stirred at room temperature for 1 hr. The solution was poured into dilute HCl, NaCl was added, and the precipitate was filtered, washed, dried, and recrystallized.

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Synthetic Estrogens, Implantation Inhibitors, and Hypocholesterolemic Agents. I. Tetrahydronaphthalene Series[1]

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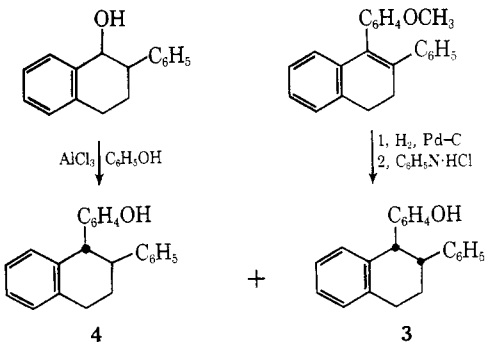
The stereochemistry of 1,2-diaryl-substituted tetrahydronaphthalene derivatives has been studied. Basic phenolic ethers and phenoxyacetic acid derivatives have been prepared in this series to achieve separation of estrogenic, antifertility, and hypocholesterolemic activities. Only partial separation of these biological features has been attained.

Several years ago a number of 3-pyridyl substituted dihydro- and tetrahydronaphthalene derivatives prepared in our laboratories were shown to inhibit the 11β- or the 17-hydroxylase enzyme systems in the biosynthesis of adrenal cortical and gonadal steroid hormones.[2]

The present report deals with the synthesis, stereochemistry, and endocrine-screening results of a number of tetrahydronaphthalene derivatives.

Chemistry.—Catalytic reduction of 1,2-disubstituted 3,4-dihydronaphthalenes resulted in tetrahydronaphthalene derivatives in which the substituents on the carbon atoms 1 and 2 are in the *cis* configuration. However, Friedel–Crafts-type alkylation of phenol by means of the carbonium ion produced by the action of a Lewis acid on 1-hydroxy-2-substituted 1,2,3,4-tetrahydronaphthalene afforded a mixture of *para*-alkylated phenols from which both the *cis* and *trans* isomers of 1,2-disubstituted tetrahydronaphthalenes could be isolated.



4 3

Thus, when 1-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalene was used to alkylate phenol, the *cis* and *trans* products (**3** and **4**) could readily be isolated by fractional crystallization. The *cis* isomer (**3**) was identical with the product obtained by demethylation of **5** (see Table I) which, in turn, was prepared by catalytic hydrogenation of the corresponding 3,4-dihydronaphthalene derivative.[3] A further proof of structure for the *cis* isomer **3** was accomplished by reductive elimination of the phenolic hydroxy group *via* the phosphate ester **7** to afford the *cis* hydrocarbon **1**, which was found to be identical with 1,2-diphenyl-1,2,-3,4-tetrahydronaphthalene prepared according to the procedure of Bergmann, *et al.*[4]

Isolation of the *cis* isomer of phenol **11** from the Friedel–Crafts alkylation reaction mixture by crystallization was unsuccessful. However, subsequent to removal of most of the *trans* isomer **12** by crystallization, the residual mixture was methylated, and the phenolic methyl ethers **13** and **14** could be separated by fractional crystallization from 2-propanol. Again **13** was found to be identical with the product of catalytic hydrogenation of the corresponding 3,4-dihydronaphthalene derivative.

The most convincing evidence for the correct stereochemical assignment of the *cis* and *trans* configurations of the 1,2-disubstituted 1,2,3,4-tetrahydronaphthalene isomers was furnished by the nmr spectra of the pure compounds.

Figure 1 illustrates the four possible conformations of the tetrahydronaphthalene derivative assuming that the alicyclic ring is in the pseudo-chair form. The *trans* form, in which the two substituents are in the equatorial positions is depicted as structure A. Flipping the bulky aromatic substituents in axial positions would result in the *thermodynamically less stable* conformation B. In the stable *trans* form A the vicinal tertiary hydrogen atoms on carbons 1 and 2 are located *trans* to each other and would be expected to show a large coupling constant in their nmr doublet signal. Indeed, $J_{1,2}$ for the C_1 hydrogen signal was found to be approximately 10 cps, which confirms the *trans* diaxial relationship of the $C_{1,2}$ hydrogen atoms. Whereas nmr clearly establishes conformation A for the *trans* isomer, the coupling constant $J_{1,2} = 5$ cps for the *cis* isomer cannot distinguish between the two conformations C and D.

(1) A communication concerning the synthesis and antifertility activity of compounds **15** and **16** described in this paper has been published: W. L. Bencze, R. W. J. Carney, L. I. Barsky, A. A. Renzi, L. Dorfman, and G. deStevens, *Experientia*, **21**, 261 (1965).

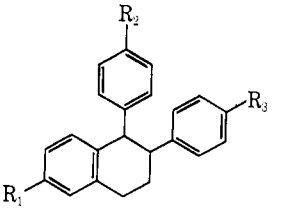
(2) W. L. Bencze and L. I. Barsky, *J. Med. Pharm. Chem.*, **5**, 1298 (1962).

(3) W. L. Bencze, L. I. Barsky, W. P. Sopchak, A. A. Renzi, N. Howie, and J. J. Chart, *ibid.*, **8**, 213 (1965).

(4) F. Bergmann, H. E. Eschinazi, and D. Schapiro, *J. Am. Chem. Soc.*, **64**, 357 (1942).

TABLE I

cis AND *trans* ISOMERS OF 1,2-DIPHENYL-1,2,3,4-TETRAHYDRONAPHTHALENE AND DERIVATIVES



No.	Isomer	R_1	R_2	R_3	Procedure	Yield, %	Bp (mm) or mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1	*cis*	H	H	H	G	61	96–97	$C_{22}H_{20}$	92.91	7.09	92.66	7.31
2	*trans*	H	H	H	G	67	61–62	$C_{22}H_{20}$	92.91	7.09	93.16	7.10
3	*cis*	H	OH	H	B	63	142–143	$C_{22}H_{20}O$	87.96	6.71	88.25	6.89
4	*trans*	H	OH	H	A	44	93–95	$C_{22}H_{20}O$	87.96	6.71	87.87	6.88
5	*cis*	H	OCH_3	H	C	78	87–89	$C_{23}H_{22}O$	87.86	7.05	87.74	6.96
6	*trans*	H	OCH_3	H	D	61	72–73	$C_{23}H_{22}O$	87.86	7.05	87.73	7.08
7	*cis*	H	$OPO(OC_2H_5)_2$	H	F	93	*a*	$C_{26}H_{29}O_4P$	71.55	6.71	71.81	6.80
8	*trans*	H	$OPO(OC_2H_5)_2$	H	F	83	*a*	$C_{26}H_{29}O_4P$	71.55	6.71	71.44	6.96
9	*cis*	H	$OCH_2CH_2N(C_2H_5)_2$	H	E	55	140 (0.6)	$C_{28}H_{33}NO$	84.16	8.33	84.21	8.44
10	*trans*	H	$OCH_2CH_2N(C_2H_5)_2$	H	E	39	59–61	$C_{28}H_{33}NO$	84.16	8.33	84.34	8.62
11	*cis*	H	OH	Cl	B	80	157–159	$C_{22}H_{19}ClO$	78.92	5.72	79.25	5.64
12	*trans*	H	OH	Cl	A	59	144–145	$C_{22}H_{19}ClO$	78.92	5.72	78.69	5.81
13	*cis*	H	OCH_3	Cl	C	64	108–110	$C_{23}H_{21}ClO$	79.17	6.07	79.09	6.03
14	*trans*	H	OCH_3	Cl	D	70	140–141	$C_{23}H_{21}ClO$	79.17	6.07	79.40	6.19
15	*cis*	H	$OCH_2CH_2N(C_2H_5)_2 \cdot HBr$	Cl	E	22	178–179	$C_{28}H_{33}BrClNO$	65.30	6.26	65.01	6.47
16	*trans*	H	$OCH_2CH_2N(C_2H_5)_2 \cdot HBr$	Cl	E	55	169–170	$C_{28}H_{33}BrClNO$	65.30	6.26	65.21	6.47
17	*cis*	OCH_3	OH	H	A	8	188–189	$C_{23}H_{22}O_2$	83.60	6.71	83.59	7.00
18	*trans*	OCH_3	OH	H	A	21	215 (0.2)	$C_{23}H_{22}O_2$	83.60	6.71	83.66	6.70
19	*cis*	OCH_3	$OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	H	E	21	183–185	$C_{29}H_{36}ClNO_2$	74.75	7.80	75.23	8.10
20	*trans*	OCH_3	$OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	H	E	47	172–174	$C_{29}H_{36}ClNO_2$	74.75	7.80	75.18	7.76
21	*cis*	H	OCH_2COOH	H	H	79	135–136	$C_{24}H_{22}O_3$	80.42	6.19	80.61	6.21
22	*trans*	H	OCH_2COOH	H	H	75	124–126	$C_{24}H_{22}O_3$	80.42	6.19	80.49	6.21
23	*cis*	H	$OC(CH_3)_2COOH$	H	I	79	160–162	$C_{26}H_{26}O_3$	80.80	6.78	80.97	6.98
24	*trans*	H	$OC(CH_3)_2COOH$	H	I	80	136–137	$C_{26}H_{26}O_3$	80.80	6.78	80.96	6.83

[a] Oil, purified by chromatography.

Preparation of the various derivatives as listed in Tables I–III was accomplished by modifications of known synthetic procedures.

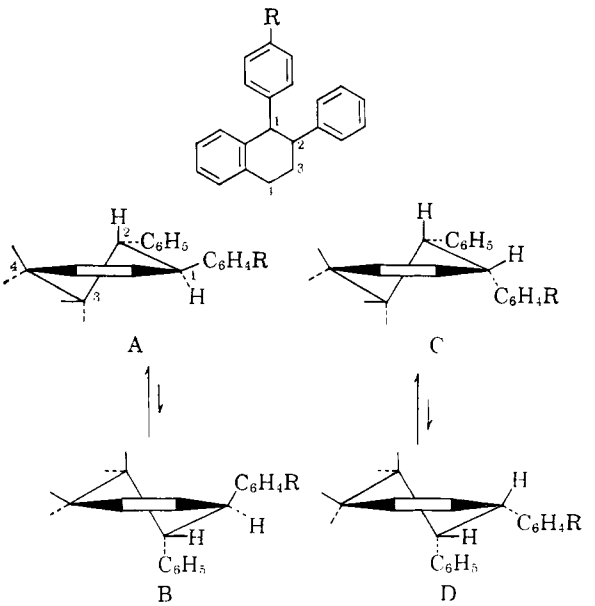
Pharmacological Procedures

Uterotrophic Activity.—The compounds were placed in suspension with carboxymethylcellulose or polyethylene glycol and given by subcutaneous injection for 3 days to immature female rats of the CIBA strain, weighing 35–40 g. On the fourth day the animals were sacrificed; the uteri were removed, expressed of fluid, cleaned of adhering tissue, and immediately weighed. The uterotrophic activity thus determined was compared with that obtained by subcutaneous administration of 2.0 μg/kg of estradiol for 3 days.

Antiestrogenic Activity.—Tests were performed with compounds that possessed uterotrophic activity, by giving them subcutaneously in a variant dose range of 0.25–50 mg/kg concomitantly with 2 or 10 μg/kg of estradiol to immature female rats for 3 days. A compound was designated to be antiestrogenic when the uterine weight of rats receiving the combination treatment was less than that observed with estradiol treatment alone.

Antifertility Activity.—The substances were administered orally at a dose of 1 mg/kg to adult female rats weighing 180–200 g, beginning on day 1 postmating and continued for 4 consecutive days. On the 14th day the rats were sacrificed and the number of fetuses or implantation sites in both uterine horns were counted. A compound was considered to offer 100% protection if no implantation sites were noted. Whenever this was the case the lowest "effective" dose was established.

Hypocholesterolemic Activity.—Male rats weighing 125–150 g were given various oral doses of 1–50 mg/kg for 7 days. Blood samples were taken from the orbital sinus or by decapitation at the termination of treatment.

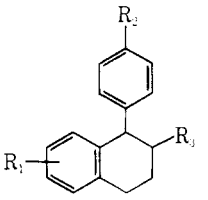


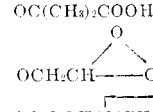
R	*trans* form: Center of C_1 doublet, cps	*trans* form: $J_{1,2}$, cps	*cis* form: Center of C_1 doublet, cps	*cis* form: $J_{1,2}$, cps
H	252	10	262	5
OH	247	10	256	5
OCH_3	246	10	258	5
$OCH_2CH_2N(C_2H_5)_2$	248	10	257	5

Figure 1.—Conformation of 1,2-diphenyl-1,2,3,4-tetrahydronaphthalene and derivatives.

TABLE II

DERIVATIVES OF 1,2-DIPHENYL-1,2,3,4-TETRAHYDRONAPHTHALENE



No.	R_1	R_2	R_3	Procedure	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
25	H	$OCH_2CH_2N(CH_2)_3CH_2 \cdot HCl$	C_6H_5	E	39	198–199	$C_{25}H_{26}ClNO$	77.49	7.43	77.44	7.54
26	H	OCH_2COOH	4-ClC_6H_4	H	66	175–176	$C_{24}H_{21}ClO_3$	73.37	5.38	73.31	5.42
27	H	$OCH_2COOC_2H_5$	4-ClC_6H_4	J	76	102–103	$C_{26}H_{25}ClO_3$	74.19	5.98	74.03	5.84
28	H	OCH_2CONH_2	4-ClC_6H_4	K	61	119–120	$C_{24}H_{22}ClNO_2$	73.55	5.65	73.42	5.81
29	H	$OCH_2CH_2NH_2 \cdot C_6H_8O_7 \cdot H_2O$	4-ClC_6H_4	L	53	[a]	$C_{30}H_{34}ClNO_9$	61.27	5.83	61.62	6.02
30	H	$OCH_2CONHCH_2CH_3$	4-ClC_6H_4	K	59	105–107	$C_{26}H_{26}ClNO_2$	74.36	6.24	74.43	6.31
31	H	$OCH_2CH_2NHCH_2CH_3 \cdot HCl$	4-ClC_6H_4	L	33	187–189	$C_{26}H_{27}Cl_2NO$	70.75	6.41	70.79	6.65
32	H	$OCH_2CONHCH_2CH_2N(C_2H_5)_2$	4-ClC_6H_4	K	63	[b]	$C_{30}H_{36}ClN_2O_2$	73.38	7.18	73.85	7.28
33	H	$OCH_2CONHCH_2CH_2CH_2N(C_2H_5)_2 \cdot C_6H_8O_7 \cdot H_2O$	4-ClC_6H_4	K	70	[a]	$C_{36}H_{47}ClN_2O_9$	62.12	6.63	62.60	6.75
34	H	$OC(CH_3)_2COOH$	4-ClC_6H_4	I	54	130–132	$C_{26}H_{25}ClO_3$	74.19	5.98	74.13	6.14
35	H		4-ClC_6H_4	M	25	96–98	$C_{26}H_{23}ClO_2$	76.81	5.92	76.84	5.77
36	H	$OCH_2CH_2N(CH_2)_3CH_2$	4-ClC_6H_4	E	22	96–97	$C_{25}H_{26}ClNO$	77.85	7.00	78.04	7.07
37	H	$OCH_2CH_2N^+CH_3(C_2H_5)_2I^-$	4-ClC_6H_4	N	85	199–200	$C_{28}H_{33}ClINO$	60.47	6.13	60.70	6.20
38	H	OH	2-FC_6H_4	A	57	120–121	$C_{22}H_{19}FO$	82.99	6.01	82.49	6.26
39	H	OCH_2COOH	2-FC_6H_4	H	82	133–136	$C_{24}H_{21}FO_3$	76.78	5.62	76.88	5.74
40	H	$OCH_2CH_2N(C_2H_5)_2 \cdot C_6H_8O_7$	2-FC_6H_4	E	89	100–102	$C_{34}H_{40}FNO_8$	66.97	6.61	67.07	6.70
41	H	OH	4-$CH_3OC_6H_4$	A	23	154–156	$C_{23}H_{22}O_2$	83.60	6.71	83.87	6.79
42	H	OCH_2COOH	4-$CH_3OC_6H_4$	H	35	158–160	$C_{25}H_{24}O_4$	77.30	6.23	77.30	6.27
43	H	$OCH_2CH_2N(C_2H_5)_2 \cdot C_6H_8O_7 \cdot H_2O$	4-$CH_3OC_6H_4$	E	37	108–111	$C_{35}H_{45}NO_{10}$	65.70	7.09	65.99	7.13
44	H	$OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	4,5-$Cl_2C_6H_3$	E	50	158–160	$C_{28}H_{32}Cl_3NO$	66.59	6.39	66.31	6.44
45	6-OCH_3	H	C_6H_5	C	86	168–170	$C_{23}H_{22}O$	87.86	7.05	88.07	7.07
46	6-OH	H	C_6H_5	B	90	188–189	$C_{22}H_{20}O$	87.96	6.71	88.33	6.70
47	6-OCH_2COOH	H	C_6H_5	H	27	208–210	$C_{24}H_{22}O_3$	80.42	6.19	80.26	6.17
48	6-OCH_3	$OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	4-ClC_6H_4	E	26	217–219	$C_{29}H_{34}Cl_2NO_2$	69.59	7.05	69.47	7.06
49	7-CH_3	$OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	C_6H_5	E	69	110–112	$C_{29}H_{36}ClNO$	77.38	8.06	77.01	7.93
50	7-Cl	$OCH_2CH_2N(C_2H_5)_2 \cdot C_6H_8O_7$	C_6H_5	E	54	98–101	$C_{34}H_{42}ClNO_8$	65.22	6.44	65.08	6.74
51	7-Cl	OCH_2COOH	C_6H_5	H	31	120–123	$C_{24}H_{21}ClO_3$	73.36	5.39	73.67	5.52

[a] Amorphous. [b] Oil, purified by chromatography.

Results and Discussion

In general, the *trans* isomers of the phenols and their methyl ethers were more potent uterotrophic substances than their corresponding *cis* isomers. Thus, compounds **12** and **14** elicited marked uterine stimulation at a dose of 40 μg/kg (2 μg/rat), while the corresponding *cis* isomers **11** and **13** were less active. The basic ethers, especially **16**, **19**, and **20**, also showed marked uterotrophic activity, though the dose–response curve was rather flat when compared with the phenols. This lack of dose–response relationship sharply distinguishes the basic ether **16** from the natural estrogens. There was little quantitative distinction in the uterine weight increase between doses of 40–5000 μg/kg.[5]

Surprisingly, the known[4] hydrocarbon **1** was found to be a very potent uterotrophic substance in this series. It produced moderate uterotrophic response at a dose as low as 8 μg/kg. In view of the theory advanced by Emmens,[6] namely, that aromatic hydrocarbons must be hydroxylated by hepatic enzymes before they can elicit estrogenic activity, it is intriguing that this particular "proestrogen" **1** should be more active than its hydroxylated derivatives **3** or **46**.

The *trans* hydrocarbon **2** was found to be less active (100 μg/kg) as an estrogen than the *cis* isomer **1** (8 μg/kg). There was practically no difference in the uterotrophic response elicited by the *cis* and *trans* isomers of the diethyl phenyl phosphates **7** and **8**. Both of these "conjugated" estrogens caused marked uterine growth at 100 μg/kg. Phenols **38**, **52**, and the basic ether **43** were also found to be potent estrogens at a dose of 100 μg/kg.

An almost complete loss of uterotrophic activity resulted when phenols **3**, **4**, **12**, **41**, **46**, **52**, and **55** were converted to their phenoxyacetic acid or -isobutyric acid derivatives **21–24**, **26**, **27**, **32**, **33**, **39**, **42**, **54**, and **57**. Similarly the pyrogallol derivatives **62** and **63** exhibited only marginal uterotrophic activity.

Antiestrogenic Effects.—No definite antiestrogenic activity could be found with any of the compounds as judged by the screening test. Compound **16** was studied more thoroughly and some of its endocrine effects might be interpreted as due to its antiestrogenic properties. Thus, **16** did not exhibit an additive uterotrophic response when given in combination with estradiol to immature female rats. Instead, with higher doses of estradiol (10 μg/kg), a weak antiestrogenic activity could be demonstrated. In ovariectomized rats, however, **16** and estradiol did elicit an additive response. This finding is similar to that observed with clomiphene, which was found to exert uterotrophic activity in ovariectomized rats, but antagonized the uterotrophic action of estradiol in the intact animal.[7]

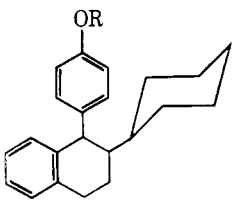
5) All biological data of **16** refer to the crystalline, free base, mp 81–82°.

6) C. W. Emmens, *J. Reprod. Fertility*, **2**, 444 (1941).

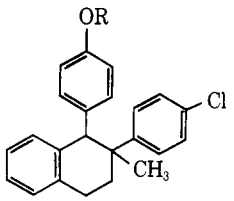
7) S. Roy, R. B. Greenblatt, and V. B. Mahesh, *Acta Endocrinol.*, **47**, 657 (1964).

TABLE III

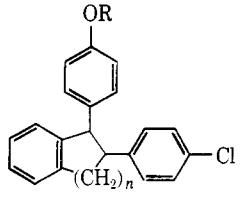
1,2-SUBSTITUTED DERIVATIVES OF TETRALINE, INDANE, AND BENZOSUBERANE



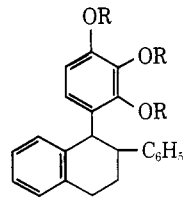
52–54



55–57



58–61



62–64

No.	R	Procedure	Yield, %	Mp, °C	Formula	—Calcd, %— C	H	—Found, %— C	H
52	H	A	51	106–107	$C_{22}H_{26}O$	86.23	8.55	86.21	8.62
53	$CH_2CH_2N(C_2H_5)_2 \cdot C_6H_8O_7$	E	66	135–136	$C_{34}H_{47}NO_5$	68.32	7.93	68.31	8.07
54	$C(CH_3)_2COOH$	I	47	133–135	$C_{26}H_{32}O_3$	79.55	8.22	79.66	8.31
55	H	A	36	136–137	$C_{23}H_{21}ClO$	79.18	6.07	79.28	6.19
56	$CH_2CH_2N(C_2H_5)_2 \cdot HCl$	E	62	186–188	$C_{29}H_{33}Cl_2NO$	71.87	7.08	71.78	7.22
57	CH_2COOH	H	21	102–106	$C_{25}H_{23}ClO_3$	73.79	5.70	73.89	5.77
58	H (n = 1)	A	29	125–126	$C_{21}H_{17}ClO$	78.62	5.34	78.55	5.23
59	$CH_2CH_2N(C_2H_5)_2 \cdot C_6H_8O_7$ (n = 1)	E	72	109–110	$C_{33}H_{38}ClNO_8$	64.75	6.26	64.57	6.23
60	H (n = 3)	A	64	138–139	$C_{23}H_{21}ClO$	79.17	6.07	79.39	6.29
61	$CH_2CH_2N(C_2H_5)_2 \cdot C_6H_8O_7$ (n = 3)	E	43	107–109	$C_{35}H_{42}ClNO_8 \cdot 0.5H_2O$	64.77	6.68	65.06	6.87
62	H	O	36	161–163	$C_{22}H_{20}O_3$	79.49	6.06	79.57	6.14
63	$COCH_3$	P	37	125–126	$C_{28}H_{28}O_6$	73.35	5.72	73.34	5.75
64	$CH_2CH_2N(C_2H_5)_2$	E	47	[a]	$C_{40}H_{59}N_3O_3$	76.27	9.44	76.60	9.53

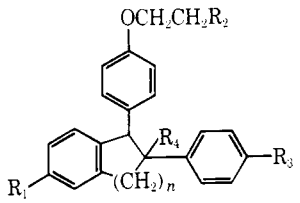
[a] Oil, purified by chromatography.

In another experiment compensatory ovarian hypertrophy subsequent to unilateral ovariectomy in the rat could be inhibited by a dose of 100 μg/kg of **16**. At the same time, under the conditions of this experiment, a marked depression of uterine weight occurred. Thus, **16** appeared to have elicited an estrogen-like gonadotrophin inhibitory effect on the remaining ovary and an antiestrogenic effect on the uterus.

Implantation Inhibition.—The most active compound in this series was the basic phenolic ether **16**, which offered complete protection against pregnancy at an oral dose of 20 μg/kg/day (approximately 4 μg/rat/day) given to female rats for four consecutive days postmating. Table IV shows the effect of a few chemical alterations on the implantation inhibitory activity and, in part, on the uterotrophic activity. The typical 6-methoxy group in the naphthalene moiety, as employed in the total synthesis of steroidal compounds, enhanced both the estrogenic and implantation inhibitory activity (see **10** and **20**). However, the same chemical change in **48** did not improve the antifertility activity of **16**.

TABLE IV

BIOLOGICAL ACTIVITY OF REPRESENTATIVE COMPOUNDS



No.	R_1	R_2	R_3	R_4	n	Uterotrophic activity, mg/kg	Antifertility activity, mg/kg
10	H	$N(C_2H_5)_2$	H	H	2	2.5	1.0
16	H	$N(C_2H_5)_2$	Cl	H	2	0.04	0.02
20	OCH_3	$N(C_2H_5)_2$[a]	H	H	2	0.002	0.1
29	H	NH_2[b]	Cl	H	2	...	>1.0[c]
31	H	NHC_2H_5[a]	Cl	H	2	...	0.1
36	H	$N(CH_2)_2CH_2$	Cl	H	2	2.5	>0.02[c]
43	H	$N(C_2H_5)_2$[b]	OCH_3	H	2	0.05	1.0
48	OCH_3	$N(C_2H_5)_2$[a]	Cl	H	2	...	0.1
56	H	$N(C_2H_5)_2$[a]	Cl	CH_3	2	0.01	0.04
59	H	$N(C_2H_5)_2$[b]	Cl	H	1	2.5	>1.0[c]
61	H	$N(C_2H_5)_2$[b]	Cl	H	3	...	1.0

[a] Hydrochloride salt. [b] Citrate salt. [c] Protection against pregnancy was incomplete at the dose indicated.

Exchange of the diethylaminoethyl group of **16** for pyrrolidyl (**36**), amino (**29**), and N-ethylamine (**31**) led to less active compounds.

Compound **16** with a chloro group substituted in the *para* position of the phenyl group at C_2 had greater activity than **10** and **43**.

Substitution of a methyl group in place of hydrogen at C_2 (**56**) increased the uterotrophic activity, but decreased the antifertility activity by one-half.

Ring contraction of the alicyclic part of the tetrahydronaphthalene ring system to afford the indane analog (**59**) of **16**, or ring expansion to a seven-membered ring system (**61**) resulted in greatly diminished antifertility activity. A heterocyclic analog of **16**, in which the tetrahydronaphthyl moiety was replaced by chromane, was active at 1 mg/kg.[8]

The following compounds afforded complete protection against pregnancy at a dose of 1 mg/kg: **9**, **35**, **40**, **44**, and **53**. Compounds showing activity at higher doses than 1 mg/kg were considered to be inactive.

Hypocholesterolemic Activity.—The implantation inhibitor, **16**, exerted a marked hypocholesterolemic response in male rats at a dose of 0.5 mg/kg given orally for 7 days. When male rats were rendered hypercholesterolemic with thiouracil, 0.1% in the feed, oral doses of **16** at 0.1 mg/kg for 10 days, did not diminish the elevated serum cholesterol concentration.

Compound **26**, a phenoxyacetic acid derivative, which had no effect on implantation and showed only

(8) R. W. J. Carney, W. L. Bencze, J. Wojtkunski, A. A. Renzi, L. Dorfman, and G. deStevens, *J. Med. Chem.*, **9**, 516 (1966).

marginal uterotrophic activity at 1 mg/kg, was found to possess hypocholesterolemic activity at the same dose in male rats maintained both on normal or cholesterol-rich diets. A number of additional compounds tested for hypocholesterolemic activity exhibited only marginal effects.

Concluding Remarks.—Compound **16** showed a peculiar dose–response curve when the uterotrophic activity was assessed.[9] A degree of self-inhibitory effect was manifested at the higher doses. It appeared that antiestrogenic metabolites might have been produced in the animal at the higher dose, which counteracted the uterotrophic response to a certain degree. In this respect **16** resembled the "impeded" estrogens described by Huggins and Jensen.[10] After a threshold dose the impeded estrogens produce a curve with only a very gradual increment of uterine weight. This type of effect was even more pronounced in the case of **16**, in as much that the slopes of the dose–response curve became flat above 200 μg/kg. Nevertheless, a distinct uterotrophic response was prevalent in the dose range at which effective implantation inhibition was obtained. Emmens[11] has advanced a tentative rule, which suggests that for typical estrogens, the daily effective dose for implantation inhibition roughly equals the dose required to give 50% of positive vaginal smear tests in the mouse. This has also been the case with substance **16**. Effective inhibition of nidation and 50% positive vaginal smears were obtained at 20 μg/kg in the rat. Hence, irrespective of antiestrogenic manifestations at higher doses, the capacity of this substance to inhibit implantation at low doses appears to be due to estrogenicity.

Whereas Emmens suggests that the implantation inhibitory activity and estrogenic activity, as determined by the Allen–Doisy test, is elicited by the same dose of an estrogenic compound, Pincus[12] and Saunders[13] claim that the dose ratios of implantation inhibitory/uterotrophic activity vary to a considerable degree from one estrogen to the other. This would mean that the dose at which 50% positive vaginal smears are observed would be an invariable index for implantation inhibitory activity. It does not mean, however, that the uterotrophic response in the rat would have no bearing on implantation. On the contrary, when uterine messenger ribonucleic acid, obtained from estrogen-treated animals, was injected into rats that had been ovariectomized after mating, implantation of fertilized ova took place.[14] Estrogenicity and implantation-preventing potency appear to be closely related properties of a great variety of steroidal and nonsteroidal substances. By measuring different manifestations of hormonal activity, a degree of separation of typical estrogenic and antifertility potencies seems to be feasible.

The aspects of dissociating hypocholesterolemic and related effects of estrogens on lipid metabolism from estrogenicity seem to be less limited. With **16**, there was no separation of estrogenicity from hypocholesterolemic activity. However, **26** showed negligible uterotrophic response at the dose at which hypocholesterolemic activity was manifest. Qualitative differentiation of the hypocholesterolemic activity of these two compounds is still under investigation.

(9) At the doses of 0, 8, 40, 200, and 1000 μg/kg the relative uterine weights were 81, 93, 144, 136, and 125 mg.

(10) C. Huggins and E. V. Jensen, *J. Exptl. Med.*, **102**, 335 (1955).

(11) C. W. Emmens, *J. Reprod. Fertility*, **9**, 277 (1965).

(12) G. Pincus in Preimplantation stages of Pregnancy, CIBA Foundation Symposium, G. E. W. Wolstenholme and M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1965, p 378; see also G. Pincus, U. Banik, and J. Jacques, *Steroids*, **4**, 657 (1964).

(13) F. J. Saunders and K. Rorig, *Fertility Sterility*, **15**, 202 (1964).

(14) Editorial, *J. Am. Med. Assoc.*, **193**, No. 6, 33 (1965).

Experimental Section[15]

The following procedures are representative of each of the types of compounds outlined in Tables I–III.

Procedure A. *cis*- and *trans*-1-*p*-Hydroxyphenyl-2-phenyl-1,2,3,4-tetrahydronaphthalene (3 and 4).—To a solution of 13.3 g (0.1 mole) of $AlCl_3$ in 37.6 g (0.4 mole) of phenol there was added dropwise during 2 hr with stirring and cooling in ice water 44.6 g (0.2 mole) of 1,2,3,4-tetrahydro-1-hydroxy-2-phenylnaphthalene and 18.8 g (0.2 mole) of phenol dissolved in a mixture of 50 ml of benzene and 50 ml of hexane. After addition was completed, stirring of the mixture was continued at room temperature for 12 hr and then the mixture was allowed to stand for 60 hr. Thereafter stirring was resumed at 50–55° for 4 hr. The reaction mixture was decomposed by pouring it into 200 ml of cold 6 *N* HCl. The organic layer was separated and the aqueous part was extracted twice with ether. The combined organic layers were washed with saturated aqueous solution of sodium acetate, dried (Na_2SO_4), filtered, and evaporated to dryness. The excess phenol was removed from the crude product by distillation at 75–80° (13 mm), bath temperature 170°. The distillation residue weighed 66.5 g. It was converted to the sodium salt in 500 ml of hot 10% NaOH. The salt was filtered off by suction and air dried. Reconversion to the free phenol by acidification with 2 *N* HCl and extraction with ether afforded 51 g of a viscous oil. Crystallization in a mixture of hexane and ether 10:1 gave 29.7 g (44% yield) of the more polar isomer, mp 66–70°. Recrystallization from the same solvent mixture raised the melting point to 70–72°. This compound represented the *trans* form; nmr: 247 cps (doublet, C_1H, $J_{1,2}$ = 10 cps). The presence of 0.5 mole of ether of crystallization was indicated at 72 (triplet, CH_3) and 211 cps (quartet, CH_2) for OCH_2CH_3.

Anal. Calcd for $C_{22}H_{20}O \cdot 0.5(CH_3CH_2)_2O$: C, 85.42; H, 7.47. Found: C, 85.68; H, 7.46.

Distillation of this isomer at 185–190° (0.1 mm) gave a colorless viscous oil.

Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.08; H, 6.67.

Evaporation of the filtrates of the *trans* isomer afforded 17.3 g of a viscous oil, which crystallized on standing. Further recrystallizations from hexane and pentane furnished the *cis* isomer, mp 142–143°. This product was found to be identical with **3** as obtained by catalytic hydrogenation of 3,4-dihydro-1-*p*-methoxyphenyl-2-phenylnaphthalene[3] and subsequent demethylation.

Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.26; H, 6.72.

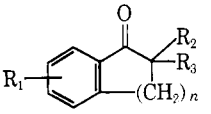
Phenols **11** and **12** were prepared by the same procedure as described above for the synthesis of **3** and **4**. Thus, 25.8 g (0.1 mole) of 2-*p*-chlorophenyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene has been employed to alkylate phenol to give 35.0 g of a crude product. Two recrystallizations from ether and hexane furnished 19.8 g (59%) of *trans* phenol **12**, mp 142–144°, 245 cps (doublet, C_1H, $J_{1,2}$ = 10 cps). Attempts to isolate the *cis* isomer **11** in a crystalline state failed at this point. Therefore, the residual mixture of products, after removal of most of the *trans* isomer by crystallization, was converted by methylation to a mixture of **13** and **14**. These two isomer phenolic methyl ethers were separated by fractional crystallization from isopropyl alcohol. The *cis* isomer (**13**) melted at 109–112°; 246 (doublet, C_1H, $J_{1,2}$ = 5.5 cps), 221 cps (singlet, OCH_3). This isomer was found to be identical with the substance obtained by catalytic reduction of the corresponding 3,4-dihydronaphthalene derivative.

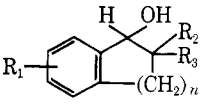
Anal. Calcd for $C_{23}H_{21}ClO$: C, 79.17; H, 6.07. Found: C, 79.04; H, 6.03.

(15) Melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Nmr spectra were taken in dilute $CDCl_3$ solutions containing $(CH_3)_4Si$ as an internal standard on a Varian A-60 spectrometer. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer. Ultraviolet spectra were determined in methanol solutions on a Cary Model 14 spectrophotometer.

TABLE V

INTERMEDIATE COMPOUNDS





					—Calcd, %—		—Found, %—			—Calcd, %—		—Found, %—	
R_1	R_2	R_3	n	Mp, °C	C	H	C	H	Mp, °C	C	H	C	H
H	H	4-ClC_6H_4	1	88–90	74.23	4.57	74.27	4.68	129–130	73.62	5.35	73.50	5.46
H	H	4-ClC_6H_4	2	108–109	74.85	5.09	75.15	5.12	129–132	74.27	5.83	74.43	5.97
H	CH_3	4-ClC_6H_4	2	52–54	75.42	5.58	75.57	5.58	113–115	74.58	6.26	74.78	6.43
H	H	C_6H_{11}	2	34–35[a]	84.16	8.83	84.19	8.86	91–95	84.43	9.63	83.50	9.58
H	H	2-FC_6H_4	2	83–85	79.97	5.45	79.94	5.41	*b*	79.30	6.14	79.07	6.28
H	H	4-$OCH_3C_6H_4$	2	111–112[c]	80.92	6.39	81.01	6.46	74–76	80.28	7.13	80.20	6.98
H	H	3,4-$Cl_2C_6H_3$	2	101–102	66.22	4.17	65.93	4.22	92–94	65.54	4.82	65.54	4.76
6-OCH_3	H	C_6H_5	2	121–122[d]	80.92	6.39	80.73	6.45	88–89	80.92	6.39	80.61	6.65
6-OCH_3	H	4-ClC_6H_4	2	98–99	71.20	5.27	71.21	5.39	109–111	70.70	5.93	70.92	5.91
7-Cl	H	C_6H_5	2	88–89[e]	74.85	5.10	74.93	5.08	84–86	74.25	5.84	74.23	5.81
7-CH_3	H	C_6H_5	2	63–64[f]	86.40	6.83	86.17	6.92	116–118	85.68	7.61	85.96	7.62
H	H	4-ClC_6H_4	3	61–62	75.40	5.58	75.63	5.57	*b*	74.84	6.28	74.67	6.56

[a] C. D. Gutsche, N. N. Saha, and H. E. Johnson [*J. Am. Chem. Soc.*, **79**, 4441 (1957)] reported bp 140° (0.13). [b] Oil, purified by chromatography. [c] M. S. Hidayetulla, R. C. Shah, and T. S. Wheeler [*J. Chem. Soc.*, 111 (1941)] reported mp 107°. [d] D. Lednicer, J. C. Babcock, S. C. Lyster, and G. W. Duncan [*Chem. Ind.* (London), 408 (1963)] reported mp 113–116°. [e] F. G. Baddar and S. Sherif [*J. Chem. Soc.*, 2309 (1960)] reported mp 85–86°. [f] M. S. Hidayetulla, R. C. Shah, and T. S. Wheeler [*ibid.*, 111 (1941)] reported mp 67°.

All the tetrahydronaphthol derivatives and analogs as employed in general procedure A for *para* alkylation of phenol were prepared according to the method described by Campbell and Kidd.[16] The intermediate tetralones and the corresponding reduced derivatives, the substituted 1-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalenes and two analogs are listed in Table V. The tetralones were reduced to the tetralols with $NaBH_4$ in ethanol, rather than $LiAlH_4$ in ether. In cases of insolubility of the tetralones in ethanol only, ethanol–tetrahydrofuran was used as solvent in the hydride reduction.

Procedure B.—Demethylation of **5**, **13**, and **45** to afford phenols **3**, **11**, and **46**, respectively, was carried out by heating the phenolic methyl ethers in pyridine hydrochloride at 245–250° for 30 min. This procedure has been described in detail in a preceding publication.[3]

Procedure C. *cis*-1-*p*-Methoxyphenyl-2-phenyl-1,2,3,4-tetrahydronaphthalene (5).—A solution of 5.4 g (0.0173 mole) of 3,4-dihydro-1-*p*-methoxyphenyl-2-phenylnaphthalene[3] in 150 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure over 1.2 g of 10% Pd–C catalyst until the calculated amount of hydrogen was absorbed (24 hr). The catalyst was removed by filtration and the filtrate was evaporated to dryness. Crystallization of the residue from 2-propanol yielded 4.23 g of product, mp 87–89°.

Procedure D. *trans*-1-*p*-Methoxyphenyl-2-*p*-chlorophenyl-1,2,3,4-tetrahydronaphthalene (14).—A solution of **12** (3.35 g, 0.01 mole) in 25 ml of dimethylformamide (DMF) and 10 ml of toluene was stirred with cooling in an ice bath and treated in portions with 0.50 g of 57% NaH–mineral oil suspension. The sodium salt of **12** did not precipitate and was treated with 1.5 g of methyl iodide in 25 ml of cold toluene. Within a few minutes the complex salt, $3HCON(CH_3)_2 \cdot NaI$ started to precipitate. Stirring was continued for 1 additional hr in an ice bath and then for 3 hr at room temperature. Benzene was added (50 ml) and the complex NaI salt was filtered off. The filtrate was evaporated to dryness *in vacuo*. The residual oily solid was crystallized from benzene–petroleum ether (bp 30–60°) (1:10) to give 2.45 g of product, mp 139–140°. Recrystallization from a mixture of ethyl acetate and ethanol (1:5) raised the melting point to 140–141°.

Procedure E. *trans*-2-[*p*-(2-*p*-Chlorophenyl-1,2,3,4-tetrahydro-1-naphthyl)phenoxy]triethylamine (16).—To the sodium salt prepared from 2.66 g (0.008 mole) of **12** in 30 ml of DMF and 20 ml of toluene with 390 mg of 53% NaH–mineral oil suspension, as described in procedure D, there was added 1.07 g of 2-diethylaminoethyl chloride in 5 ml of toluene. The reaction mixture was stirred at room temperature for 5 hr and allowed to stand for 15 hr. After removal of the precipitated NaCl by filtration and evaporation of the solvents *in vacuo*, the residual oil was diluted with ether and extracted with 2 *N* HCl. Due to the poor solubility of the hydrochloride of the product the acidic extracts were turbid. Upon rendering these extracts alkaline, the product was extracted with ether to yield 3.0 g of the crude product which crystallized spontaneously. Recrystallization from hexane furnished 2.17 g (62%) of the pure product, mp 81–82°.

Anal. Calcd for $C_{28}H_{32}ClNO$: C, 77.49; H, 7.43. Found: C, 77.36; H, 7.49.

Procedure F. Diethyl *cis*-*p*-(2-Phenyl-1,2,3,4-tetrahydro-1-naphthyl)phenyl Phosphate (7).—Four grams (0.026 mole) of ethyl phosphorochloridate was added dropwise over a 20-min period with stirring to a chilled solution of 6.0 g (0.02 mole) of **3** and 0.88 g (0.022 mole) of NaOH in 24 ml 20% ethanol. The mixture was stirred at room temperature for 3 hr and then partitioned by addition of 50 ml of ether and 15 ml of water. The aqueous layer was extracted with 20 ml of ether. The combined organic layers were washed three times with water. The ethereal part furnished 8.6 g of a yellowish viscous oil which was chromatographed on 300 g of Al_2O_3 (Woelm, neutral, activity grade 3). Benzene and mixtures of benzene and ether eluted 8.1 g (93%) of a colorless oil. A sample of the product was dried at 80° (0.01), 5 hr for analysis.

Procedure G. *cis*-1,2-Diphenyl-1,2,3,4-tetrahydronaphthalene (1).—A solution of 5.2 g (0.012 mole) of the ethyl phenyl phosphate ester **7** in 5 ml of ether was diluted with 50 ml of liquid ammonia. The mixture was heated and stirred with the addition of 0.14 g (0.02 g-atom) of Li over a 30-min period. Ether was added and the NH_3 was allowed to evaporate. After addition of water, the mixture was stirred for 30 min and the two clear layers were separated. The ethereal portion was washed twice with water, 10% H_2SO_4, and Claisen's alkali. Upon evaporation of the ether 3.1 g of crystalline product was obtained, which was recrystallized from 95% ethanol to give 2.1 g (61%) of product, mp 94–95°. Distillation of this substance at 150–160° (0.5 mm) followed by recrystallization from ethanol raised the melting point to 96–97°. A specimen prepared according to the procedure of Bergmann, *et al.*,[4] was found to be identical with this hydrocarbon. The two samples furnished identical infrared spectra, and an admixture melted undepressed.

Procedure H. *cis*-*p*-(2-Phenyl-1,2,3,4-tetrahydro-1-naphthyl)-phenoxyacetic Acid (21).—A solution of 30 g (0.1 mole) of **3** in 200 ml of acetone was stirred and heated to gentle reflux in the presence of 10 g (0.25 mole) of NaOH pellets, while 14.0 g (0.15 mole) of chloroacetic acid in 50 ml of acetone was added dropwise. A slightly exothermic reaction commenced and the sodium salt of the product gradually precipitated. To facilitate stirring 200 ml more of acetone was added and the reaction mixture was heated with stirring under reflux for 2 hr. The sodium salt of the product was collected, washed with acetone, and dried in air. The free acid was obtained by acidifying the aqueous

(16) N. Campbell and D. Kidd, *J. Chem. Soc.*, 2154 (1954).

solution of the sodium salt with 2 *N* HCl and extraction with ether. The crude product was recrystallized from benzene and pentane, 28.3 g (79%), mp 128–131°. A sample recrystallized for analysis from ethanol and water, gave white crystals, mp 135–136°.

Procedure I. ***cis*-2-Methyl-2-*p*-(2-phenyl-1,2,3,4-tetrahydro-1-naphthyl)phenoxypropionic Acid (23).**—A solution of 9.6 g (0.032 mole) of **3** in 100 ml of acetone was stirred and heated to gentle reflux in the presence of 7.0 g (0.175 mole) of NaOH pellets while 4.5 g (0.038 mole) of $CHCl_3$ was added dropwise. After the addition was complete (20 min) the reaction mixture was stirred and heated under reflux for 3 hr. The sodium salt of the product was collected and washed with acetone. The free acid was isolated as in procedure *H*. The crude product was recrystallized from hexane to yield 10.2 g of substance, mp 157–159°. Recrystallization from ethanol and water afforded 9.05 g of pure product, mp 161–162°.

Procedure J. Ethyl *trans*-*p*-(2-*p*-Chlorophenyl-1,2,3,4-tetrahydro-1-naphthyl)phenoxyacetate (27).—Twelve grams (0.03 mole) of **26** was heated under reflux in 50 ml of dry ethanol in the presence of 1 ml of H_2SO_4 for 16 hr. After removal of most of the ethanol, ice water and $NaHCO_3$ were added until the pH of the suspension was alkaline. The product was extracted with ethyl acetate. Crystallization from 95% ethanol afforded the pure product, 9.8 g (76%), mp 102–103°.

Procedure K. ***trans*-N-Ethyl-*p*-(2-*p*-chlorophenyl-1,2,3,4-tetrahydro-1-naphthyl)phenoxyacetamide (30).**—The acid chloride was prepared from 6.0 g (0.015 mole) of the substituted phenoxyacetic acid **26** by heating it to boiling in 25 ml of $SOCl_2$ for 40 min. Excess of $SOCl_2$ was removed by evaporation *in vacuo* and dilution of the resulting oil with 50 ml of benzene followed by evaporation to dryness three times. The acid chloride, dissolved in 50 ml of benzene was added dropwise with stirring to an ice-cold solution of ethylamine in ether. The reaction mixture was evaporated to dryness and the crude product was taken up in $CHCl_3$, washed with water, dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting crude material was crystallized from hexane to give 5.1 g of product, mp 90–94°, which was then recrystallized from ethanol and water (5:1) to yield 4.4 g (59%) of pure substance, mp 106–107°. The basic amides of **32** and **33** were prepared by boiling the acid chloride of **26** with a threefold excess of N,N-diethylethylenediamine and -propylenediamine, respectively, in benzene for 90 min.

Procedure L. ***trans*-2-[*p*-(2-*p*-Chlorophenyl-1,2,3,4-tetrahydro-1-naphthyl)phenoxy]diethylamine Hydrochloride (31).**—Four grams (0.01 mole) of **30** was reduced with 1.0 g of $LiAlH_4$ by heating the mixture under reflux with stirring in 50 ml of ether and 25 ml of THF for 30 hr. The excess reducing agent was decomposed by dropwise addition of wet ether, water, and 2 *N* HCl. The organic solvents were removed *in vacuo*, and the aqueous residue was made basic with 2 *N* KOH solution. The product was extracted with ether to give 3.5 g of a semisolid oily product. The crude product was taken up in ether and converted to the hydrochloride by addition of ether saturated with HCl. Recrystallization of the white solid from acetone furnished 1.40 g of pure product, mp 187–189°, in 33% yield.

Procedure M. 1,2-Epoxy-3-[*p*-(2-*p*-chlorophenyl-1,2,3,4-tetrahydro-1-naphthyl)phenoxy]propane (35).—A solution of 6.2 g (0.02 mole) of **12**, 0.90 g (0.0225 mole) of NaOH, and 2.0 g (0.022 mole) of epichlorohydrin in 50 ml of ethanol and 30 ml of water was stirred at room temperature for 2 hr. A gummy precipitate appeared. A clear solution resulted after addition of 25 ml of ethanol and 25 ml of ether. The reaction mixture was allowed to stand for 20 hr. Thereafter 2 g more of epichlorohydrin was added and stirring was resumed for 5 hr. The ethanol and ether were removed from the reaction mixture *in vacuo* and the product was extracted with ether to give 8.0 g of a viscous oil. The oily product was chromatographed on 240 g of Al_2O_3 (Woelm, neutral, activity grade 3). Benzene–hexane (1:1) eluted 3.9 g of oil which crystallized spontaneously. Recrystallization from hexane–ether gave 2.0 g (25%) of pure product, mp 96–98°.

Procedure N. ***trans*-2-[*p*-(2-*p*-Chlorophenyl-1,2,3,4-tetrahydro-1-naphthyl)phenoxy]triethylamine Methiodide (37).**—A solution of 4.3 g (0.01 mole) of the free base of **16** and 1.56 g (0.011 mole) of methyl iodide in 100 ml of acetone was allowed to stand at room temperature for 5 days. The solvent was removed *in vacuo* to yield 5.7 g of the crude product, mp 192–200°. Recrystallization of this substance from ethanol gave 4.9 g (85%) of pure product, mp 199–200°.

Procedure O. 2-Phenyl-1-(2,3,4-trihydroxyphenyl)-1,2,3,4-tetrahydronaphthalene (62).—To a suspension of 12.6 g (0.1 mole) of pyrogallol in 30 ml of glacial acetic acid and 1.2 ml of H_2SO_4 was added, dropwise with stirring over a period of 45 min at 5–10°, 22.4 g (0.1 mole) of 1-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalene dissolved in 45 ml of acetic acid. The reaction mixture was allowed to stand at room temperature for 60 hr and then poured into ice water, and the pH of the resulting solution was adjusted to approximately 5. The product was extracted four times with ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution, dried, and evaporated to dryness to give 26.0 g of a yellowish viscous oil which slowly solidified. Three crystallizations of this solid substance from benzene and hexane afforded 12.0 g (36%) of the pure product, mp 161–163°.

Procedure P. 2-Phenyl-1-(2,3,4-triacetoxyphenyl)-1,2,3,4-tetrahydronaphthalene (63).—A solution of 1.8 g of crude **62** in 4 ml of pyridine and 3 ml of acetic anhydride was allowed to stand at room temperature for 24 hr and then poured into water. The product was extracted with ether and isolated as a gummy residue, which on crystallization from benzene and hexane three times, and once from ethanol, yielded 910 mg (37%) of a crystalline compound, mp 125–126°.

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