inhibitor. Quintana points out, however, that such relationships do not necessarily hold outside a particular homologous or isomeric series and should be used with caution. Molecular models of IX–XI show that sufficient free rotation exists about the bond linking the benzene ring and the methylene group to allow the ring to orient in a plane parallel to the enzyme surface. Such an orientation would permit a greater degree of hydrophobic interaction than is possible for the nonaromatic analogs shown in Tables I and II. It is interesting to note that the most active xylylene analog (IX) has a configuration analogous to that of the more active *cis*-ethenylene isomer (V), a fact which is in agreement with the possible existence of a spatial factor.

Acknowledgment.—The authors wish to thank Dr. A. Lasslo for reading the manuscript, Miss J. S. Hendrix for technical assistance, and particularly, The National Science Foundation for support of the research.

Mammalian Antifertility Agents. IV. Basic 3,4-Dihydronaphthalenes and 1,2,3,4-Tetrahydro-1-naphthols[1,2]

DANIEL LEDNICER, STANLEY C. LYSTER, AND GORDON W. DUNCAN

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

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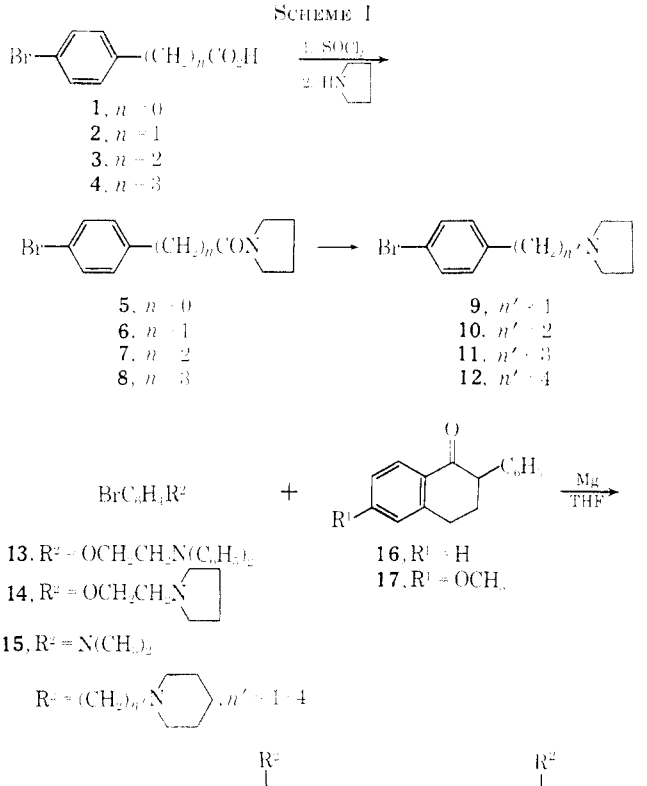
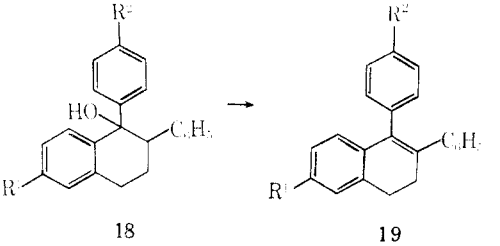
The preparation of basic ethers of 1,2-diphenyl-3,4-dihydronaphthalenes, 1-(pyridyl)-2-phenyl-3,4-dihydronaphthalenes, and 2-(3-pyridyl)-1-aryloxy-3,4-dihydronaphthalenes is described. Further transformations of some of these products are recorded. Many of the compounds prepared were found to be highly potent antifertility agents in rats; some of the active compounds were also potent uterotropic agents while others antagonized the effect of concurrently administered estrogens on uterine weight.

Appropriately substituted derivatives of the 2-phenyl-3,4-dihydronaphthalene systems have previously been shown to exhibit uterotropic activity.[3] More recently[1,4] compounds related to 1,2-diphenyl-3,4-dihydronaphthalene were also found to elicit a uterotropic response. In the continuing search for an orally effective nonsteroidal contraceptive, basic derivatives of the 1,2-diaryl-3,4-dihydronaphthalene system were investigated since the inclusion of basic groups into inherently estrogenic molecules has occasionally been found to lead to estrogen antagonists, which in turn exhibit antifertility activity.[5,6]

Basic Derivatives of 1,2-Diphenyl-3,4-dihydronaphthalenes.—In one of the preferred methods of synthesis, a substituted 2-phenyl-1-tetralone was allowed to react with the Grignard reagent from a basic derivative of bromobenzene. The derivatives of *p*-bromophenol were prepared as described previously.[6] In order to prepare the pyrrolidinoalkylbromobenzenes, the appropriate ω-bromoalkanoic acid[7] was converted to its acid chloride and treated with an excess of pyrrolidine (Table I). Reduction of the amide thus obtained with lithium aluminum hydride afforded the desired bases (Table II). These were carefully purified by distillation and used in the ensuing step (see Scheme I).

SCHEME I





Reaction of the Grignard reagents prepared from basic ethers of *p*-bromophenols[8] **13** and **14** with 6-me-

(1) Previous paper in this series: D. Lednicer, S. C. Lyster, B. D. Aspergren, and G. W. Duncan, *J. Med. Chem.*, **9**, 172 (1966).

(2) Parts of this paper have been published: D. Lednicer, S. C. Lyster, and G. W. Duncan, *Chem. Ind.*, 408 (1963); presented in part at the Symposium on Nonsteroidal Antifertility Agents, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963.

(3) C. Mentzer and G. Urbain, *Compt. Rend.*, **215**, 554 (1942).

(4) W. L. Beneze, L. I. Barsky, W. P. Sopchak, A. A. Renzi, N. Howie and J. J. Chart, *J. Med. Chem.*, **8**, 213 (1965).

(5) L. S. Lerner, F. S. Holthaus, Jr., and C. R. Thompson, *Endocrinology*, **63**, 295 (1958).

(6) D. Lednicer, J. C. Babcock, S. C. Lyster, J. C. Stucki, and G. W. Duncan, *Chem. Ind.*, 2098 (1961).

(7) Compounds **1**, **2**, and **4** are commercially available; **3** was prepared by the method of L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938).

(8) D. Lednicer, J. C. Babcock, P. E. Marlatt, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **8**, 52 (1965).

TABLE I
N-[ω-(p-BROMOPHENYL)ALKANOYL]PYRROLIDINES

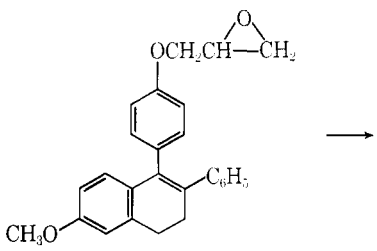
$p\text{-BrC}_6\text{H}_4(\text{CH}_2)_n\text{CON}$

Compd	n	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
5	0	77–79	$C_{11}H_{12}BrNO$	51.98	52.12	4.76	4.63
6	1	116.5–119	$C_{12}H_{14}BrNO$	53.75	54.22	5.26	5.18
7	2	52–60	$C_{13}H_{16}BrNO$	55.33	55.43	5.72	5.78
8	3	44–47	$C_{14}H_{18}BrNO$	56.77	56.87	6.16	6.31

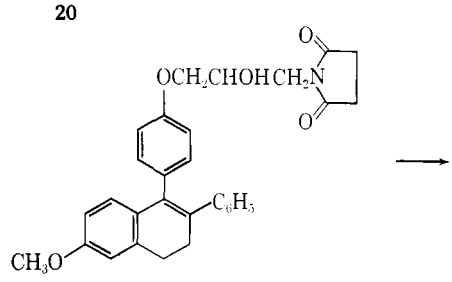
thoxy-1-tetralone[1] led directly to the desired dihydronaphthalenes **19**. In absence of the methoxyl group **16**,[9] the naphthols such as **18** were the products isolated. Dehydration of these latter compounds was effected efficiently by heating the hydrochloride salts to their melting point; refluxing the salt in benzene in the presence of *p*-toluenesulfonic acid led to the recovery of unchanged starting material.

As in the case of the basic ethers of *p*-bromophenol, the tertiary amino halides **9**–**12** readily formed Grignard reagents in tetrahydrofuran. Reaction of these with the tetralone **17** again led directly to the dihydronaphthalenes.

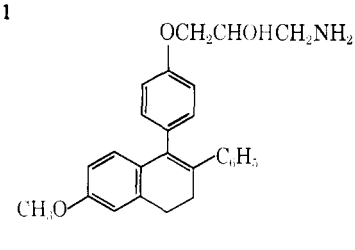
The amino alcohol was prepared by a modification of the Gabriel synthesis.[10] Thus, the epoxy ether **20**[1] was



20



21

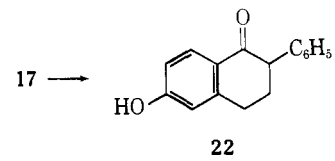


28

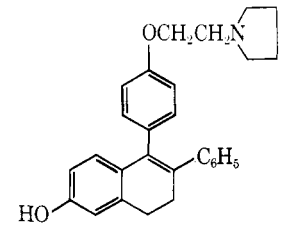
opened with succinimide to afford **21**. Basic hydrolysis of this last product led cleanly to **28**.

To assess the properties of the phenolic amine, the starting tetralone **17** was demethylated by means of aluminum chloride to give **22**. Reaction of the phenolic ketone (as its tetrahydropyranyl ether) with the appropriate Grignard reagent followed by mild hydrolysis led to the aminophenol **27** (Tables III and IV).

(9) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 2947 (1938).
(10) V. Petrow and O. Stephenson, *J. Pharm. Pharmacol.*, **5**, 359 (1953).



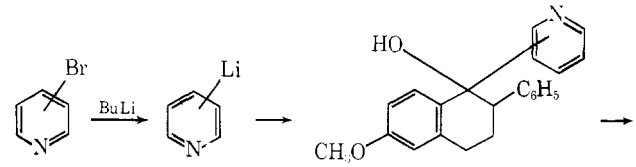
22



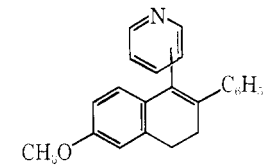
27

Derivatives of Pyridylarylnaphthalenes.—To obtain the 1-pyridyl compounds, the lithio derivatives of 2- and 4-bromopyridine were prepared by the halogen metal intraconversion with freshly prepared butyllithium[11] (see Scheme II). Reaction of these reagents

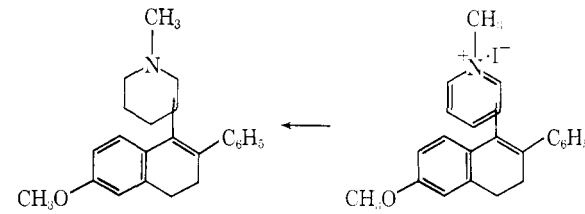
SCHEME II



36, 2-pyridyl
37, 4-pyridyl



38, 2-pyridyl
39, 4-pyridyl



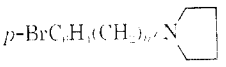
42, 2-piperidyl
43, 4-piperidyl

40, 2-piperidinium
41, 4-piperidinium

with the tetralone **17** led in each case to the isolation of the corresponding carbinol. The dihydronaphthalenes were prepared by heating the carbinols in toluene in the

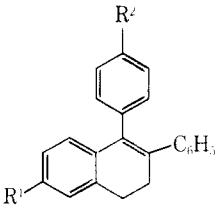
(11) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).

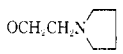
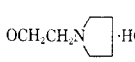
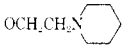
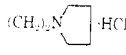
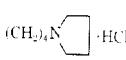
TABLE II
N-[ω-(*p*-BROMOPHENYL)ALKYL]PYRROLIDINES



Compd	*n'*	Bp, °C (mm)	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Bromine, % Calcd	Bromine, % Found
9	1	88–92 (0.4)	$C_{11}H_{14}BrN$	55.01	55.82	5.88	5.94	33.28	33.08
10	2	102–106 (0.4)	$C_{12}H_{16}BrN$	56.70	56.22	6.35	6.22		
11	3	135–139.5 (5)	$C_{13}H_{18}BrN$	58.21	59.31	6.76	7.02	29.08	29.80
12	4	123–124.5 (0.4)	$C_{14}H_{20}BrN$	59.58	60.05	7.14	7.43		

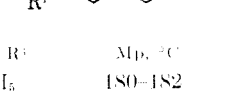
TABLE III
BASIC DERIVATIVES OF 1,2-DIPHENYL-3,4-DIHYDRONAPHTHALENES

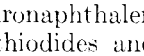
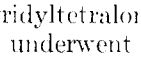


Compd	R^1	R^2	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
23	H	$OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	174–178	$C_{28}H_{32}ClNO$	76.84	76.30	7.29	7.11
24	H		203–204	$C_{28}H_{30}ClNO$	75.69[c]	75.66	7.20	7.06
25	CH_3O	$OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	171–173	$C_{29}H_{34}ClNO_2$	75.07	75.23	7.39	7.67
26	CH_3O		164–167	$C_{29}H_{32}ClNO_2$	75.38	75.18	6.68	7.17
27	HO		170–174	$C_{30}H_{38}ClNO_2$	73.74[b]	73.85	7.34	7.08
28	CH_3O	$OCH_2CHOHCH_2NH_2 \cdot HCl$	176–184	$C_{26}H_{28}ClNO_3$	71.30	71.33	6.44	6.89
29	CH_3O	$N(CH_3)_2$	130–133	$C_{25}H_{25}NO$	84.47	84.63	7.09	7.41
30	CH_3O		230–233	$C_{28}H_{30}ClNO$	77.85	77.11	7.00	6.83
31	CH_3O		195–197	$C_{29}H_{32}ClNO$	76.55[c]	76.77	7.31	7.27
32	CH_3O		114–117	$C_{30}H_{34}INO$	64.07[c]	63.59	6.32	6.57
33	CH_3O		172–174.5	$C_{31}H_{38}ClNO$	76.60	76.35	7.74	7.97

[a] Calcd for hemi-ethyl acetate solvate. [b] Calcd for methanol solvate. [c] Calcd for ethyl acetate solvate.

TABLE IV
BASIC 1,2,3,4-TETRAHYDRO-1-NAPHTHOLS



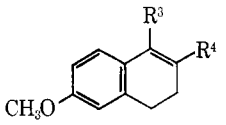
Compd	R^1	R^2	R^3	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
34	H	$p\text{-}C_6H_4OCH_2CH_2N(C_2H_5)_2 \cdot HCl$	C_6H_5	180–182	$C_{28}H_{34}ClNO_2$	74.39	74.04	7.58	7.55
35	H		C_6H_5	203–205	$C_{28}H_{32}ClNO_2$	73.27	72.92	7.68	7.36
36	OCH_3		C_6H_5	127–129.5	$C_{22}H_{21}NO_2$	79.73	79.80	6.39	6.66
37	OCH_3		C_6H_5	182–185	$C_{22}H_{21}NO_2$	79.73	79.65	6.39	6.59
45	OCH_3	C_6H_5		207–209	$C_{22}H_{21}NO_2$	79.73	79.25	6.39	6.85

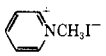
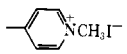
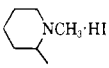
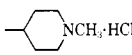
presence of an excess of *p*-toluenesulfonic acid. The 2- and 4-pyridyldihydronaphthalenes were then converted to their methiodides and these were reduced catalytically to the N-methylpiperidines (Table V).

Although the 2-pyridyltetralone **44**, prepared by the method of Bencze,[12] underwent reaction with phenylmagnesium bromide to give a naphthol (**45**), reaction with anisylmagnesium bromide under the same conditions afforded the dihydronaphthalene (**46**). It is of note that throughout this series, the presence of two electron-rich groups *para* to the carbinol intermediate of the Grignard adduct leads to spontaneous dehydration. When only one such group is present (as above

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

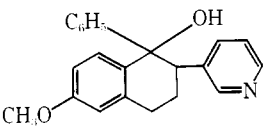
TABLE V
PYRIDYL AND PIPERIDYL DERIVATIVES



Compd	R^3	R^4	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
38	2-Pyridyl	C_6H_5	139–142	$C_{22}H_{19}NO$	84.31	84.19	6.11	6.18
39	4-Pyridyl	C_6H_5	134–136.5	$C_{22}H_{19}NO$	84.31	84.12	6.11	6.39
40		C_6H_5	224–226	$C_{23}H_{22}INO$	60.67	60.61	4.87	4.81
41		C_6H_5	285–286	$C_{23}H_{22}INO$	60.67	60.85	4.87	5.20
42		C_6H_5	222–223[a]	$C_{23}H_{28}INO$	59.87	60.10	6.12	6.29
43		C_6H_5	232–236[b]	$C_{23}H_{28}ClNO$	74.67	74.23	7.63	7.92
46	p-$C_6H_4OCH_3$	3-Pyridyl·HCl	230–232	$C_{23}H_{22}ClNO_2$	72.72	71.76	5.84	5.52

[a] λ_{max} 283 mμ (ε 17,800). [b] λ_{max} 289, 309 mμ (ε 10,600).

or in the reactions leading to **34** or **35**, Table IV) the carbinol can be isolated without difficulty.



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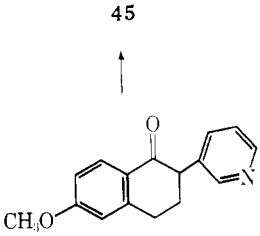
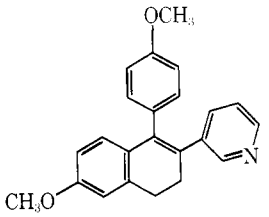


44

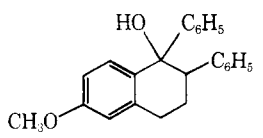


46

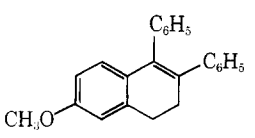
Biological Activity.—The compounds obtained above were tested for antifertility activity in the manner described previously.[6] The results of the testing of these agents on oral administration are presented in Tables VI and VII.

Uterotropic and antiestrogenic activity of several derivatives were evaluated in 60–70-g ovariectomized female rats treated orally for 10 days. On the 11th day the animals were autopsied and their uteri weighed immediately and compared with appropriate standards (Table VIII).

In a previous report,[1] we noted that the nonbasic compounds **47** and **48** are both potent estrogens in the uterine weight assay. The pyridyl derivatives **36** and **39**, basic isosteres of **47** and **48**, also exhibit classic uterotropic activity; **36** is roughly equal in potency



47



48

to **47**. These data and the finding that the aniline derivative **29** induces a classical estrogen response demonstrate that simple incorporation of a basic group into an estrogen does not suffice for the design of an estrogen antagonist.

The data presented here do tend toward the conclusion that the presence of a basic group *at a given position in space* is required to obtain a molecule which will antagonize the effects of concurrent estrogen administration. The finding that the oxygen in the basic ethers can be replaced by a methylene group to afford compounds which show the same potency as both antifertility agents and estrogen antagonists bolsters this hypothesis. Further support comes from the increasing antifertility potency in the series **30–33** as the most suitable chain length is approached.

The importance of the 6-methoxy group, first encountered in the indene series[6] is again displayed in the present series of compounds; thus, for example, **26** is more potent than **24** by a factor of 20. Another carryover from the previous findings is the importance of the nature of the basic group, indeed the potentiation obtained by replacement of diethylamine by pyrrolidine is tenfold in the present series (**24** and **26**).

Jensen has recently shown[13] that in the rat, compound **26** competes with estradiol for active sites in the uterus. We speculate at this time that the observed antifertility potency of a given compound, neglecting for the moment such factors as absorption and metabolism, is to some measure a reflection of the "fit" of the molecule to an estrogen site of action.

Experimental Section[14]

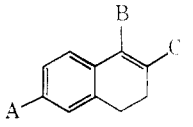
The experimental procedures given below are representative for all compounds prepared in Tables I–V. Detailed procedure are outlined where the preparations differ significantly from the general ones.

N-[(*p*-Bromophenyl)acetyl]pyrrolidine (6).—A mixture of 30 g of *p*-bromophenylacetic acid and 60 ml each of benzene and $SOCl_2$ was heated under reflux for 4 hr. The solvent and excess reagent were then evaporated *in vacuo*. A solution of the crude acid chloride in 100 ml of benzene was added over 30 min to 35 ml of pyrrolidine in 100 ml of benzene. Following an additional 2 hr of stirring the solution was washed in turn with water, 2.5 *N* HCl, and brine. The solid which remained when the organic

(13) E. V. Jensen, Abstracts, Endocrinology Society Meeting, New York, N. Y., June 1965.

(14) The authors are indebted to the Physical and Analytical Chemistry Unit of The Upjohn Company for elemental analyses and spectral determinations.

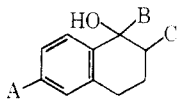
TABLE VI
ANTIFERTILITY ACTIVITY OF DIHYDRONAPHTHALENES IN THE RAT



Compd	A	B	C	MED_{100},[a] mg rat⁻¹ day
23	H	*p*-$C_6H_4OCH_2CH_2N(C_2H_5)_2$·HCl	C_6H_5	0.25
24	H	*p*-$C_6H_4OCH_2CH_2$N⟨⟩·HCl	C_6H_5	0.10
25	CH_3O	*p*-$C_6H_4OCH_2CH_2N(C_2H_5)_2$·HCl	C_6H_5	0.05
26	CH_3O	*p*-$C_6H_4OCH_2CH_2$N⟨⟩·HCl	C_6H_5	0.005
27	HO	*p*-$C_6H_4OCH_2CH_2$N⟨⟩·HCl	C_6H_5	0.1
28	CH_3O	*p*-$C_6H_4OCH_2CHOHCH_2NH_2$·HCl	C_6H_5	0.025
29	CH_3O	*p*-$C_6H_4N(CH_3)_2$	C_6H_5	0.05
30	CH_3O	*p*-$C_6H_4CH_2$N⟨⟩·HCl	C_6H_5	>10
31	CH_3O	*p*-$C_6H_4(CH_2)_2$N⟨⟩·HCl	C_6H_5	0.05
32	CH_3O	*p*-$C_6H_4(CH_2)_3$N⟨⟩·HCl	C_6H_5	0.005
33	CH_3O	*p*-$C_6H_4(CH_2)_4$N⟨⟩·HCl	C_6H_5	0.005
38	CH_3O	⟨N⟩	C_6H_5	0.1
39	CH_3O	⟨N⟩	C_6H_5	0.1
42	OCH_3	⟨N(CH)⟩·HCl	C_6H_5	0.5
43	OCH_3	⟨NCH⟩·HCl	C_6H_5	5
46	OCH_3	*p*-$C_6H_4OCH_3$	⟨N⟩·HCl	10

[a] Minimal effective dose for 100% inhibition of pregnancy, oral administration.

TABLE VII
ANTIFERTILITY ACTIVITY OF
1,2,3,4-TETRAHYDRO-1-NAPHTHOLS IN THE RAT



Compd	A	B	C	MED_{100},[a] mg/ rat/day
34	H	*p*-$C_6H_4OCH_2CH_2N(C_2H_5)_2$·HCl	C_6H_5	0.5
36	OCH_3	⟨N⟩	C_6H_5	0.01
37	OCH_3	⟨N⟩	C_6H_5	0.05
45	OCH_3	C_6H_5	⟨N⟩	2

[a] See footnote *a*, Table I.

layer was taken to dryness was recrystallized from benzene–cyclohexane to give 31.62 g of the amide (see Table I).

N-(*p*-Bromophenyl)ethylpyrrolidine (10).—A solution of 31.62 g of the N-(*p*-bromophenylacetyl)pyrrolidine in 400 ml of ether was added over 1.5 hr to a suspension of 10 g of $LiAlH_4$ in 100 ml of ether. Following 3 hr of heating under reflux the mixture was cooled in ice and treated in turn with 10 ml of water, 10 ml of 15% aqueous NaOH, and 30 ml of water. The precipitated solid was collected and washed thoroughly with ether. The combined filtrates were washed with water and brine and the organic layer was taken to dryness. The residual oil was distilled twice through a short fractionating column to afford on the second distillation 12.26 g of oil, bp 102–106° (0.4 mm) (see Table II).

1-[*p*-(2-Diethylaminoethoxy)phenyl]-1,2,3,4-tetrahydro-2-phenyl-1-naphthol Hydrochloride (34).—A solution of 11.0 g of 2-phenyl-1-tetralone in 100 ml of THF was added to the Grignard reagent prepared from 13.6 g of *p*-(2-diethylaminoethoxy)-bromobenzene and 1.24 g of Mg in 130 ml of THF. Following 16 hr of standing at room temperature the mixture was treated with 5 ml of water. The resulting gel was removed by filtration through Celite, the filtrate diluted with ether, washed with water, and taken to dryness. The residue was dissolved in ether and extracted with 2.5 *N* HCl. This last solution was extracted with 250 ml of ether in several portions. These last extracts were taken to dryness and the residue was recrystallized twice from methylene chloride–benzene. There was obtained 6.30 g of product, mp 180–182° dec (see Table III).

1-{[*p*-(2-Diethylamino)ethoxy]phenyl}-3,4-dihydro-6-methoxy-2-phenylnaphthalene Hydrochloride (25).—Proceeding exactly as above 7.55 g of 2-phenyl-6-methoxy-1-tetralone was allowed to react with the Grignard reagent from 8.15 g of *p*-(2-diethylaminoethoxy)bromobenzene. The product was isolated in the same way and recrystallized from CH_2Cl_2–ethyl acetate to afford 3.42 g of product, mp 171–173°. Work-up of the neutral fraction led to the recovery of 3.60 g of starting ketone, mp 113–115°, mmp (with authentic material) 113–116°.

1-{[*p*-(2-Diethylamino)ethoxy]phenyl}-3,4-dihydro-2-phenylnaphthalene Hydrochloride (23).—A melt of 5 g of the carbinol **34** was heated in an oil bath maintained at 195–200° until effervescence stopped (30 min). The glass which was obtained on cooling

TABLE VIII
ORAL UTEROTROPIC ACTIVITY[a]

No.	Daily dose, μg	Av uterine wt, mg
	Without Concomitant Estradiol	
25	10	49
	20	56
26	2.5	30
	5	45
	25	57
29	25	69
	50	89
	100	96
32	1	43
	2.5	53
	10	70
39	10	99
	50	128
36	0.5	64
	1	82
	2	102
45	40	37
	80	42
Estradiol	0.00	25
	0.01	39
	0.02	58
	0.06	121
	With Concomitant Estradiol, 0.04 μg/day	
25	250	58
26	2.5	106
	5	83
	25	67
32	20	80
	40	70
36	250	158
	500	164
37	100	106
	200	116
Estradiol	0.00	25
	0.04	115

[a] Five rats used per treatment except for estradiol standard for which 10 rats were used.

was crystallized by trituration with ethyl acetate. Two recrystallizations from CH_2Cl_2–ethyl acetate gave 3.79 g of product, mp 174–178°.

6-Hydroxy-2-phenyl-1-tetralone (22).—Aluminum chloride (30.3 g) was added to a solution of 28.6 g of the ketone in 500 ml of benzene. Following 4 hr of heating under reflux the solution was allowed to cool. Chloroform and 2.5 *N* HCl were then added and the mixture was allowed to stir for several hours. The organic layer was separated, washed with water and aqueous $NaHCO_3$, and taken to dryness. The residual solid was recrystallized from chloroform to afford 18.25 g of the phenol, mp 180–185°.

The analytical sample, mp 183–185.5°, was recrystallized from the same solvent.

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.19; H, 6.17.

7,8-Dihydro-6-phenyl-5-[*p*-(2-piperidinoethyl)phenyl]-2-naphthol Hydrochloride (27).—A mixture of 4.60 g of the phenol, 5 ml of dihydropyran, and 0.10 g of *p*-toluenesulfonic acid was stirred at room temperature; the solid slowly went into solution as a new solid precipitated. At the end of 18 hr the mixture was taken to dryness, the residue was suspended in 80 ml of ether, and the solid was collected on a filter. There was obtained 4.0 g of the crude pyranyl ether, which shows only traces of OH absorption in the infrared.

A solution of the above ether in 50 ml of THF was added to the Grignard reagent prepared from 5.72 g of *p*-[2-(N-piperidino)-ethoxy]bromobenzene and 0.50 g of Mg in 60 ml of THF. Following 18 hr of heating under reflux the mixture was allowed to cool and treated with a small amount of water. The precipitated gel was removed by filtration, and the filtrate was diluted with ether and washed well with water. The residue which remained when the solution was taken to dryness was taken up in a mixture of ether and 2.5 *N* HCl. The crystalline solid which came out of this mixture was collected on a filter and recrystallized twice from methanol–2.5 *N* HCl. There was obtained 1.04 g of the hydrochloride salt, mp 170–174°.

N-{2-Hydroxy-3-[*p*-(3,4-dihydro-6-methoxy-2-phenyl-1-naphthyl)phenoxy]propyl}succinimide (21).—A mixture of the epoxide **20**, 0.80 g of succinimide, and 4 drops of piperidine in 100 ml of absolute ethanol was heated under reflux for 17 hr. The volume was reduced to 30 ml *in vacuo*, and the mixture was diluted with water. The gellike precipitate was taken up in CH_2Cl_2. The solution was washed with water and brine and taken to dryness. The residue was recrystallized twice from aqueous methanol to give 2.63 g of **21**, mp 142–148°.

Anal. Calcd for $C_{30}H_{29}NO_5$: C, 74.51; H, 6.05. Found: C, 74.23; H, 6.06.

1-Amino-3-[*p*-(3,4-dihydro-6-methoxy-2-phenyl-1-naphthyl)-phenoxy]-2-propanol Hydrochloride (28).—A mixture of 4.19 g of the imide **21** and 16 g of NaOH in 320 ml of 95% ethanol was heated under reflux for 20 hr. The bulk of the solvent was removed under reduced pressure. The residue was taken up in a small amount of CH_2Cl_2 and water. The organic layer was evaporated, washed with water, and shaken with 100 ml of 2.5 *N* HCl to afford a solid precipitate. This was recrystallized from methanol–2.5 *N* HCl to yield 3.10 g of **28**, mp 178–184°.

The analytical sample, obtained from another run, melted at 176–184°.

6-Methoxy-2-phenyl-1-(2-pyridyl)-1,2,3,4-tetrahydro-1-naphthol (36).—Over the period of 20 min a solution of 3.16 g of 2-bromopyridine in 30 ml of ether was added to 26.5 ml of freshly prepared 0.75 *M* butyllithium in ether in an ice-methanol bath.[15] After an additional 20 min of stirring, a solution of 5.28 g of the tetralone in 75 ml of THF was added over the period of 30 min with continued cooling. The mixture was then stirred for 1 hr and decomposed with 25 ml of saturated NH_4Cl solution. The organic layer was separated, washed with water, and extracted with 250 ml of 2.5 *N* HCl. The precipitate which was obtained when the extract was made basic was recrystallized three times from aqueous methanol to yield 1.30 g of **36**, mp 127–129.5°.

From the neutral fractions there was obtained 3.28 g of recovered ketone.

2-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthyl)pyridine (38).—A mixture of 2.58 g of the carbinol **36** and 1.70 g of *p*-toluenesulfonic acid in 100 ml of toluene was heated at reflux under a Dean–Stark trap for 5 hr. The solvent was then evaporated under vacuum and the residue was dissolved in methylene chloride. The residual solid was recrystallized from methanol to yield 2.0 g, mp 143–145°. The analytical sample from another run melted at 139–142°.

2-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthyl)-1-methylpyridinium Iodide (40).—A solution of 1.0 g of the pyridine in 25 ml of CH_3I was allowed to stand at room temperature. Within 15 min solid started to separate. At the end of 17 hr the excess reagent was removed on the rotary evaporator and the residue was recrystallized from acetonitrile. There was obtained 1.05 g of the quaternary salt, mp 224–226°.

2-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthyl)-1-methylpiperidinium Iodide (42).—A mixture of 3.0 g of the quaternary salt and 0.53 g of PtO_2 in 250 ml of ethanol was shaken under an atmosphere of hydrogen for 24 hr. At the end of this time slightly over the theoretical amount of gas had been absorbed. The catalyst was removed by filtration and the filtrate taken to dryness *in vacuo*. The residue was dissolved in methylene chloride and this solution was washed with aqueous $NaHCO_3$. The gum which remained when the solvent was removed was dissolved in 20 ml of ethanol and treated with 50 ml of saturated ethanolic picric acid. The precipitated picrate was recrystallized from acetonitrile to give 1.67 g of product, mp 222–226°. An analytical sample melted at 224–225°.

Anal. Calcd for $C_{29}H_{30}N_4O_8$: C, 61.91; H, 5.38; N, 9.96. Found: C, 62.13; H, 5.76; N, 10.05.

The picrate was suspended in 100 ml of ether and 100 ml each of NH_4OH and water. The mixture was stirred until the solid was all in solution and the organic layer separated. This was

(15) The reaction mixture needs to be cooled in Dry Ice–acetone at this point for the preparation of the 4-pyridyl analogs.

washed again with water and taken to dryness. The residue was dissolved (CH_2Cl_2) and washed with 20% HI, and the former solution was taken to dryness. The residual solid was recrystallized from methylene chloride–ethyl acetate to afford 1.17 g of **42**, mp 220–222°. An extensively purified sample melted at 222–223°, λ_{max} 283 mμ (ε 17,800).

Acknowledgment.—We wish to express our indebtedness to Mr. Brooke D. Aspergren of these laboratories for generous supplies of 2-phenyl-6-methoxy-1-tetralone, and to Mr. Richard D. Eliasen for help in the preparation of some of these compounds.

Substituted Aminoalkoxytriarylhaloethylenes[1]

FRANK P. PALOPOLI, VERNON J. FEIL, ROBERT E. ALLEN, DORSEY E. HOLTKAMP, AND ALFRED RICHARDSON, JR.[2]

The Departments of Organic Research and Endocrinology, Scientific Laboratories, The Wm. S. Merrell Company, Division of Richardson-Merrell, Inc., Cincinnati, Ohio 45215

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A series of triarylhaloethylene compounds were synthesized and screened for their effects on pituitary gonadotrophins in animals. One, 2-[*p*-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine dihydrogen citrate (**1**, clomiphene citrate) was selected for further testing in animals and in humans.

Robson and Schönberg[3] reported that triphenylethylene and triphenylchloroethylene were estrogens of low potency but of unusual duration of action. Shelton, *et al.*,[4] and others[5,6] have shown that substitution with alkoxy groups increased the potency of these derivatives. This report concerns a series of substituted aminoalkoxytriarylhaloethylenes having gonadotrophin inhibitory properties when tested in rats (see Table I).

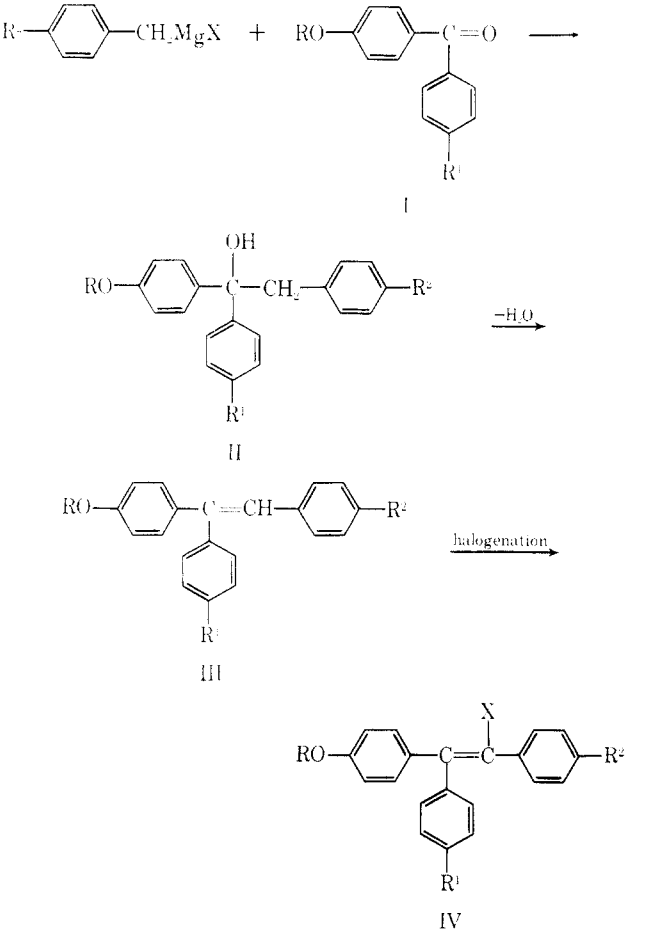
The compounds were prepared by the reaction of appropriate benzylmagnesium halides with substituted diaryl ketones (I), followed by dehydration of the resulting ethanols (II) to the triarylethylenes (III), which upon halogenation yielded the haloethylenes (IV) (Scheme I).

The basic substituted ketones I were generally prepared by the reaction of a substituted aminoalkyl halide with the sodium salt of the hydroxybenzophenone in ethanol.

Halogenation was attempted by a variety of methods,[7] the most successful being direct chlorination in chloroform. The use of N-chlorosuccinimide or N-bromosuccinimide was found to be less satisfactory, as the products obtained with these agents required considerable purification. In one case, direct bromination of 1-[*p*-(β-dimethylaminoethoxy)phenyl]-1-phenyl-2-(*p*-methoxyphenyl)ethanol gave a low yield of the desired haloethylene.

Noncrystalline hydrochloride salts of the compounds were converted to the bases with 10% sodium hydroxide solution and then to dihydrogen citrate salts with an equivalent amount of citric acid in butanone. The dihydrogen citrate salts are subsequently recrystallized from butanone or 2-propanol.

SCHEME I



Repeated recrystallization of certain of the hydrochloride salts of these compounds allowed the separation of the compounds into their *cis*[8] and *trans*[8] isomers (*i.e.*, **1a** and **1b**) which were subsequently characterized.

Tests for gonadotrophin inhibition were performed on intact immature male rats. The test compounds were administered subcutaneously in an oil vehicle at an initial dose of 50 mg/kg/day for 10 days. Lower doses were utilized in subsequent studies. Autopsies were

(1) Presented in part at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961, Abstracts, p 20N.

(2) To whom correspondence should be addressed.

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(4) R. S. Shelton, M. G. Van Campen, Jr., D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen, and K. K. Wycoff, *J. Am. Chem. Soc.*, **75**, 5491 (1953).

(5) E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, *Proc. Roy. Soc.* (London), **B127**, 140 (1939).

(6) C. R. Thompson and H. W. Werner, *Proc. Soc. Exptl. Biol. Med.*, **77**, 494 (1951).

(7) R. E. Allen, F. P. Palopoli, E. L. Schumann, and M. G. Van Campen, Jr., U. S. Patent 2,914,563 (1959); *Chem. Abstr.*, **54**, 5581*e* (1960).

(8) *cis* and *trans* are defined here in terms of the geometric relationship of the two unsubstituted phenyl rings.