

2.05, 2.09 (6-, 7-, and 17-OCOCH₃). *Anal.* (C₂₈H₃₆O₈) *m/e* 500.

General Procedure for the Preparation of 17-Esters of 6-Chloro-16-methylene-4,6-pregnadiene-17 α -ol-3,20-dione (1, X = Cl). A soln, or suspension, of 1.0 g of 6-chloro-16-methylene-17 α -hydroxy-4,6-pregnadiene-3,20-dione^{##} and 100 mg of pTSA·H₂O 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 = CH₃CO and CH₂CH₂CO). 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 Et₂O-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).

Acknowledgments. We are indebted to J. Morton of the Physical Organic Chemistry Department for helpful discussions of the nmr spectra.

References

- (1) E. L. Shapiro, T. Legatt, L. Weber, M. Steinberg, A. Watnick, M. Eisler, M. G. Hennessey, C. T. Coniglio, W. Charney, and E. P. Oliveto, *J. Med. Pharm. Chem.*, **5**, 975 (1962).
- (2) E. P. Oliveto, R. Rausser, and E. B. Hershberg, U. S. Patent 3,312,692 (April 4, 1967).
- (3) S. Rocky and R. Neri, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 624 (1968).
- (4) C. Casmer, F. Fielder and R. Neri, Northeast Conference of Comparative Endocrinology, Boston University, Boston, Mass., 1968.
- (5) R. Neri, *Proc. Int. Congr. Horm. Steroids*, **3rd**, 1970, 1022 (1971).
- (6) (a) Z. Cekan, M. Seda, J. Mikulaskova, and K. Syhora, *Steroids*, **8**, 205 (1966); (b) Z. Cekan and O. Horesovsky, *Acta Endocrinol.*, **66**, 317 (1971).
- (7) E. L. Shapiro, H. L. Herzog, and L. Weber, U. S. Patent, 3,493,588 (Feb 3, 1970).
- (8) (a) K. Syhora and R. Mazac, *Collect. Czech. Chem. Commun.*, **31**, 2768 (1966); (b) K. Syhora, M. Seda, R. Mazac, and Z. Cekan, Czechoslovakian Patent 125,136 (Dec 15, 1967); *Chem. Abstr.*, **69**, 97008u (1968).
- (9) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).
- (10) (a) K. Syhora, Czechoslovakian Patent 104,667 (Aug 15, 1962); *Chem. Abstr.*, **60**, 8100 (1963); (b) D. N. Kirk, V. Petrow, M. Stansfield, and D. M. Williamson, *J. Chem. Soc.*, 2385 (1960).
- (11) E. L. Shapiro, T. L. Popper, L. Weber, R. Neri, and H. L. Herzog, *J. Med. Chem.*, **12**, 631 (1969).
- (12) (a) H. L. Dryden and M. J. Kalm, U. S. Patent 3,270,009 (Aug 30, 1966); (b) K. Syhora and R. Mazac, Belgium Patent 664,224 (Sept 16, 1965); *Chem. Abstr.*, **65**, 3943c (1966).
- (13) G. Nominé, D. Bertini, and A. Pierdet, *Tetrahedron*, **8**, 217 (1960).
- (14) (a) A. L. Nussbaum, G. Brabazon, T. L. Popper, and E. P. Oliveto, *J. Amer. Chem. Soc.*, **80**, 2722 (1958); (b) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Org. Chem.*, **25**, 2258 (1960); **29**, 3486 (1964).
- (15) H. Laurent, G. Schulz, and R. Wiechert, *Chem. Ber.*, 2570 (1969).
- (16) K. Brückner, B. Hampel, and U. Johnsen, *ibid.*, **94**, 1225 (1961).
- (17) E. L. Shapiro, L. Finckenor, H. Pluchet, L. Weber, C. H. Robinson, E. P. Oliveto, H. L. Herzog, I. I. A. Tabachnick, and E. Collins, *Steroids*, **9**, 143 (1967).
- (18) H. J. Mannhardt, F. v. Werder, K. H. Bork, H. Metz, and K. Brückner, *Tetrahedron Lett.*, **16**, 21 (1960).
- (19) M. K. McPhail, *J. Physiol. (London)*, **83**, 145 (1934).

^{##}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

Rolf Paul,* John A. Coppola, and Elliott Cohen

Metabolic Disease Therapy Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965. Received November 2, 1971

Upon finding (\pm)-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 (\pm , \pm)-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 interest¹ 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.

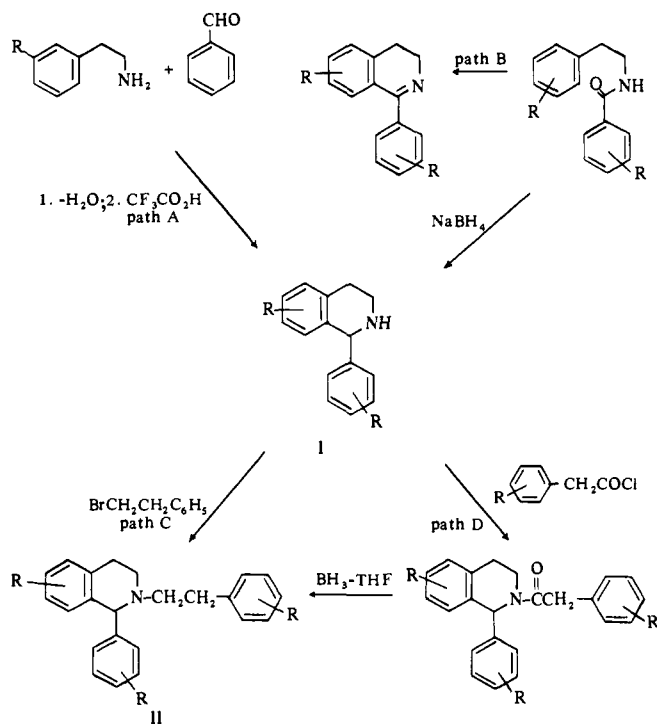
Chemistry. Two synthetic schemes were used to make the 2-unsubstituted tetrahydroisoquinolines. If a phenethylamine had substituents which activated the position ortho to the ethylamine side chain, the Pictet-Spengler reaction, Scheme I, path A, was used. Trifluoroacetic acid proved to be a much better cyclization catalyst than the usual acids² 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 Webster³ using polyphosphoric acid worked well if there were no methoxy groups in the starting amide. With methoxy groups POCl₃ 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 BH₃-THF,⁴ much better yields were obtained.

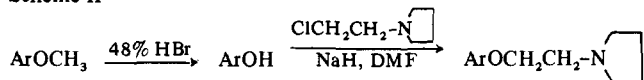
The pyrrolidinoethoxy derivatives were prepared *via* Scheme II. A sample of 1-phenyl-1,2,3,4-tetrahydroisoquinoline[†] was resolved by the method of Leithe⁵ and both isomers alkylated by Scheme I, path C. Table I lists the analogs

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

Scheme I



Scheme II



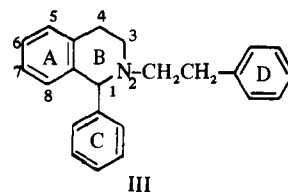
of 1 while Tables II and III list the intermediates used to make the various analogs.

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 uterotrophic assay, which measured estrogenic or antiestrogenic activity, female rats (50–60 g) received single daily oral doses, on a $\mu\text{g/day}$ 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 com-

pounds 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).



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 C₇ (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

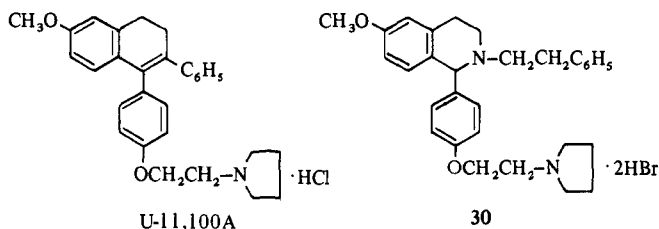
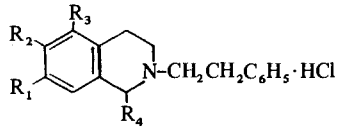
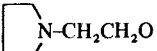
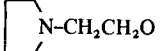
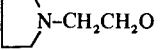

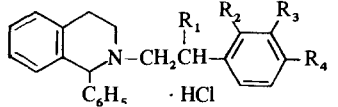


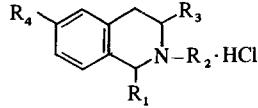






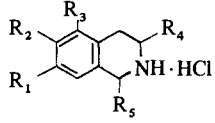
Table I. Derivatives of 1,2-Disubstituted 1,2,3,4-Tetrahydroisoquinoline

No.	R ₁	R ₂	R ₃	R ₄	Proce- dure	Yield, %	Mp, °C ^a	Formula ^b	Anti- fertility ^c rank	Estrogenic ^d rank
										
1	(±)H	H	H	C ₆ H ₅	C	35	221-222	C ₂₃ H ₂₃ N·HCl·0.25H ₂ O	3	3
2	(+H)	H	H	C ₆ H ₅	C	58 ^e	208.5-217	C ₂₃ H ₂₃ N·HCl	0	
3	(-H)	H	H	C ₆ H ₅	C	39 ^f	210.5-218.5	C ₂₃ H ₂₃ N·HCl	4	3
4	CH ₃ O	CH ₃ O	H	C ₆ H ₅	C	17	201-203	C ₂₅ H ₂₇ NO ₂ ·HCl	2	1
5	CH ₃ O	CH ₃ O	H	<i>p</i> -C ₆ H ₄ OCH ₃	C	65	202.5-205 dec	C ₂₆ H ₂₉ NO ₃ ·HCl·0.5C ₂ H ₅ OH	0	
6	CH ₃ O	CH ₃ O	H	<i>o</i> -C ₆ H ₄ Cl	C	45	202-204	C ₂₅ H ₂₅ ClNO ₂ ·HCl	0	
7	HO	HO	H	C ₆ H ₅	C	20	173-176	C ₂₃ H ₂₃ NO ₂ ·HCl·0.25CH ₃ OH	1	3
8		H	H	C ₆ H ₅	F	29	80-112 ^g	C ₂₉ H ₃₄ N ₂ O·HBr·H ₂ O	0	
9	NO ₂	H	H	C ₆ H ₅	C	31	251-255	C ₂₃ H ₂₂ N ₂ O ₂ ·HCl	1	1
10	Cl	H	H	C ₆ H ₅	C	26	224-230	C ₂₃ H ₂₂ ClN·HCl	0	
11	CH ₃ O	H	H	C ₆ H ₅	C	51	217-220	C ₂₄ H ₂₅ NO·HCl	3	3
12	HO	H	H	C ₆ H ₅	E	57	236-247.5	C ₂₃ H ₂₃ NO·HCl	2	1
13	CH ₃	H	H	C ₆ H ₅	D	81	221-223.5	C ₂₄ H ₂₅ N·HCl	3	2
14	H	CH ₃ O	H	C ₆ H ₅	C	48	239-244	C ₂₄ H ₂₅ NOCl	5	3
15	H	OH	H	C ₆ H ₅	E	81	241-248.5	C ₂₃ H ₂₃ NO·HCl·0.25H ₂ O	3	3
16	H		H	C ₆ H ₅	F	76	250-257	C ₂₉ H ₃₄ N ₂ O·2HCl·0.5H ₂ O	0	
17	H	H	CH ₃ O	C ₆ H ₅	C	20	247.5-252	C ₂₄ H ₂₅ NO·HCl	5	3
18	H	H	OH	C ₆ H ₅	E	79	283-290	C ₂₃ H ₂₃ NO·HCl	2	3
19	H	H		C ₆ H ₅	F	57	142-152	C ₂₉ H ₃₄ N ₂ O·2HCl·H ₂ O	0	
20	H	H	H	<i>o</i> -C ₆ H ₄ Cl	C	50	232-236	C ₂₃ H ₂₂ ClN·HCl	0	
21	H	H	H	<i>m</i> -C ₆ H ₄ Cl	C	53	240-255	C ₂₃ H ₂₂ ClN·HCl	0	
22	H	H	H	<i>p</i> -C ₆ H ₄ Cl	C	26	203-209	C ₂₃ H ₂₂ ClN·HCl	3	1
23	H	H	H	<i>p</i> -C ₆ H ₄ F	C	43	185-188.5	C ₂₃ H ₂₂ FN·HCl·0.25H ₂ O	2	3
24	H	H	H	<i>p</i> -C ₆ H ₄ OCH ₃	D	42	229-235	C ₂₄ H ₂₅ NO·HCl	1	1
25	H	H	H	<i>p</i> -C ₆ H ₄ SO ₂ CH ₃	D	84	223.5-229	C ₂₄ H ₂₅ NO ₂ S·HCl·0.25H ₂ O	0	
26	H	H	H	<i>p</i> -C ₆ H ₄ -C ₆ H ₅	D	87	230-239.5	C ₂₉ H ₂₇ N·HCl	1	1
27	H	H	H	<i>p</i> -C ₆ H ₄ CF ₃	D	88	180.5-182.5	C ₂₄ H ₂₂ F ₃ N·HCl	0	
28	H	H	H	<i>p</i> -C ₆ H ₄ CH ₃	C	88	225-228.5	C ₂₄ H ₂₅ N·HCl·0.25H ₂ O	0	
29	H	CH ₃ O	H	<i>p</i> -C ₆ H ₄ OH	D	94	238-242 dec	C ₂₄ H ₂₅ NO ₂ ·HCl	0	
30	H	CH ₃ O	H	<i>p</i> -C ₆ H ₄ OCH ₂ CH ₂ - 	F	35	220-225	C ₃₀ H ₃₆ N ₂ O ₂ ·2HBr	3	NP
										
31	H	H	H	OH	D	35	270-276	C ₂₃ H ₂₃ NO·HCl	0	
32	H	H	H	OCH ₃	D	85	177.5-179.5	C ₂₄ H ₂₅ NO·HCl	0	
33	H	H	H	NO ₂	C	22	108.5-114	C ₂₃ H ₂₂ N ₂ O ₂ ·HCl· <i>i</i> -C ₃ H ₇ OH	0	

34	H	H	H	OCH ₂ CH ₂ -N 	F	62	174-184	C ₂₉ H ₃₄ N ₂ O·2HCl·0.25H ₂ O	0	
35	H	OH	H	H	D	40	230-237.5	C ₂₃ H ₂₃ NO·HCl·0.5H ₂ O ^h	0	
36	H	OCH ₃	H	H	D	69	233-236 dec	C ₂₄ H ₂₅ NO·HCl	0	
37	H	H	OH	H	D	28	226-238	C ₂₃ H ₂₃ NO·HCl	0	
38	H	H	OCH ₃	H	D	52	211.5-218.5	C ₂₄ H ₂₅ NO·HCl	0	
39	CH ₃	H	H	H	D	58	206-217	C ₂₄ H ₂₅ N·HCl	5	5
40	C ₆ H ₅	H	H	H	D	63 ⁱ	205-222	C ₂₉ H ₂₇ N·HCl·0.25H ₂ O	0	
41	C ₂ H ₅	H	H	H	D	83	204-212	C ₂₅ H ₂₇ N·HCl·0.25H ₂ O	5	5
42	OH	H	H	H	H	60	243-245 dec	C ₂₃ H ₂₃ NO·HCl	1	3
43	OH	H	H	H	H	22	214-219	C ₂₃ H ₂₃ NO·HCl	3	3
44	OCH ₂ CH ₂ -N 	H	H	H	F ^{j,k}	22	97-143	C ₂₉ H ₃₄ N ₂ O·2HCl	0	
										
45	C ₆ H ₅	CH ₂ C ₆ H ₅	H	H	C	43	207-209	C ₂₂ H ₂₁ N·HCl·0.5C ₂ H ₅ OH	0	
46	C ₆ H ₅	(CH ₂) ₃ C ₆ H ₅	H	H	C	52	178-181	C ₂₄ H ₂₅ N·HCl	3	1
47	C ₆ H ₅	(CH ₂) ₄ C ₆ H ₅	H	H	D	85	207-209	C ₂₅ H ₂₇ N·HCl	1	1
48	C ₆ H ₅	CH ₂ CH ₂ OC ₆ H ₅	H	H	C	73	219-223	C ₂₃ H ₂₃ NO·HCl	2	2
49	C ₆ H ₅	(CH ₂) ₃ OC ₆ H ₅	H	H	C	52	222-227	C ₂₄ H ₂₅ NO·HCl	0	
50	<i>p</i> -C ₆ H ₄ Cl	(CH ₂) ₃ C ₆ H ₅	H	H	C	16	186-190	C ₂₄ H ₂₄ ClN·HCl	0	
51	C ₆ H ₅	CH ₂ CH ₂ C(CH ₃) ₃	H	H	D	58	239-248	C ₂₁ H ₂₇ N·HCl	1	3
52	C ₆ H ₅	CH ₂ CH ₂ - 	H	H	D	87	213-215.5	C ₂₂ H ₂₇ N·HCl	0	
53	C ₆ H ₅	CH ₂ CH=CHC ₆ H ₅	H	H	C	53	110-112.5	C ₂₄ H ₂₃ N	0	
54	C ₆ H ₅	COCH ₂ C ₆ H ₅	H	H	D	94	119.5-123.5	C ₂₃ H ₂₁ NO	0	
55	C ₆ H ₅	CH ₂ COC ₆ H ₅	H	H	G	37	121-123	C ₂₃ H ₂₁ NO	1	1
56	C ₆ H ₅	CH ₂ CH ₂ C ₆ H ₅	CH ₃	H	D	82	241-250	C ₂₄ H ₂₅ N·HCl	2	1
57	C ₆ H ₅	CH ₂ CHNH ₂ CH ₂ C ₆ H ₅	H	H	D ^l	16	231-239	C ₂₄ H ₂₆ N ₂ ·2HCl·0.5C ₂ H ₅ OH	0	
58	C ₆ H ₅ CH ₂	CH ₂ CH ₂ C ₆ H ₅	H	H	C ^m	28	193.5-196	C ₂₄ H ₂₅ N·HCl·0.25C ₂ H ₅ OH	0	
59	C ₆ H ₅	CH ₂ CH ₂ NHC ₆ H ₅	H	H	D, ⁿ	30	210.5-218.5 dec	C ₂₃ H ₂₄ N ₂ ·2HCl·0.25H ₂ O	0	
60	C ₆ H ₅	(CH ₂) ₃ C ₆ H ₅	H	CH ₃ O	C	77	175-176	C ₂₅ H ₂₇ NO·HCl	3	1
61	<i>p</i> -C ₆ H ₄ OCH ₂ CH ₂ -N 	CH ₂ CHCH ₃ C ₆ H ₅	H	CH ₃ O	D, ^k	80	51-59 dec	C ₃₁ H ₃₈ N ₂ O ₂ ·2HCl	5	NP
62	<i>p</i> -C ₆ H ₄ OCH ₂ CH ₂ -N 	CH ₂ CHCH ₃ C ₆ H ₅	H	H	D, ^k	68	91-145	C ₃₀ H ₃₆ N ₂ O·2HCl	6	NP
63	<i>p</i> -ClC ₆ H ₄	CH ₂ CH ₂ C ₆ H ₅	H	CH ₃ O	D	86	231-235	C ₂₄ H ₂₆ ClNO·HCl	3	3
64	<i>p</i> -C ₆ H ₄ OCH ₂ CH ₂ -N 	CH ₂ CH ₂ C ₆ H ₅	H	H	D, ^k	81	81-113	C ₂₉ H ₃₄ N ₂ O·2HCl	4	NP

^aRecrystallization solvents generally EtOH-HCl gas or MeOH-HCl gas. ^bAnalyses 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. ^cAntifertility rank is defined as potency relative to estrone whose ED₁₀₀ = 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. ^dEstrogen 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. ^ePrepared from the (-)-1-phenyl-1,2,3,4-tetrahydroisoquinoline which is (+) as the hydrochloride. **2** has [α]²⁵_D +123 ± 0.5° (c 6, EtOH). ^f[α]²⁵_D -134.5 ± 1.2° (c 2.6, EtOH). ^gOne spot on tlc. ^hCl: calcd, 9.46; found, 9.93. ⁱThe BH₃-THF reduction took 7 hr instead of the usual 1 hr. ^jCarried out on isomer **42**. ^kThe 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. ^lPrepared using carbobenzyoxy-(±)-phenylalanine as the acid portion. Since the carbobenzyoxy group was not removed using BH₃-THF an extra step using HBr gas-HOAc was used. ^m1-Benzyl-1,2,3,4-tetrahydroisoquinoline from Aldrich Chem. ⁿPrepared using *N*-carbobenzyoxy-*N*-phenylglycine (see *l*).

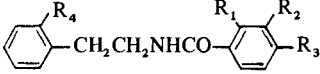
Table II. Intermediates for Table I. N-Unsubstituted 1,2,3,4-Tetrahydroquinolines



No.	R ₁	R ₂	R ₃	R ₄	R ₅	Proce- dure or lit. ref	Yield, ^a %	Mp, °C	Formula ^b	Starting ^c material
65	(±) H	H	H	H	C ₆ H ₅	7				
66	(-) N	H	H	H	C ₆ H ₆	5				
67	(+) H	H	H	H	C ₆ H ₅	5				
68	CH ₃ O	CH ₃ O	H	H	C ₆ H ₅	A	75	263-265	C ₁₇ H ₁₉ NO ₂ ·HCl	
69	CH ₃ O	CH ₃ O	H	H	<i>p</i> -C ₆ H ₄ OCH ₃	A	68	265-267 ^d	C ₁₈ H ₂₁ NO ₃ ·HCl	
70	CH ₃ O	CH ₃ O	H	H	<i>o</i> -C ₆ H ₄ Cl	A	89	218 ^e	C ₁₇ H ₁₈ ClNO ₂ ·HCl ^f	
71	HO	HO	H	H	C ₆ H ₅	A	11	140-156, 240-246	C ₁₅ H ₁₅ NO ₂ ·HCl·C ₂ H ₅ OH	
72	NO ₂	H	H	H	C ₆ H ₅	I	58	251-254	C ₁₅ H ₁₄ N ₂ O ₂ ·HCl	Ref 3
73	Cl	H	H	H	C ₆ H ₅	B	33	274-277	C ₁₅ H ₁₄ ClN·HCl ^g	Ref 9
74	CH ₃ O	H	H	H	C ₆ H ₅	B	44	280-283	C ₁₆ H ₁₇ NO·HCl	Ref 10
75	CH ₃	H	H	H	C ₆ H ₅	B	76	261-268	C ₁₆ H ₁₇ N·HCl·0.25CH ₃ OH	Ref 11
76	H	CH ₃ O	H	H	C ₆ H ₅	A	82	277-279	C ₁₆ H ₁₇ NO·HCl	
77	H	H	CH ₃ O	H	C ₆ H ₅	B	20	291.5-294.5	C ₁₆ H ₁₇ NO·HCl·0.25CH ₃ OH	90
78	H	H	H	H	<i>o</i> -C ₆ H ₄ Cl	B	68	244.5-249	C ₁₅ H ₁₄ ClN·HCl	91
79	H	H	H	H	<i>m</i> -C ₆ H ₄ Cl	B	90	127 dec	C ₁₅ H ₁₄ ClN·HCl·0.25Et ₂ O	92
80	H	H	H	H	<i>p</i> -C ₆ H ₄ Cl	B	88	233-236	C ₁₅ H ₁₄ ClN·HCl	Ref 12
81	H	H	H	H	<i>p</i> -C ₆ H ₄ F	B	80	252-258	C ₁₅ H ₁₄ FN·HCl	93
82	H	H	H	H	<i>p</i> -C ₆ H ₄ OCH ₃	B	43	244-250	C ₁₆ H ₁₇ NO·HCl ^h	94
83	H	H	H	H	<i>p</i> -C ₆ H ₄ SO ₂ CH ₃	B	86	325-330 dec ⁱ	C ₁₆ H ₁₇ ClNO ₂ S·HCl	95
84	H	H	H	H	<i>p</i> -C ₆ H ₄ -C ₆ H ₅	B	27	122-124.5 ^j	C ₂₁ H ₁₉ N·0.125C ₂ H ₅ OH	96
85	H	H	H	H	<i>p</i> -C ₆ H ₄ CF ₃	B	19	315-317	C ₁₆ H ₁₄ F ₃ N·HCl ^k	97
86	H	H	H	H	<i>p</i> -C ₆ H ₄ CH ₃	B	78	282-286	C ₁₆ H ₁₇ N·HCl	98
87	H	CH ₃ O	H	H	<i>p</i> -C ₆ H ₄ OH	A	51	266-270	C ₁₆ H ₁₇ NO ₂ ·HCl·0.25CH ₃ OH	
88	H	H	H	CH ₃	C ₆ H ₅	B	23	265-266 ^l	C ₁₆ H ₁₇ N·HCl·0.25C ₂ H ₅ OH	Ref 14
89	H	CH ₃ O	H	H	<i>p</i> -C ₆ H ₄ Cl	A	85	279-282	C ₁₆ H ₁₆ ClNO·HCl	

^aSamples were recrystallized from EtOH-HCl gas or MeOH-HCl gas. ^bAnalyses 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. ^cIf not commercially available. ^dWeinbach and Hartung⁸ describe this product as having mp 151-152°. The structure of 69 was confirmed by nmr. ^eWeinbach and Hartung⁸ give mp 210-212°. ^fC: calcd, 60.01; found, 59.39. ^gCl: calcd, 25.31; found, 24.82. ^hH: calcd, 6.58; found, 7.08. ⁱRecrystallized from 1 N HCl. ^jRecrystallized from C₆H₆-petroleum ether. The solvation came from the NaBH₄-EtOH reduction. ^kH: calcd, 4.82; found, 5.44. ^lLit.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 ₂ CH ₃	H	MeOH	80	186-187	C ₁₆ H ₁₇ NO ₃ S
96	H	H	C ₆ H 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 ₃ NO
98	H	H	CH ₃	H	EtOAc-petr ether	91	78-79	C ₁₆ H ₁₇ NO

^aSynthesized by procedure D without the NaBH₄ reduction. ^bAnalyses 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 uterotrophic 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 uterotrophic 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 uterotrophic 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 uterotrophic 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 uterotrophic activity, *per se*, *i.e.*, the doses of 1 and 4 $\mu\text{g}/\text{rat}$ per day (20 and 80 $\mu\text{g}/\text{kg}$ per day) in the uterotrophic assay bracket the antifertility ED₁₀₀ (50 $\mu\text{g}/\text{kg}$ per day). Therefore, even with such compounds, antifertility and estrogenicity were apparently inseparable.

Substances that are estrogenic are frequently hypocholeremic 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)ethylamine¹⁷ and 4.77 g (45.0 mmoles) of benzaldehyde in 100 ml of C₆H₆ 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 Na₂CO₃. The combined organic layers (400 ml) from three Et₂O extns were dried (Na₂SO₄) 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-

Table IV. Estrogenic and Antiestrogenic Effects in Immature Female Rats

Group	No. rats	$\mu\text{g}/\text{rat}$ per day $\times 3$		Uterine weight ratio (treated/control)
		Estrone	62	
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
	10	3.3	12.0	2.70
D	10	3.3	37.0	2.20
	10	3.3	111.0	2.05

^aApproximate antifertility dose.

tetrahydroisoquinoline-HCl, 76, mp 277–279°. *Anal.* (C₁₆H₁₈ClNO) 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 P₂O₅ 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 alkalized with concd aqueous KOH. (NaOH gave a heavy salt ppt.) The oily dihydroisoquinoline was extd into C₆H₆ and the aqueous phase extd twice more with Et₂O. The combined exts were dried (Na₂SO₄) 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 NaBH₄ was added. After standing at room temp overnight, the soln was refluxed for 1 hr then concd under vacuum. The residue was dil with 200 ml of water and extd 3 times with Et₂O. The combined organic ext was dried (Na₂SO₄) 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.* (C₁₅H₁₅Cl₂N) 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 Et₂O, 80 ml of water, and 20 ml of concd NH₄OH, the aqueous layer was extd twice more with Et₂O. The combined ethereal exts were dried (Na₂SO₄) and concd under vacuum to the cryst free base, [α]²⁵_D –40.8 ± 0.3° (*c* 5.3, Et₂O), lit.⁵ [α]²⁵_D –43.4° (*c* 6, Et₂O). The base was dissolved in 35 ml of EtOH and added to 1.06 g (10.0 mmoles) of anhyd Na₂CO₃ 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 Et₂O and dil aqueous NaHCO₃. The Et₂O ext was dried (Na₂SO₄) 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)—Et₂O, 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°, [α]²⁵_D –134.5 ± 1.2° (*c* 2.6, ethanol), whose *ir* was similar to that of the (±) material. *Anal.* (C₂₃H₂₄ClN) 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 CHCl₃, 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 (Na₂SO₄) and evapn gave a residual crude oily amide which was dissolved in 100 ml of THF and added dropwise, under N₂, to 30 ml (30 mmoles) of 1 *N* BH₃-THF⁴ 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 alkalized with aqueous KOH and extd with Et₂O. Drying the Et₂O soln (Na₂SO₄) and saturating it with HCl (g) gave an oil which crystd on titration with 10 ml of EtOH. The 7.46 g of white solid, mp 224–

[‡]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.* (C₂₄H₂₆ClNO₂S·0.25H₂O) 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 NaHCO₃ and extd 3 times with 1:1 Et₂O-*n*-BuOH. After the organic ext had been evapd to dryness, the residue was crystd from EtOH-HCl (g)-Et₂O 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.* (C₂₃H₂₄ClNO) 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 NaHCO₃. Next the organic phase was extd with 1 *N* HCl, the ext basified with NaOH, and the resulting oil extd with CHCl₃. After drying (Na₂SO₄), the CHCl₃ 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 Et₂O which gave an oily ppt. The supernatant was decanted and the residue triturated with Et₂O. After standing in Et₂O 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.* (C₃₀H₃₈Br₂N₂O₂) 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 CHCl₃ and NH₄OH, then drying (Na₂SO₄), and concentration under vacuum. After dissolving the cryst free base in 50 ml of THF, it was placed under N₂ and 9.25 ml (0.020 mole) of 2.16 *M* methylolithium in Et₂O 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 tic 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 NaHCO₃. After sepn, the organic layer was dried (Na₂SO₄) 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.* (C₂₃H₂₁NO) 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 NaBH₄ 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 NaBH₄ was decompd with 6 *N* HCl and neutralized with KHCO₃, and the mixt concd under vacuum. The residue was leached with Et₂O 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 Et₂O. Cooling gave 6.62 g (60%) of cryst alcohol 42, mp 243–245° dec. A sample was recrystd for analysis from MeOH-HCl (g)-Et₂O giving mp 243.5–248°. *Anal.* (C₂₃H₂₃NO·HCl) C, H, Cl, N.

The combined mother liquors were concd and recrystd twice from MeOH-HCl (g)-Et₂O to give 2.37 g of 43, mp 214–219°. An nmr confirmed the diastereomeric relationship of 42 and 43. *Anal.* (C₂₃H₂₃NO·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-dihydroisoquinoline³ in 100 ml of concd HNO₃ was cooled to 0°, 200 ml

of fuming HNO₃ 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 CHCl₃ and 60 ml of 17 *N* NH₄OH. The organic phase was washed with water, dried (Na₂SO₄), 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.* (C₁₅H₁₇N₂O₂) 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. McCoubrey¹⁸ 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-HNO₃, 1-phenyl-7-nitro-3,4-dihydroisoquinolinium nitrate (100) was obtained, mp 173° dec. *Anal.* (C₁₅H₁₇N₂O₂·HNO₃) 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 NaBH₄ added. After stirring overnight, the soln was concd under vacuum, dild with water, and extd into Et₂O. Upon drying (Na₂SO₄), 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 CHCl₃ 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.* (C₁₅H₁₄N₂O₂·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 Et₂O 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 Et₂O until it was colorless. Then the aqueous portion was acidified (HCl) and extd with Et₂O. After washing the Et₂O with brine, it was dried (Na₂SO₄) and concd under vacuum to an oil which crystd from CHCl₃-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.* (C₁₆H₁₅NO₄·H₂O) C, H, N

Acknowledgments. We thank Mr. L. Brancone and group for the analysis and Mr. W. Fulmor and group for the spectra.

References

- (1) D. Lednicer, "Contraception: The Chemical Control of Fertility," M. Dekker, Inc., New York, N. Y., 1969, p 197.
- (2) W. M. Whaley and T. R. Govindachari, *Org. React.*, 6, 151 (1951).
- (3) J. G. Cannon and G. L. Webster, *J. Amer. Pharm. Ass. Sci. Ed.*, 47, 353 (1958).
- (4) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, 86, 3566 (1964).
- (5) W. Leithe, *Monatsh. Chem.*, 53–54, 956 (1929).
- (6) W. V. Curran and R. B. Angier, *J. Org. Chem.*, 31, 3867 (1966).
- (7) C. I. Brodrick and W. F. Short, *J. Chem. Soc.*, 2587 (1949).
- (8) E. C. Weinbach and W. H. Hartung, *J. Org. Chem.*, 15, 676 (1950).
- (9) J. S. Buck, *J. Amer. Chem. Soc.*, 55, 2593 (1933).
- (10) R. Holbein and R. Perrot, *Ann. Sci. Univ. Besancon, Chim.*, 2, 13 (1956); *Chem. Abstr.*, 53, 6120i (1959).
- (11) J. Pritzkow, H. Schaefer, P. Pabst, A. Ebenroth, and J. Beger, *J. Prakt. Chem.*, 29, 123 (1965).
- (12) A. McCoubrey, *J. Chem. Soc.*, 1833 (1950).
- (13) B. B. Dey and V. S. Ramanathan, *Proc. Nat. Inst. Sci. India*, 9, 193 (1943); *Chem. Abstr.*, 43, 5025i (1949).
- (14) P. L. Couturier, *Ann. Chim. (Paris)*, 10, 559 (1938).
- (15) D. Lednicer, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, 10, 78 (1967).
- (16) C. W. Emmens, *Brit. Med. Bull.*, 26, 45 (1970).
- (17) R. Grewe, E. Nolte, and R.-H. Rotzell, *Chem. Ber.*, 89, 600 (1956).
- (18) A. McCoubrey and D. W. Mathieson, *J. Chem. Soc.*, 696 (1949).

**We thank Mr. J. E. Lancaster of our Stamford labs for this experiment.