 mg of pTSA·H_2O in 10 ml of the esterifying acid is prepd and cooled to 15° with stirring. Four ml of TFAA is added as rapidly as possible, but maintaining the temp below 20°. After 30 min the reaction is poured into 100 ml of water and stirred for 30 min. When a ppt results, it is collected by filtration, washed, and dried: **1** (X = Cl; R = CH_3CO and CH_3CH_2CO). When preparing the butyrate, valerate, caproate, and heptanoate, the presence of the excess acid makes it desirable to extract with an organic solvent, wash 1 time with 5% NaOH and 3 times with water (the formate prepn never goes to completion; the reaction is extd as with the higher acids). The dried organic exts are then chromatogd on 100 g of 100–200 mesh silica gel, eluting with Et_2O–hexane. The fractions contg the desired ester (detd by tlc) are combined and crystd (MeOH) to yield the desired product. Yields of esters were: formate, 14%; propionate, 71%; butyrate, 77%; valerate, 82%; caproate, 84%; heptanoate, 64% (Table III).

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##Obtained by saponification of the 17-acetate with KOH in aqueous MeOH.

1-Phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinolines. A New Series of Nonsteroidal Female Antifertility Agents

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Upon finding (±)-1-phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline·HCl (**1**) active as a female antifertility agent in the rat, a series of analogs was synthesized. Whereas **1** and most of its analogs were frank estrogens, four analogs, of which (±,±)-1-{*p*-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2-(β-methylphenethyl)-1,2,3,4-tetrahydroisoquinoline · 2HCl (**62**) was the most active, proved to be impeded estrogens.

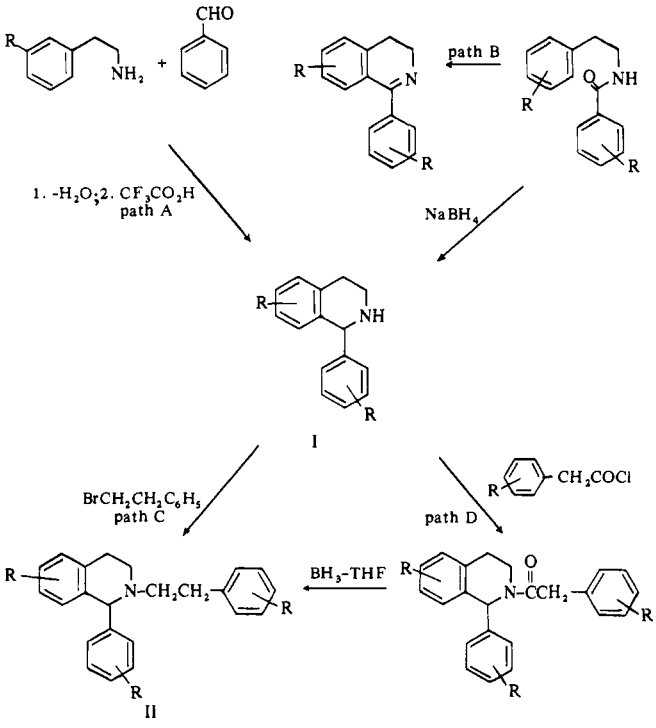
The success of various steroids in the control of human reproduction has elicited considerable interest[1] in finding nonsteroidal female antifertility agents. In particular, research has been directed toward reducing or eliminating hormonal side effects; thus far these efforts have not met with success. During a search for a nonsteroidal compound, 1-phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**1**) was found to be active in female rats as an antifertility agent. A study was undertaken to improve its activity and lower its estrogenicity.

Chemistry. Two synthetic schemes were used to make the 2-unsubstituted tetrahydroisoquinolines. If a phenethylamine had substituents which activated the position ortho to the ethylamine side chain, the Pictet-Spengler reaction, Scheme I, path A, was used. Trifluoroacetic acid proved to be a much better cyclization catalyst than the usual acids[2] used in this reaction. When there was no activation ortho to the ethylamine, the Bischler-Napieralski reaction, Scheme I, path B, was used. Here the procedure of Cannon and Webster[3] using polyphosphoric acid worked well if there were no methoxy groups in the starting amide. With methoxy groups $POCl_3$ was used in place of polyphosphoric acid. Initially the tetrahydroisoquinolines I were alkylated directly to II but the yields were low. Using the two-step procedure, Scheme I, path D, of acylating with phenylacetyl chloride followed by reduction with BH_3–THF,[4] much better yields were obtained.

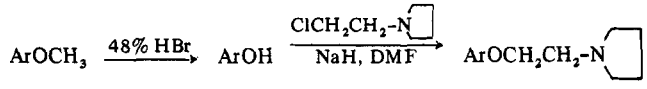
The pyrrolidinoethoxy derivatives were prepared *via* Scheme II. A sample of 1-phenyl-1,2,3,4-tetrahydroisoquinoline† was resolved by the method of Leithe[5] and both isomers alkylated by Scheme I, path C. Table I lists the analogs

†Unless otherwise noted, all compounds capable of optical activity are racemic.

Scheme I



Scheme II

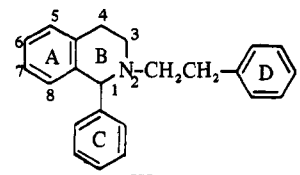


of **1** while Tables II and III list the intermediates used to make the various analogs.

Biological Testing. In all bioassays, Wistar strain rats, obtained from the Royal Hart Colony and maintained under standard laboratory conditions, were used. Compounds were dissolved or suspended in propylene glycol, and appropriate doses were given orally in a volume of 0.25 ml. In the antifertility test, female rats (225-250 g) received single daily oral doses, on a mg/kg basis, for 10 days. During the entire treatment period, they were cohabited, on a 3:4 male-female basis, with proven fertile males, and, 24 hr after the last dose, the females were autopsied and examined for the presence or absence of fetal implantation sites. A minimum of 8 females were tested at each dose level, and estrone was used as the reference standard. Under these conditions, simultaneously performed vehicle control groups yielded pregnancy rates of approximately 90%, and the ED_{100} of estrone was consistently 0.5 mg/kg per day. For comparative purposes, the ED_{100} of estrone divided by the ED_{100} of the test compound was used for relative potency estimations. In the uterotropic assay, which measured estrogenic or antiestrogenic activity, female rats (50-60 g) received single daily oral doses, on a μg/day basis, for 3 days. The uteri were removed and weighed 24 hr after the last dose. A minimum of five rats were tested at each dose level, and here, also, estrone was used as reference standard. The average uterine weights of the estrone or test compound treated rats were divided by the average uterine weight of simultaneously performed vehicle controls in order to estimate the degree of uterine hypertrophy. Thus, for example, a ratio of 1.25 indicated a 25% increase in uterine weight above control values.

Structure-Activity Relationships. After finding **1** active as a female antifertility agent in the rat, the resolved compounds **2** and **3** were prepared. The activity resided in **3** but so did all the estrogenicity. A systematic study was then begun to change each portion of the molecule in order to enhance the antifertility activity and reduce or change the nature of the frank estrogenicity associated with it.

The effect of substituents on the aromatic rings were dependent upon the nature of the group and its location. A hydroxy group anywhere on ring A of III, singly or in pairs, generally lowered the potency but did not affect the estrogenicity (*cf.* **7**, **12**, **15**, **18** *vs.* **1**).



III

A 6-methoxy derivative (**14**) enhanced potency while estrogenicity remained the same. However, combining the 6-methoxy with a 7-methoxy (**4**) or longer side chain (**60**) lowered both potency and estrogenicity. Activity was also lost when the 6-methoxy and ring C para chloro (**63**) or para hydroxyl group (**29**) were combined. The use of 3 substituents including the dimethoxy group in ring A and an additional group in ring C demolished all activity (*cf.* **5**, **6**).

A 5-methoxy derivative (**17**) was equivalent to the 6-methoxy (**14**) but a methoxy at C_7 (**11**) or in the para position in ring C (**24**) was of no value.

A chloro substituent (**22**) on ring C para was as effective as the parent compound (**1**) but much less estrogenic. Moving the chloro to the ortho or meta positions on ring C, or to ring A removed all activity (*cf.* **20**, **21** and **10**). A fluoro group (**23**) in place of chloro (**22**) was less potent and more estrogenic while a trifluoromethyl group (**27**) was inactive.

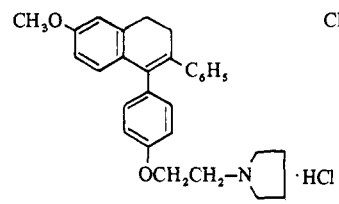
A methyl group on rings A, B, or C decreased potency and/or estrogenicity (*cf.* **1** *vs.* **13**, **28**, **56**); whereas a nitro group on ring A or phenyl group on ring C decreased both potency and estrogenicity (*cf.* **1** *vs.* **9** and **26**).

Substitutions on ring D invariably led to inactive compounds. Hydroxyl or methoxy groups ortho, meta, and para were ineffective as were para nitro or para pyrrolidinoethoxy (*cf.* **31-38**).

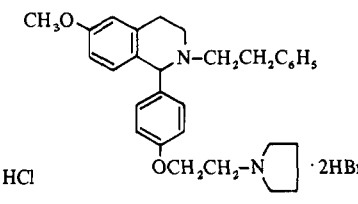
The most dramatic change was caused by substitution of a pyrrolidinoethoxy group in the para position of ring C (*cf.* **64** *vs.* **1**). Not only was the antifertility potency enhanced, but the compound exhibited a flat estrogen dose-response curve indicative of an impeded rather than a frank estrogen.

When a 6-methoxy group was added to **64** yielding **30**, there was no increase in potency. In fact, there was a moderate decrease. This was surprising due to the close similarity of **30** to the known antifertility agent, U-11,100A, where the removal of the methoxy group decreased the potency to 0.05 of that of U-11,100A.[15]

Next, the effect of alterations on the side chain was studied. A methyl or ethyl substituent on the β position of

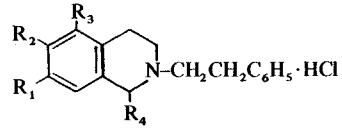
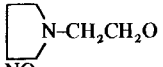
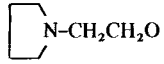
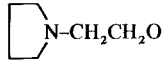
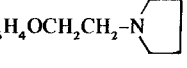
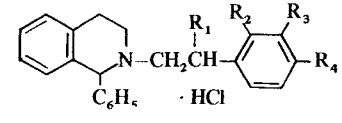


U-11,100A

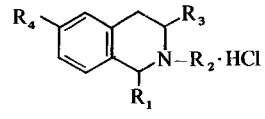


30

Table I. Derivatives of 1,2-Disubstituted 1,2,3,4-Tetrahydroisoquinoline

No.	R_1	R_2	R_3	R_4	Procedure	Yield, %	Mp, °C[a]	Formula[b]	Antifertility[c] rank	Estrogenic[d] rank
										
1	(±)H	H	H	C_6H_5	C	35	221–222	$C_{23}H_{23}N\cdot HCl\cdot 0.25H_2O$	3	3
2	(+)H	H	H	C_6H_5	C	58[e]	208.5–217	$C_{23}H_{23}N\cdot HCl$	0	
3	(−)H	H	H	C_6H_5	C	39[f]	210.5–218.5	$C_{23}H_{23}N\cdot HCl$	4	3
4	CH_3O	CH_3O	H	C_6H_5	C	17	201–203	$C_{25}H_{27}NO_2\cdot HCl$	2	1
5	CH_3O	CH_3O	H	p-$C_6H_4OCH_3$	C	65	202.5–205 dec	$C_{26}H_{29}NO_3\cdot HCl\cdot 0.5C_2H_5OH$	0	
6	CH_3O	CH_3O	H	o-C_6H_4Cl	C	45	202–204	$C_{25}H_{26}ClNO_2\cdot HCl$	0	
7	HO	HO	H	C_6H_5	C	20	173–176	$C_{23}H_{23}NO_2\cdot HCl\cdot 0.25CH_3OH$	1	3
8		H	H	C_6H_5	F	29	80–112[g]	$C_{29}H_{34}N_2O\cdot HBr\cdot H_2O$	0	
9	NO_2	H	H	C_6H_5	C	31	251–255	$C_{23}H_{22}N_2O_2\cdot HCl$	1	1
10	Cl	H	H	C_6H_5	C	26	224–230	$C_{23}H_{22}ClN\cdot HCl$	0	
11	CH_3O	H	H	C_6H_5	C	51	217–220	$C_{24}H_{25}NO\cdot HCl$	3	3
12	HO	H	H	C_6H_5	E	57	236–247.5	$C_{23}H_{23}NO\cdot HCl$	2	1
13	CH_3	H	H	C_6H_5	D	81	221–223.5	$C_{24}H_{25}N\cdot HCl$	3	2
14	H	CH_3O	H	C_6H_5	C	48	239–244	$C_{24}H_{25}NOCl$	5	3
15	H	OH	H	C_6H_5	E	81	241–248.5	$C_{23}H_{23}NO\cdot HCl\cdot 0.25H_2O$	3	3
16	H		H	C_6H_5	F	76	250–257	$C_{29}H_{34}N_2O\cdot 2HCl\cdot 0.5H_2O$	0	
17	H	H	CH_3O	C_6H_5	C	20	247.5–252	$C_{24}H_{25}NO\cdot HCl$	5	3
18	H	H	OH	C_6H_5	E	79	283–290	$C_{23}H_{23}NO\cdot HCl$	2	3
19	H	H		C_6H_5	F	57	142–152	$C_{29}H_{34}N_2O\cdot 2HCl\cdot H_2O$	0	
20	H	H	H	o-C_6H_4Cl	C	50	232–236	$C_{23}H_{22}ClN\cdot HCl$	0	
21	H	H	H	m-C_6H_4Cl	C	53	240–255	$C_{23}H_{22}ClN\cdot HCl$	0	
22	H	H	H	p-C_6H_4Cl	C	26	203–209	$C_{23}H_{22}ClN\cdot HCl$	3	1
23	H	H	H	p-C_6H_4F	C	43	185–188.5	$C_{23}H_{22}FN\cdot HCl\cdot 0.25H_2O$	2	3
24	H	H	H	p-$C_6H_4OCH_3$	D	42	229–235	$C_{24}H_{25}NO\cdot HCl$	1	1
25	H	H	H	p-$C_6H_4SO_2CH_3$	D	84	223.5–229	$C_{24}H_{25}NO_2S\cdot HCl\cdot 0.25H_2O$	0	
26	H	H	H	p-C_6H_4-C_6H_5	D	87	230–239.5	$C_{29}H_{27}N\cdot HCl$	1	1
27	H	H	H	p-$C_6H_4CF_3$	D	88	180.5–182.5	$C_{24}H_{22}F_3N\cdot HCl$	0	
28	H	H	H	p-$C_6H_4CH_3$	C	88	225–228.5	$C_{24}H_{25}N\cdot HCl\cdot 0.25H_2O$	0	
29	H	CH_3O	H	p-C_6H_4OH	D	94	238–242 dec	$C_{24}H_{25}NO_2\cdot HCl$	0	
30	H	CH_3O	H	p-$C_6H_4OCH_2CH_2$- 	F	35	220–225	$C_{30}H_{36}N_2O_2\cdot 2HBr$	3	NP
										
31	H	H	H	OH	D	35	270–276	$C_{23}H_{23}NO\cdot HCl$	0	
32	H	H	H	OCH_3	D	85	177.5–179.5	$C_{24}H_{25}NO\cdot HCl$	0	
33	H	H	H	NO_2	C	22	108.5–114	$C_{23}H_{22}N_2O_2\cdot HCl\cdot i$-$C_3H_7OH$	0	

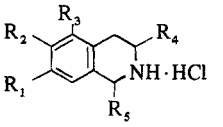
34	H	H	H	OCH_2CH_2-N⟨ ⟩	F	62	174–184	$C_{29}H_{34}N_2O \cdot 2HCl \cdot 0.25H_2O$	0	
35	H	OH	H	H	D	40	230–237.5	$C_{23}H_{23}NO \cdot HCl \cdot 0.5H_2O$[h]	0	
36	H	OCH_3	H	H	D	69	233–236 dec	$C_{24}H_{25}NO \cdot HCl$	0	
37	H	H	OH	H	D	28	226–238	$C_{23}H_{23}NO \cdot HCl$	0	
38	H	H	OCH_3	H	D	52	211.5–218.5	$C_{24}H_{25}NO \cdot HCl$	0	
39	CH_3	H	H	H	D	58	206–217	$C_{24}H_{25}N \cdot HCl$	5	5
40	C_6H_5	H	H	H	D	63[i]	205–222	$C_{29}H_{27}N \cdot HCl \cdot 0.25H_2O$	0	
41	C_2H_5	H	H	H	D	83	204–212	$C_{25}H_{27}N \cdot HCl \cdot 0.25H_2O$	5	5
42	OH	H	H	H	H	60	243–245 dec	$C_{23}H_{23}NO \cdot HCl$	1	3
43	OH	H	H	H	H	22	214–219	$C_{23}H_{23}NO \cdot HCl$	3	3
44	OCH_2CH_2-N⟨ ⟩	H	H	H	F[j,k]	22	97–143	$C_{29}H_{34}N_2O \cdot 2HCl$	0	



45	C_6H_5	$CH_2C_6H_5$	H	H	C	43	207–209	$C_{22}H_{21}N \cdot HCl \cdot 0.5C_2H_5OH$	0	
46	C_6H_5	$(CH_2)_3C_6H_5$	H	H	C	52	178–181	$C_{24}H_{25}N \cdot HCl$	3	1
47	C_6H_5	$(CH_2)_4C_6H_5$	H	H	D	85	207–209	$C_{25}H_{27}N \cdot HCl$	1	1
48	C_6H_5	$CH_2CH_2OC_6H_5$	H	H	C	73	219–223	$C_{23}H_{23}NO \cdot HCl$	2	2
49	C_6H_5	$(CH_2)_3OC_6H_5$	H	H	C	52	222–227	$C_{24}H_{25}NO \cdot HCl$	0	
50	p-C_6H_4Cl	$(CH_2)_3C_6H_5$	H	H	C	16	186–190	$C_{24}H_{24}ClN \cdot HCl$	0	
51	C_6H_5	$CH_2CH_2C(CH_3)_3$	H	H	D	58	239–248	$C_{21}H_{27}N \cdot HCl$	1	3
52	C_6H_5	CH_2CH_2-⟨ ⟩	H	H	D	87	213–215.5	$C_{22}H_{27}N \cdot HCl$	0	
53	C_6H_5	$CH_2CH{=}CHC_6H_5$	H	H	C	53	110–112.5	$C_{24}H_{23}N$	0	
54	C_6H_5	$COCH_2C_6H_5$	H	H	D	94	119.5–123.5	$C_{23}H_{21}NO$	0	
55	C_6H_5	$CH_2COC_6H_5$	H	H	G	37	121–123	$C_{23}H_{21}NO$	1	1
56	C_6H_5	$CH_2CH_2C_6H_5$	CH_3	H	D	82	241–250	$C_{24}H_{25}N \cdot HCl$	2	1
57	C_6H_5	$CH_2CHNH_2CH_2C_6H_5$	H	H	D[l]	16	231–239	$C_{24}H_{26}N_2 \cdot 2HCl \cdot 0.5C_2H_5OH$	0	
58	$C_6H_5CH_2$	$CH_2CH_2C_6H_5$	H	H	C[m]	28	193.5–196	$C_{24}H_{25}N \cdot HCl \cdot 0.25C_2H_5OH$	0	
59	C_6H_5	$CH_2CH_2NHC_6H_5$	H	H	D,J[n]	30	210.5–218.5 dec	$C_{23}H_{24}N_2 \cdot 2HCl \cdot 0.25H_2O$	0	
60	C_6H_5	$(CH_2)_3C_6H_5$	H	CH_3O	C	77	175–176	$C_{25}H_{27}NO \cdot HCl$	3	1
61	p-$C_6H_4OCH_2CH_2$-N⟨ ⟩	$CH_2CHCH_3C_6H_5$	H	CH_3O	D,F[k]	80	51–59 dec	$C_{31}H_{38}N_2O_2 \cdot 2HCl$	5	NP
62	p-$C_6H_4OCH_2CH_2$-N⟨ ⟩	$CH_2CHCH_3C_6H_5$	H	H	D,F[k]	68	91–145	$C_{30}H_{36}N_2O \cdot 2HCl$	6	NP
63	p-ClC_6H_4	$CH_2CH_2C_6H_5$	H	CH_3O	D	86	231–235	$C_{24}H_{24}ClNO \cdot HCl$	3	3
64	p-$C_6H_4OCH_2CH_2$-N⟨ ⟩	$CH_2CH_2C_6H_5$	H	H	D,F[k]	81	81–113	$C_{29}H_{34}N_2O \cdot 2HCl$	4	NP

[a]Recrystallization solvents generally EtOH–HCl gas or MeOH–HCl gas. [b]Analyses were obtained for C, H, N and when those elements were present for Cl, Br, F or S. Unless the samples melted below or near 100° all the solvated samples were dried at 100° (0.1 mm) and retained their solvation. [c]Antifertility rank is defined as potency relative to estrone whose ED_{100} = 0.5 mg/kg per day. 0 = <0.01; 1 = 0.01–0.05; 2 = 0.06–0.1; 3 = 0.11–0.5; 4 = 0.6–1.0; 5 = 1.1–5.0; 6 = >5.0. [d]Estrogen rank is defined as the potency relative to estrone 0 = <0.001; 1 = 0.001–0.005; 2 = 0.006–0.01; 3 = 0.011–0.05; 4 = 0.051–0.1; 5 = 0.11–0.5. In each case where a number is assigned the dose response of the compound paralleled that of estrone. If it does not, the estrogenic rank is called NP, nonparallel. [e]Prepared from the (−)-1-phenyl-1,2,3,4-tetrahydroisoquinoline which is (+) as the hydrochloride. **2** has $[\alpha]^{25}D$ + 123 ± 0.5° (*c* 6, EtOH). [f]$[\alpha]^{25}D$ −134.5 ± 1.2° (*c* 2.6, EtOH). [g]One spot on tlc. [h]Cl: calcd, 9.46; found, 9.93. [i]The BH_3–THF reduction took 7 hr instead of the usual 1 hr. [j]Carried out on isomer **42**. [k]The product was an amorphous solid giving one spot on tlc. Its structure was confirmed by nmr and mass spectrometry since no reasonable analysis could be obtained for it. [l]Prepared using carbobenzoxy-(±)-phenylalanine as the acid portion. Since the carbobenzoxy group was not removed using BH_3–THF an extra step using HBr gas–HOAc was used.[6] [m]1-Benzyl-1,2,3,4-tetrahydroisoquinoline from Aldrich Chem. [n]Prepared using *N*-carbobenzoxy-*N*-phenylglycine (see *l*).

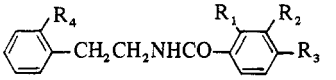
Table II. Intermediates for Table I. N-Unsubstituted 1,2,3,4-Tetrahydroquinolines



No.	R_1	R_2	R_3	R_4	R_5	Procedure or lit. ref	Yield,[a] %	Mp, °C	Formula[b]	Starting[c] material
65	(±) H	H	H	H	C_6H_5	7				
66	(−) N	H	H	H	C_6H_5	5				
67	(+) H	H	H	H	C_6H_5	5				
68	CH_3O	CH_3O	H	H	C_6H_5	A	75	263-265	$C_{17}H_{19}NO_2 \cdot HCl$	
69	CH_3O	CH_3O	H	H	p-$C_6H_4OCH_3$	A	68	265-267[d]	$C_{18}H_{21}NO_3 \cdot HCl$	
70	CH_3O	CH_3O	H	H	o-C_6H_4Cl	A	89	218[e]	$C_{17}H_{18}ClNO_2 \cdot HCl$[f]	
71	HO	HO	H	H	C_6H_5	A	11	140-156, 240-246	$C_{15}H_{15}NO_2 \cdot HCl \cdot C_2H_5OH$	
72	NO_2	H	H	H	C_6H_5	I	58	251-254	$C_{15}H_{14}N_2O_2 \cdot HCl$	Ref 3
73	Cl	H	H	H	C_6H_5	B	33	274-277	$C_{15}H_{14}ClN \cdot HCl$[g]	Ref 9
74	CH_3O	H	H	H	C_6H_5	B	44	280-283	$C_{16}H_{17}NO \cdot HCl$	Ref 10
75	CH_3	H	H	H	C_6H_5	B	76	261-268	$C_{16}H_{17}N \cdot HCl \cdot 0.25CH_3OH$	Ref 11
76	H	CH_3O	H	H	C_6H_5	A	82	277-279	$C_{16}H_{17}NO \cdot HCl$	
77	H	H	CH_3O	H	C_6H_5	B	20	291.5-294.5	$C_{16}H_{17}NO \cdot HCl \cdot 0.25CH_3OH$	**90**
78	H	H	H	H	o-C_6H_4Cl	B	68	244.5-249	$C_{15}H_{14}ClN \cdot HCl$	**91**
79	H	H	H	H	m-C_6H_4Cl	B	90	127 dec	$C_{15}H_{14}ClN \cdot HCl \cdot 0.25Et_2O$	**92**
80	H	H	H	H	p-C_6H_4Cl	B	88	233-236	$C_{15}H_{14}ClN \cdot HCl$	Ref 12
81	H	H	H	H	p-C_6H_4F	B	80	252-258	$C_{15}H_{14}FN \cdot HCl$	**93**
82	H	H	H	H	p-$C_6H_4OCH_3$	B	43	244-250	$C_{16}H_{17}NO \cdot HCl$[h]	**94**
83	H	H	H	H	p-$C_6H_4SO_2CH_3$	B	86	325-330 dec[i]	$C_{16}H_{17}ClNO_2S \cdot HCl$	**95**
84	H	H	H	H	p-C_6H_4-C_6H_5	B	27	122-124.5[j]	$C_{21}H_{19}N \cdot 0.125C_2H_5OH$	**96**
85	H	H	H	H	p-$C_6H_4CF_3$	B	19	315-317	$C_{16}H_{14}F_3N \cdot HCl$[k]	**97**
86	H	H	H	H	p-$C_6H_4CH_3$	B	78	282-286	$C_{16}H_{17}N \cdot HCl$	**98**
87	H	CH_3O	H	H	p-C_6H_4OH	A	51	266-270	$C_{16}H_{17}NO_2 \cdot HCl \cdot 0.25CH_3OH$	
88	H	H	H	CH_3	C_6H_5	B	23	265-266[l]	$C_{16}H_{17}N \cdot HCl \cdot 0.25C_2H_5OH$	Ref 14
89	H	CH_3O	H	H	p-C_6H_4Cl	A	85	279-282	$C_{16}H_{16}ClNO \cdot HCl$	

[a] Samples were recrystallized from EtOH-HCl gas or MeOH-HCl gas. [b] Analyses were obtained for C, H, N, Cl and when that element was present for S. Unless the samples melted below or near 100° all the solvated samples were dried at 100° (0.4 mm) and retained their solvation. [c] If not commercially available. [d] Weinbach and Hartung[8] describe this product as having mp 151-152°. The structure of **69** was confirmed by nmr. [e] Weinbach and Hartung[8] give mp 210-212°. [f] C: calcd, 60.01; found, 59.39. [g] Cl: calcd, 25.31; found, 24.82. [h] H: calcd, 6.58; found, 7.08. [i] Recrystallized from 1 *N* HCl. [j] Recrystallized from C_6H_6-petroleum ether. The solvation came from the $NaBH_4$-EtOH reduction. [k] H: calcd, 4.82; found, 5.44. [l] Lit.[13] mp 255-256°.

Table III. Intermediates for Table II. Secondary Amides



No.	R_1	R_2	R_3	R_4	Recrystallization solvent	Yield,[a] %	Mp, °C	Formula[b]
90	H	H	H	OCH_3	EtOH-water	81	81.5-82.5	$C_{16}H_{17}NO_2$
91	Cl	H	H	H	EtOH	73	98-101.5	$C_{15}H_{14}ClNO$
92	H	Cl	H	H	EtOAc	65	96-98	$C_{15}H_{14}ClNO$
93	H	H	F	H	EtOH	85	123-124.5	$C_{15}H_{14}FNO$
94	H	H	OCH_3	H	EtOAc	95	116-118	$C_{16}H_{17}NO_2$
95	H	H	SO_2CH_3	H	MeOH	80	186-187	$C_{16}H_{17}NO_3S$
96	H	H	C_6H_5	H	EtOH	88	184-188	$C_{21}H_{19}NO$
97	H	H	CF_3	H	EtOH	89	159.5-161.5	$C_{16}H_{14}F_3NO$
98	H	H	CH_3	H	EtOAc-petr ether	91	78-79	$C_{16}H_{17}NO$

[a] Synthesized by procedure D without the $NaBH_4$ reduction. [b] Analyses were obtained for C, H, N and when necessary F, Cl, and S.

the side chain enhanced potency but estrogenicity was increased accordingly (*cf.* **1**, **39** and **41**). When the "branch" was phenyl (**40**) or pyrrolidinoethoxy (**44**) all activity was lost, and an hydroxyl substituent in either stereochemical conformation was of no advantage (*cf.* **1**, **42**, and **43**).

The effect of a methyl branch on the antifertility potency was also apparent with the impeded estrogens (*cf.* **61** and **62** *vs.* **64**). In fact, the methyl branch in the side chain afforded the most potent compound (**62**) in the series. Combining the previously found effect of a 6-methoxy group with a branched methyl was not nearly as effective as the methyl alone (*cf.* **62** *vs.* **61**).

Lengthening the side chain one carbon maintained potency and lowered estrogenicity (*cf.* **46** *vs.* **1**) whereas an extension of two carbons lowered both potency and estrogenicity (*cf.* **47** *vs.* **1**). Shortening the side chain by one carbon eliminated all activity (**45**).

An ether oxygen in the two-carbon side chain lowered both potency and estrogenicity (*cf.* **48** *vs.* **1**) while the addition of oxygen to the three-carbon chain (*cf.* **49** *vs.* **46**) or nitrogen in the two-carbon chain (*cf.* **59** *vs.* **1**) completely eliminated antifertility activity. Also ineffective were "keto" side chains **54** and **55**.

Replacement of the phenyl group with *tert*-butyl main-

tained estrogenicity but lowered potency (*cf.* **51** *vs.* **1**) while exchange of phenyl with cyclopentyl removed all activity (*cf.* **52** *vs.* **1**).

Replacement of the ring A phenyl with benzyl (**58**) or adding unsaturation to the side chain (**53**) caused a complete loss of activity.

Discussion

Excluding **30**, **61**, **62**, and **64**, all compounds produced frank estrogenic effects as judged by the parallel nature of their dose-response relationships with estrone in the uterotropic assay (Table I). Although the relative degrees of estrogenicity *vs.* antifertility potency varied with different structural modifications, a true separation of the two effects never occurred. In fact, in every instance uterotropic activity was always associated with the effective antifertility dose. These data suggested that the estrogenic potential was the apparent basis for the antifertility efficacy. However, the nonparallel nature of the four previously stated exceptions indicated that they were not frank estrogens but that they belonged to a class of agents known as "impeded estrogens."[16] To illustrate this further, the biologic effects of the most potent member of the four, *viz.* **62**, are summarized in Table IV.

Compared to estrone, where the degree of uterine hypertrophy was directly proportional to the dose, **62** yielded an essentially flat relationship (Table IV). This effect is characteristic of impeded estrogens, and the mechanism of action is not clearly understood. However, such agents also antagonize the uterotropic effect of exogenously administered frank estrogen.[16] This was also true for **62** (Table IV). It can be seen that **62** markedly antagonized, in a dose-related manner, the uterotropic response normally elicited by estrone. Nevertheless, the compound's apparent antiestrogenicity was not the basis for its antifertility effect since contraceptive doses were associated with intrinsic uterotropic activity, *per se*, *i.e.*, the doses of 1 and 4 μg/rat per day (20 and 80 μg/kg per day) in the uterotropic assay bracket the antifertility ED_{100} (50 μg/kg per day). Therefore, even with such compounds, antifertility and estrogenicity were apparently inseparable.

Substances that are estrogenic are frequently hypocholesteremic and that was the case in this series. Since the activity exactly paralleled the estrogenicity, it was not of interest.‡

Experimental Section§,#

The following examples are representative of each procedure.

Procedure A. 1-Phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline·HCl (76). A soln of 6.04 g (40.0 mmoles) of 2-(*m*-methoxyphenyl)ethylamine[17] and 4.77 g (45.0 mmoles) of benzaldehyde in 100 ml of C_6H_6 was refluxed through a Dean–Stark trap until no more water was collected (1 hr). After concg the solution under vacuum, 40 ml of trifluoroacetic acid was added and the soln refluxed for 5 hr. With electron-donating groups on the benzaldehyde, a longer reflux period was necessary. The resulting black soln was poured into water and made alk with solid Na_2CO_3. The combined organic layers (400 ml) from three Et_2O extns were dried (Na_2SO_4) and acidified with ethanolic HCl. Collecting the thick ppt gave 11.63 g of solid, mp 269–276°. Recrystn from 180 ml of MeOH containing a little HCl (g) gave 8.98 g (82%) of 1-phenyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline·HCl, **76**, mp 277–279°. *Anal.* ($C_{16}H_{18}ClNO$) C, H, Cl, N.

Procedure B. 1-*p*-Chlorophenyl-1,2,3,4-tetrahydroisoquinoline·HCl (80). A stirred mixt of 20.0 g (72.2 mmoles) of *N*-phenethyl-*p*-chlorobenzamide, 245 g of polyphosphoric acid, and 5 g of P_2O_5 was heated to 200–205° for 3 hr as described by Cannon and Webster.[3] The hot, black syrup was cautiously poured into ice. A little concd aqueous KOH was added to break up the pptd oil. The still strongly acid mixt was filtered through Celite giving a clear green soln which was alkalinized with concd aqueous KOH. (NaOH gave a heavy salt ppt.) The oily dihydroisoquinoline was extd into C_6H_6 and the aqueous phase extd twice more with Et_2O. The combined exts were dried (Na_2SO_4) and concd under vacuum. To the residual yellow oil, which was dissolved in 200 ml of MeOH and cooled in an ice bath, 7.56 g (0.2 mole) of $NaBH_4$ was added. After standing at room temp overnight, the soln was refluxed for 1 hr then concd under vacuum. The residue was dild with 200 ml of water and extd 3 times with Et_2O. The combined organic ext was dried (Na_2SO_4) and satd with HCl (g). The cryst ppt was collected giving 18.96 g (95%), mp 232–234.5°, of product. Recrystn from EtOH–HCl gas gave 17.57 g (88%) of **80**, mp 233–236°. *Anal.* ($C_{15}H_{15}Cl_2N$) C, H, Cl, N.

Procedure C. (−)-1-Phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline·HCl (3). After suspending 6.00 g (16.7 mmoles) of (−)-1-phenyl-1,2,3,4-tetrahydroisoquinolinium-*d*-tartrate (**66**) between 100 ml of Et_2O, 80 ml of water, and 20 ml of concd NH_4OH, the aqueous layer was extd twice more with Et_2O. The combined ethereal exts were dried (Na_2SO_4) and concd under vacuum to the cryst free base, $[\alpha]^{25}D$ −40.8 ± 0.3° (*c* 5.3, Et_2O), lit.[5] $[\alpha]^{25}D$ −43.4° (*c* 6, Et_2O). The base was dissolved in 35 ml of EtOH and added to 1.06 g (10.0 mmoles) of anhyd Na_2CO_3 and 0.1 g of KI. Then the mixt was stirred and refluxed while a soln of 3.10 g (16.7 mmoles) of 2-(bromoethyl)benzene in 15 ml of EtOH was added dropwise over 2 hr. Reflux was continued for an additional 7.5 hr, after which the reaction mixt was concd under vacuum and distributed between Et_2O and dil aqueous $NaHCO_3$. The Et_2O ext was dried (Na_2SO_4) and taken to dryness *in vacuo*. Chromatographing the residue on silica gel separated it into product–fast moving–and recovered starting material–slow moving. The product was recrystd from EtOH–HCl (g)–Et_2O, then dil HCl and again from the first system, to give 2.27 g (39%) of (−)-1-phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline·HCl (**3**), mp 210.5–218.5°, $[\alpha]^{25}D$ −134.5 ± 1.2° (*c* 2.6, ethanol), whose ir was similar to that of the (±) material. *Anal.* ($C_{23}H_{24}ClN$) C, H, Cl, N.

Procedure D. 1-*p*-Methylsulfonylphenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline·HCl (25). To a cooled, rapidly stirred, mixt of 4.86 g (15.0 mmoles) of 1-*p*-methylsulfonylphenyl-1,2,3,4-tetrahydroisoquinoline·HCl, **83**, 100 ml of $CHCl_3$, and enough 1 *N* NaOH to just give a pink color with phenolphthalein was added 2.63 g (17.0 mmoles) of phenacetyl chloride. Additional 1 *N* NaOH was used to maintain the pink color. After stirring for 1 hr at ambient temp, the organic layer was separated, washed with brine, 1 *N* HCl, and brine. Drying (Na_2SO_4) and evapn gave a residual crude oily amide which was dissolved in 100 ml of THF and added dropwise, under N_2, to 30 ml (30 mmoles) of 1 *N* BH_3–THF^4 at 0°. The soln was refluxed for 1 hr, cooled to 0°, and decomposed with 10 ml of 6 *N* HCl. After boiling off the solvent, the residue was alkalinized with aqueous KOH and extd with Et_2O. Drying the Et_2O soln (Na_2SO_4) and saturating it with HCl (g) gave an oil which crystd on trituration with 10 ml of EtOH. The 7.46 g of white solid, mp 224–

Table IV. Estrogenic and Antiestrogenic Effects in Immature Female Rats

Group	No. rats	μg/rat per day × 3 Estrone	μg/rat per day × 3 **62**	Uterine weight ratio (treated/control)
A	10			1.0
B	10	0.37		1.45
	10	1.1		2.55
	10	3.3		3.45
C	10		1.0	1.94
	10		4.0[a]	2.21
	10		12.0	2.20
	10		37.0	2.14
	10		111.0	2.03
D	10	3.3	12.0	2.70
	10	3.3	37.0	2.20
	10	3.3	111.0	2.05

[a] Approximate antifertility dose.

‡We thank Dr. H. Albers of these labs for running this assay.

§ All melting points were taken in a Mel-Temp block and are uncorrected.

#Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of theory.

229°, was twice recrystd from EtOH–HCl (g) to give an overall yield of 5.42 g (84%) of **25**, mp 223.5–229°. *Anal.* ($C_{24}H_{26}ClNO_2S \cdot 0.25H_2O$) C, H, Cl, N, S.

Procedure E. 1-Phenyl-2-phenethyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline·HCl (12). 1-Phenyl-2-phenethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline·HCl **(11)** (0.41 g, 1.08 mmoles) was refluxed for 3.5 hr with 4.1 ml of 48% HBr and enough HOAc (3 ml) to give a soln. Then the soln was neutralized with aqueous $NaHCO_3$ and extd 3 times with 1:1 Et_2O–*n*-BuOH. After the organic ext had been evapd to dryness, the residue was crystd from EtOH–HCl (g)–Et_2O to give 0.38 g (95%) of phenol, mp 229–236°. Recrystn from the same solvent system gave 0.23 g (57%) of **12**, mp 236–247.5°. *Anal.* ($C_{23}H_{24}ClNO$) C, H, Cl, N.

Procedure F. 1-{*p*-[2-(1-Pyrrolidinyl)ethoxy]phenyl}-2-phenethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline·2HBr (30). To a slurry of 3.96 g (0.010 mole) of 1-*p*-hydroxyphenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline·HCl, **29**, in 25 ml of DMF was added 0.96 g (0.020 mole) of 50% NaH in mineral oil. After 30 min of stirring at room temp all the phenol had dissolved, and 2.67 g (0.020 mole) of *N*-chloroethylpyrrolidine was added. The brown soln was stirred overnight, then poured into EtOAc, and washed with aqueous $NaHCO_3$. Next the organic phase was extd with 1 *N* HCl, the ext basified with NaOH, and the resulting oil extd with $CHCl_3$. After drying (Na_2SO_4), the $CHCl_3$ soln was concd under vacuum and the residue dissolved in HOAc. HBr (g) was added until the soln was saturated, followed by an excess of Et_2O which gave an oily ppt. The supernatant was decanted and the residue triturated with Et_2O. After standing in Et_2O for several hours a solid formed which was collected, 5.18 g (84%), mp 215–220°. This was recrystd from EtOH–HBr (g) twice to give 2.13 g (35%) of 1-{*p*-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2-phenethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline·2HBr **(30)**, mp 231–236°.

A sample was recrystd again from EtOH–HBr (g) for analysis, mp 220–225°. (The higher melting product was also analyzed and appeared to contain some excess HBr.) *Anal.* ($C_{30}H_{38}Br_2N_2O_2$) C, H, Br, N.

Procedure G. 1-Phenyl-2-phenacyl-1,2,3,4-tetrahydroisoquinoline (55). Conversion of 4.91 g (0.020 mole) of 1-phenyl-1,2,3,4-tetrahydroisoquinoline·HCl **(65)** into its free base was accomplished by distribution between $CHCl_3$ and NH_4OH, then drying (Na_2SO_4), and concentration under vacuum. After dissolving the cryst free base in 50 ml of THF, it was placed under N_2 and 9.25 ml (0.020 mole) of 2.16 *M* methyllithium in Et_2O was added. A dark brown soln formed, accompanied by the evolution of gas. Then 3.09 g (0.020 mole) of phenacyl chloride, in 10 ml of THF was injected into the reaction mixt. During the addition, the reactn turned light brown, then red. After standing for a few days, a crystn ppt formed which was collected and dried to give 0.92 g of solid, mp 202–209°. An ir spectra and tlc indicated this was a 19% yield of crude, recovered 1-phenyl-1,2,3,4-tetrahydroisoquinoline·HCl, mp 227.5–228.5°. The filtrate was distributed between EtOAc and aqueous $NaHCO_3$. After sepn, the organic layer was dried (Na_2SO_2) and concd under vacuum to a brown oil. Petr ether extn of the oil caused crystn to a brown solid, mp 81–104°. Two recrystns from EtOH gave 2.40 g (37%) of cream-colored needles, **55**, mp 121–123°. An nmr spectra supported N-alkylation. *Anal.* ($C_{23}H_{21}NO$) C, H, N.

Procedure H. 1-Phenyl-2-(2-hydroxy-2-phenethyl)-1,2,3,4-tetrahydroisoquinoline·HCl (42 and 43). A stirred mixt of 9.81 g (30.0 mmoles) of 1-phenyl-2-phenacyl-1,2,3,4-tetrahydroisoquinoline **(55)** and 1.13 g (30.0 mmoles) of $NaBH_4$ in 100 ml of EtOH and 30 ml of THF was warmed on a steam bath until a yellow soln formed. After standing overnight, the excess $NaBH_4$ was decompd with 6 *N* HCl and neutralized with $KHCO_3$, and the mixt concd under vacuum. The residue was leached with Et_2O then satd with HCl (g). A ppt of 10.35 g of solid, mp 222–231° dec, was collected and recrystd from 130 ml of MeOH–HCl (g)–100 ml of Et_2O. Cooling gave 6.62 g (60%) of cryst alcohol **42**, mp 243–245° dec. A sample was recrystd for analysis from MeOH–HCl (g)–Et_2O giving mp 243.5–248°. *Anal.* ($C_{23}H_{23}NO \cdot HCl$) C, H, Cl, N.

The combined mother liquors were concd and recrystd twice from MeOH–HCl (g)–Et_2O to give 2.37 g of **43**, mp 214–219°. An nmr confirmed the diasteriomeric relationship of **42** and **43**. *Anal.* ($C_{23}H_{23}NO \cdot HCl$) C, H, Cl, N.

Procedure I. 1-Phenyl-7-nitro-1,2,3,4-tetrahydroisoquinoline·HCl (72). After a soln of 20.7 g (0.10 mole) of 1-phenyl-3,4-dihydroisoquinoline[3] in 100 ml of concd HNO_3 was cooled to 0°, 200 ml of fuming HNO_3 was slowly added using the procedure for 7-nitration of 3,4-dihydroisoquinolines.[12] The brown soln was permitted to stand overnight, then poured onto ice. Alkalinization with KOH gave a fluffy ppt which changed into a tacky solid. This solid was distributed between 200 ml of $CHCl_3$ and 60 ml of 17 *N* NH_4OH. The organic phase was washed with water, dried (Na_2SO_4), and concd under vacuum to give 13.74 g of solid, mp 145–150.5°. Recrystn from 350 ml of EtOH gave 10.60 g (42%) of 1-phenyl-7-nitro-3,4-dihydroisoquinoline **(99)**, mp 148.5–152°. A sample was recrystd from MeOH for analysis, mp 149.5–152.5°. *Anal.* ($C_{15}H_{22}N_2O_2$) C: Calcd 71.41; found 70.93; H, N. Both ir and nmr confirmed the monosubstituted 1-phenyl ring. Nmr spin decoupling spectra** of **72** located the nitro group in the 7 position. McCoubrey[18] reported this compd in 1.9% yield, mp 203° *via* a Bischler–Napieralski reaction on *N*-benzoyl-2-*p*-nitrophenylethylamine. The only evidence was an N analysis that was 0.7% off.

On recrystg the free base from MeOH–HNO_3, 1-phenyl-7-nitro-3,4-dihydroisoquinolinium nitrate **(100)** was obtained, mp 173° dec. *Anal.* ($C_{15}H_{12}N_2O_2 \cdot HNO_3$) C, H, N.

The free base **99**, 10.31 g (41.1 mmoles), was dissolved in 200 ml of MeOH and 100 ml of THF and 3.0 g (80 mmoles) of $NaBH_4$ added. After stirring overnight, the soln was concd under vacuum, dild with water, and extd into Et_2O. Upon drying (Na_2SO_4), the ext was satd with HCl (g) to give a ppt, 13.75 g, mp 243–249°. This was triturated with 100 ml of boiling $CHCl_3$ leaving 8.94 g of solid which was recrystd from 150 ml of EtOH–25 ml of MeOH–HCl (g) to give 6.95 g (58%) of 1-phenyl-7-nitro-1,2,3,4-tetrahydroisoquinoline·HCl **(9)**, mp 250–255°. A sample was recrystd from EtOH–HCl (g) for analysis, mp 251–254°. *Anal.* ($C_{15}H_{14}N_2O_2 \cdot HCl$) C, H, N, Cl.

Procedure J. *N*-Carbobenzoxy-*N*-phenylglycine (101). To a dark brown mixt of 7.50 g (50 mmoles) of *N*-phenylglycine, in 50 ml of 1 *N* NaOH and 100 ml of Et_2O in an ice bath was added 10 g (59 mmoles) of carbobenzoxy chloride with rapid stirring. The pH was kept alk with more NaOH throughout the addition. After completion, the aqueous layer was separated and washed with several portions of Et_2O until it was colorless. Then the aqueous portion was acidified (HCl) and extd with Et_2O. After washing the Et_2O with brine, it was dried (Na_2SO_4) and concd under vacuum to an oil which crystd from $CHCl_3$–petr ether, mp 55–108°. A recrystn from the same solvents followed by another from EtOAc–petr ether gave 5.46 g (38%) of **101**, mp 70–82°. An analytical sample was recrystd from EtOAc–petr ether to give mp 76–82°. *Anal.* ($C_{16}H_{15}NO_4 \cdot H_2O$) C, H, N

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