was refluxed with zinc dust (27 g.) for 15 min. The solution was filtered and the filtrate was diluted with cold water. The precipitate was collected, washed with water, and air-dried to give IXa (6.5 g.), m.p. 119–119.5° (lit.[16] m.p. 119–120°). The n.m.r. showed a triplet at 312, 323, and 331 c.p.s.

3α-Bromo-17α-methyl-5α-androstane-2β,17β-diol (VIb).—A cooled solution of Vb (containing an undeterminable small amount of the $\Delta^{3,4}$-isomer) (32.0 g.) treated as above gave the crude bromohydrin. Recrystallization from methanol gave VIb (15 g.), m.p. 164–167°, $[\alpha]^{25}D$ +38.5°.

Anal. Calcd. for $C_{20}H_{33}BrO_2$: C, 62.33; H, 8.63. Found: C, 62.46; H, 8.59.

Crystallization of the first portion of the benzene eluate from methanol gave additional VIb (5.2 g., 47.2% total), while the latter portion gave pure 3α-bromo-17α-methyl-5α-androstane-4β,17β-diol (Xb, 0.7 g.), m.p. 182–184° dec., $[\alpha]^{25}D$ −22.5°.

Anal. Calcd. for $C_{20}H_{33}BrO_2$: C, 62.33; H, 8.62. Found: C, 62.14; H, 8.44.

3α-Bromo-17α-methyl-5α-androstan-17β-ol-2-one (VIIb).—Treatment of VIb (1.0 g.) with standard chromic acid solution[9] as described above gave a crude product. Recrystallization from acetone–hexane gave VIIb (550 mg.).

17β-Hydroxy-17α-methyl-5α-androst-3-en-2-one (VIIIb). General Method.—Freshly prepared VIIb (14.8 g.) was refluxed with lithium chloride (4.0 g.) and lithium carbonate (3.2 g.) in dimethylformamide (200 ml.) for 5.5 hr. and allowed to stand at room temperature overnight. Water (150 ml.) was added and the solution was extracted with ether. The ether extract was washed with 10% HCl solution, 5% $NaHCO_3$ solution, and water. The extract was dried over anhydrous Na_2SO_4 containing Darco, and the solvent was removed *in vacuo* to give a solid, λ_{max} 229.5 mμ (log ε 3.65). The product was purified by chromatography on silica gel. Crystallization of the benzene–ethyl acetate (17:3) eluates from acetone gave pure VIIIb (4.5 g.), λ_{max} 232 mμ (log ε 3.80).

3α-Bromo-17α-methyl-5α-androstan-17β-ol-4-one (XIb). General Method.—To a stirred solution of Xb (2.35 g.) in glacial acetic acid (35 ml.) was added with cooling chromic anhydride (1.05 g.) in glacial acetic acid (15 ml.) and water (1.1 ml.). The addition required 15 min. The reaction was stirred at room temperature overnight and poured into ice and water. The precipitate was collected, washed with water, and air-dried. The crude product was dissolved in methanol and treated with Darco. The solvent was removed *in vacuo*, and the residue was recrystallized from methanol–water to give XIb (1.2 g.).

Acknowledgment.—The authors are indebted to Dr. F. B. Colton for his helpful suggestions and continued interest.

Mammalian Antifertility Agents. I. Derivatives of 2,3-Diphenylindenes[1]

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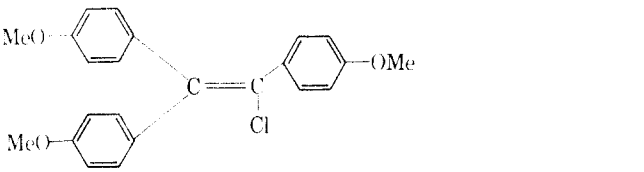
A series of basic ethers of 2,3-diphenylindenes was prepared by the reaction of substituted 2-phenyl-1-indanones. Methods are given for the preparation of the latter. Several of the agents were found to be highly potent antifertility agents in the rat. Structure–activity relations in this series are discussed.

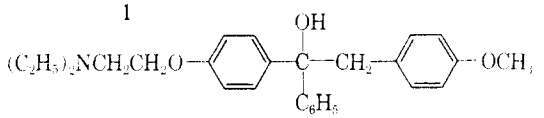
Reproduction of the species is known to be an intricate process dependent at several stages on subtle balances of naturally occurring hormones. Thus, it has been demonstrated that in animals the processes of ovulation, egg transport, and nidation can all be altered by varying the relative hormonal balances.[2] By introducing an exogenous antagonist to a hormone upon which the reproductive process is dependent, it may prove possible to interrupt the chain of events which normally leads to the implantation of a fertilized ovum in the uterus.

Along these lines it has been shown that some basic ethers of compounds related to the synthetic estrogen **1** such as **2** and **3**[3] will exhibit antifertility activity in laboratory animals.[4,5]

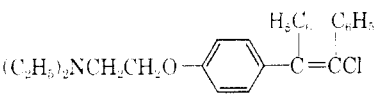
It is of particular interest that while some of these agents show weak estrogenic properties, they will antagonize the effects of concurrently administered estrogen.[6,7] Although such lines of evidence can seldom be relied upon, we nevertheless decided to investigate basic ethers of synthetic estrogens. The report[8,9] that indenes such as **4** are relatively potent estrogens made these molecules, which possess a rigid



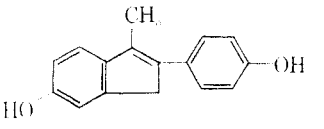
1



2



3



4

(1) Published in preliminary form as a Communication to the Editor, D. Lednicer, J. C. Babcock, S. C. Lyster, J. C. Stucki, and G. W. Duncan, *Chem. Ind.* (London), 2098 (1961); presented in part at the Symposium on Nonsteroidal Antifertility Agents, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963.

(2) "Sex and Internal Secretions," W. C. Young, Ed., Williams and Wilkins Co., Baltimore, Md., 1961.

(3) R. E. Allen, F. P. Palopoli, E. L. Schumann, and M. G. VanCampen, Jr., U.S. Patents 2,914,562 and 2,914,563 (1959).

(4) S. J. Segal and W. O. Nelson, *Proc. Soc. Exptl. Biol. Med.*, **98**, 431 (1958).

(5) D. E. Holtkamp, J. G. Greslin, C. A. Root, and L. J. Lerner, *ibid.*, **105**, 197 (1960).

(6) L. E. Barnes and R. K. Meyer, *Fertility Sterility*, **13**, 472 (1962).

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

(8) W. Salzer, *Z. Physiol. Chem.*, **274**, 39 (1946).

(9) M. Silverman and M. T. Bogert, *J. Org. Chem.*, **11**, 51 (1946).

TABLE I

2-3-DIPHENYLPROPIONIC ACIDS

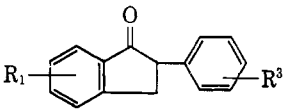
$R^1C_6H_4CH_2CH(C_6H_4R^3)CO_2H$

R^1	R^3	M.p., °C.	Yield, %[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	*p*-F	93.5–95	70	$C_{15}H_{13}FO_2$	73.76	73.44	5.36	5.78
H	*p*-CH_3	104–107[b]	52	$C_{16}H_{14}FO_2$	...	...	...	...
H	*p*-Cl	115–116.5	57	$C_{15}H_{13}ClO_2$	69.10	69.32	5.02	5.24
H	*p*-OCH_3	106–108[c]	67	$C_{16}H_{14}O_3$	...	...	...	...
m-OCH_3	H	Oil[b]	85	$C_{16}H_{14}O_3$	...	...	...	...
m-OCH_3	*m*-OCH_3	90.5–93	76	$C_{17}H_{16}O_4$	71.31	71.61	6.34	6.26
m-OCH_3	*p*-OCH_3	96–100[d]	55	$C_{17}H_{16}O_4$	...	...	...	...
m-OCH_3	*p*-CH_3	81–85[b]	62	$C_{17}H_{16}O_3$	...	...	...	...
m-OCH_3	*p*-Cl	93–95	75	$C_{16}H_{15}ClO_3$	66.09	66.24	5.20	4.88
p-OCH_3	H	118.5–120[e]	67	$C_{16}H_{14}O_3$				
m,*p*-$(OCH_3)_2$	H	Oil[b]	94	$C_{17}H_{16}O_4$				

[a] Based on arylpropionic acid. [b] The crude material was used for the cyclization without further purification. [c] P. C. Jocelyn [*J. Chem. Soc.*, 1640 (1954)] gives m.p. 108°. [d] D. S. Morris [*ibid.*, 1913 (1950)] gives m.p. 104°. [e] Lit.[c] m.p. 119°.

TABLE II

2-PHENYLINDANONES



R^1	R^3	M.p., °C.	Yield, %[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	H	79–82[b]	60	$C_{15}H_{12}O$	...	...	...	...
H	*p*-F	55.5–58	68	$C_{15}H_{11}FO$	79.62	79.45	4.90	4.70
H	*p*-CH_3	b.p. 155–160 (2 mm.)	55	$C_{16}H_{14}O$	86.45	86.52	6.35	6.58
H	*p*-Cl	79.5–81[c]	78[d]	$C_{15}H_{11}ClO$	74.23	74.14	4.57	4.39
H	*p*-OCH_3	79–81	49	$C_{16}H_{14}O_2$	80.64	80.55	5.92	5.99
5-OCH_3	H	108–111.5[e]	68	$C_{16}H_{14}O_2$	...	...	...	...
5-OCH_3	*m*-OCH_3	93–96	65	$C_{17}H_{16}O_3$	76.10	76.65	6.01	6.32
5-OCH_3	*p*-OCH_3	90–93[f]	78	$C_{17}H_{16}O_3$	...	...	...	...
5-OCH_3	*p*-Cl	116.5–119	78	$C_{16}H_{13}ClO_2$	70.45	70.12	4.80	4.55
5-OCH_3	*p*-CH_3	99–103	64	$C_{17}H_{16}O_2$	80.92	80.99	6.39	6.52
6-OCH_3	H	152–154[g,h]	26	$C_{16}H_{14}O_2$	...	...	...	...
5,6-$(OCH_3)_2$	H	153–156[i]	58	$C_{17}H_{16}O_3$	...	...	...	...

[a] All cyclizations are by HF unless otherwise indicated. [b] Lit.[10] m.p. 82°. [c] Methylene chloride used as cosolvent. [d] Based on acid consumed. [e] Table I, footnote *c* gives m.p. 115°. [f] Lit.[10] m.p. 96°. [g] Lit.[10] m.p. 153°. [h] Cyclization by aluminum chloride method. [i] Lit.[10] m.p. 156°.

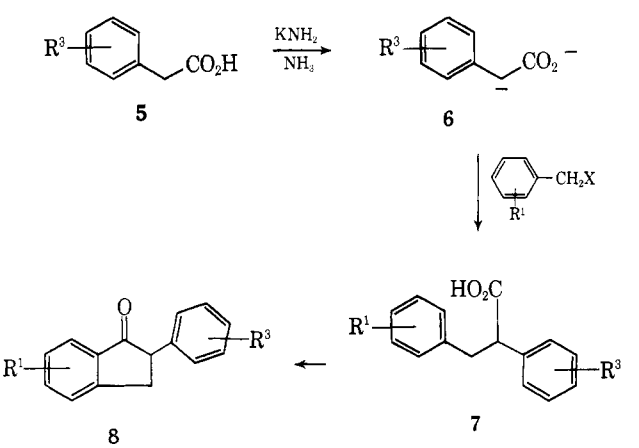
moiety comparable to the A/B rings of a steroid, an interesting starting point.

We envisaged as final compounds a series of basic ethers of 1,2-diphenylindenes. The usual method for the introduction of an aminoalkoxy group consists in the alkylation of the corresponding phenol. Since some of the compounds we desired would contain methoxy groups as well, this approach would necessitate the selective demethylation of a single phenolic ether. In order to circumvent the need for such a selective reaction, a route was devised in which the phenyl bearing the basic ether grouping would be introduced as the final step by condensation of the Grignard reagent of the basic ether of *p*-bromophenol with a suitable indanone.

Preparation of Indanones.—The general method used to prepare the intermediate indanones is shown in Scheme I. The dipotassio salt of the phenylacetic acid was formed by the elegant method of Hauser[10] by means of potassium amide in liquid ammonia. The appropriate benzyl halide was then added to the dianion and the ammonia was evaporated to afford the propionic acid upon a relatively simple work-up.

(10) C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956).

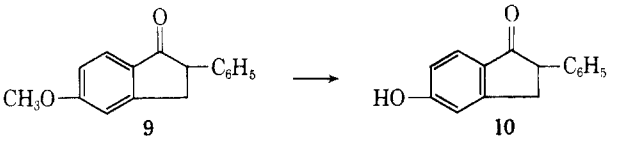
SCHEME I



The indanone was obtained from the acid by dissolving the latter in liquid HF and allowing the reagent to evaporate at room temperature. The physical and analytical constants of the acids and ketones are listed in Tables I and II, respectively. The generality of this scheme is demonstrated by the variety of substituents which are stable under these conditions. In one case (R^1 = H; R^3 = *p*-Cl), the insolubility of the

propionic acid in liquid HF necessitated the addition of methylene chloride to the reaction mixture. Although a two-phase mixture resulted, the ketone was formed in good yield. Where this method gave a poor yield (*e.g.*, R^1 = *m*-OCH_3; R^3 = H), the ketone was obtained by conversion of the acid to its chloride followed by cylization by means of aluminum chloride.

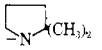
In order to prepare some indenes having a free phenolic group, the indanone **9** was demethylated by means of aluminum chloride in benzene to afford the free phenol **10**.



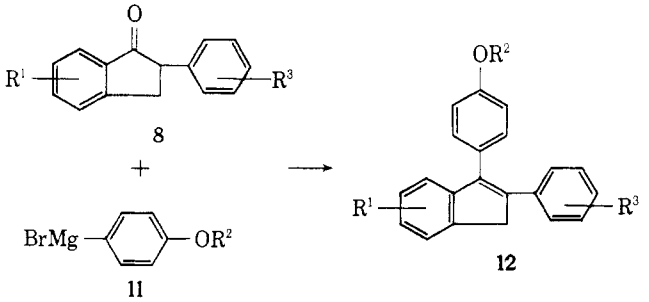
9 **10**

Preparation of Basic Ethers of *p*-Bromophenol.—A series of phenyl cycloalkylaminoethyl ethers was prepared from bromophenol by alkylation with the desired β-chloroethylamine in methanol containing sodium methoxide. The products were then carefully purified by distillation. Without further characterization, the corresponding Grignard reagents were prepared in tetrahydrofuran (induced by the preparation of a trace of methylmagnesium iodide in the reaction flask). Occasionally, however, this reaction took an aberrant course and magnesium was consumed without formation of the desired reagent. The physical properties of the ethers are listed in Table III.

TABLE III
AMINOALKOXY ETHERS OF *p*-BROMOPHENOL
p-$BrC_6H_4OCH_2CH_2A$

A	B.p., °C. (mm.)
	119–123 (2.5)
	128–130 (0.4)
	127–133 (1.5)
	147–149 (3)

Preparation of 2,3-Diphenylindenes.—These products were prepared by reaction of the Grignard reagent and the selected indanone.

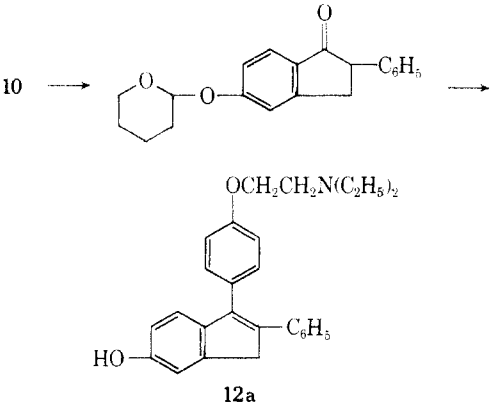


8 **11** **12**

The best results in the condensation were obtained when the solution of the ketone was added to that of the Grignard reagent at 0°, followed by heating overnight under reflux. The product (along with other basic materials found in the reaction mixture) was separated from the neutral portion by extraction with acid. The crude basic product was then heated briefly in benzene in the presence of *p*-toluenesulfonic acid to insure that dehydration, which often occurred during the first acid extraction, was complete.

The yield of product in the condensation–dehydration step ranged from 10–42%. A cursory chromatographic examination of the neutral fraction in one case (R^1 = 5-OCH_3; R^3 = H) showed that at least part of this consisted of recovered starting material, produced presumably by the Grignard reagent through formation of the magnesium enolate.

In order to prepare a phenolic indene, the indanone **10** was converted to the tetrahydropyranyl ether. This compound was then condensed in the usual way with the basic Grignard reagent. Brief treatment of the final product with aqueous acid led to the desired aminophenol.



12a

Since the free bases in this series tended to be low melting, poorly crystalline materials, the products were handled as their hydrohalide salts. It is surprising that these tend to be far more soluble in organic solvents such as chloroform than in aqueous media. The physical and analytical properties of the final products and their antifertility potencies are listed in Table IV.

Antifertility Screening Method.—Compounds were assayed for antifertility activity by a standard method. On the day prior to mating, compounds were administered orally to 200-g. mature female Sprague–Dawley rats. The animals were then allowed to mate and the vaginal smear was checked to insure that insemination had occurred. Oral administration of the compound was then continued daily for an additional 6 days. Forty eight hours after the last treatment animals were sacrificed and the uteri were examined for implantation sites. The lowest dose which completely prevented implantation[11] was considered the MED_{100} and is recorded in Table IV. The maximum daily screening dose for any compound was 2 mg./rat; compounds inactive at this dose were not followed further.

Structure–Activity Relationships.—Using this assay, it was found that relatively small structural changes had profound and unpredictable effects on the antifertility potency of compounds within the indene series.

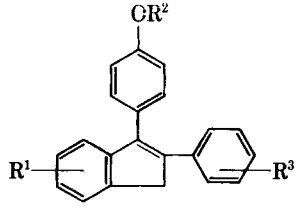
Introduction of a methoxyl group into position 5 (**12f**) of the parent compound (**12a**) had little effect on potency. A methoxyl group at the 6-position[12]

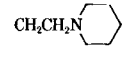
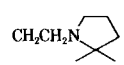
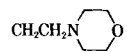
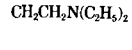
(11) Determined by successive decrements to 50% the previous active dose.

(12) If the molecule is compared to a steroid, this would be considered the counterpart of the 3-position in the latter, a position usually bearing oxygen.

TABLE IV

BASIC ETHERS OF 2,3-DIPHENYLINDENES



Compd.	R¹	R²	R³	HX	Yield, %	M.p., °C.	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found	MED_{100},[a] mg./rat/day
a	H	$CH_2CH_2N(C_2H_5)_2$	H	$HClO_4$	13	156–157.5	$C_{27}H_{29}NO \cdot HClO_4$	67.00	67.05	6.25	6.36	2.89	3.10	0.5
b	H	$CH_2CH_2N(C_2H_5)_2$	*p*-F	HI	42	181–183	$C_{27}H_{28}FNO \cdot HI$	61.27	61.22	5.52	5.68	2.65	2.73	>2
c	H	$CH_2CH_2N(C_2H_5)_2$	*p*-CH_3	HBr	41	188–190	$C_{28}H_{31}NO \cdot HBr$	70.28	70.12	6.74	7.02	2.93	2.95	>2
d	H	$CH_2CH_2N(C_2H_5)_2$	*p*-OCH_3	HCl	20	170–172	$C_{28}H_{31}NO_2 \cdot HCl$	74.73	74.36	7.17	7.32	3.11	3.31	0.5
e	H	$CH_2CH_2N(C_2H_5)_2$	*p*-Cl	HCl	30	206–208	$C_{27}H_{27}NO \cdot HCl$	71.36[b]	70.19	6.43	6.87	3.08	2.94	>2
f	5-OCH_3	$CH_2CH_2N(C_2H_5)_2$	H	HCl	33	131–135	$C_{28}H_{31}NO_2 \cdot HCl$	74.73[b]	73.42	7.17	6.62	3.11	3.05	0.5
g	6-OCH_3	$CH_2CH_2N(C_2H_5)_2$	H	HCl	25	176.7–178	$C_{28}H_{31}NO_2 \cdot HCl$	74.73	74.45	7.17	7.03	3.11	3.15	0.1
h	6-OCH_3	$CH_2CH_2N(C_2H_5)_2$	*m*-OCH_3	HCl	31	175.5–177.5	$C_{29}H_{33}NO_3 \cdot HCl$	72.56	72.56	7.14	6.97	2.92	3.15	>2
i	6-OCH_3	$CH_2CH_2N(C_2H_5)_2$	*p*-CH_3	HCl	32	210–212	$C_{29}H_{33}NO_2 \cdot HCl$	75.02	74.25	7.38	7.20	3.02	3.08	1.0
j	6-OCH_3	$CH_2CH_2N(C_2H_5)_2$	*p*-Cl	HCl	33	199–201	$C_{28}H_{30}ClNO_2 \cdot HCl$	69.41	69.43	6.45	6.48	2.91	2.89	>2
k	6-OCH_3	$CH_2CH_2N(C_2H_5)_2$	*p*-OCH_3	HI	40	156–160	$C_{29}H_{33}NO_3 \cdot HI$	62.94[c]	63.09	6.11	5.98	2.29	2.45	0.5
l	5,6-diOCH_3	$CH_2CH_2N(C_2H_5)_2$	H	HCl	19	210–212	$C_{29}H_{33}NO_3 \cdot HCl$	72.56[b]	71.01	7.14	7.06	2.92	2.77	2.0
m	6-OCH_3		H	HCl	24	211.5–213.5	$C_{29}H_{31}NO_2 \cdot HCl$	75.38	75.06	6.98	7.04	3.03	3.09	0.1
n	6-OCH_3		H	HCl	12	213–216	$C_{28}H_{29}NO_2 \cdot HCl$	75.07[b]	74.32	6.15	6.82	3.13	3.44	0.025
o	6-OCH_3		H	HCl	26	183–184	$C_{30}H_{33}NO_2 \cdot HCl$	75.69	76.07	7.20	8.04	2.94	3.27	0.1
p	6-OCH_3		H	Free base	41	108–112	$C_{28}H_{29}NO_3$	78.66	78.51	6.84	7.34	3.28	3.46	2.0
q	6-OH	$CH_2CH_2N(C_2H_5)_2$	H	Free base	10	154–155.5	$C_{27}H_{27}NO_2$	81.17	80.74	7.32	7.47	3.51	3.82	2.0

[a] Minimal 100% effective oral antifertility dose. [b] Compound contains ethyl acetate of solvation as determined by infrared melt solvate technique. [c] Benzene of solvation by infrared melt solvate.

on the other hand (**12g**) increased the potency by a factor of 5 relative to the parent. It is noteworthy that the potentiating effect of the 6-methoxyl group does not appear to be additive; the 5,6-dimethoxy compound (**12l**) is less potent than the unsubstituted indene **12a** by a factor of 4. Though demethylation of phenolic ethers frequently occurs in biological systems, the aminophenol which would result from such a transformation (**12g**) shows but one-twentieth the potency of the methylated analog.

Modification of the pattern of substitution in the phenyl group at position 2 of the indene similarly altered the potency of these compounds. Substitution of a methoxyl group in the *para* position of **12a** gave a compound (**12d**) with the same potency. When the same change is made on the 6-methoxylated compound **12k**, however, the potency is reduced by a factor of 5. The introduction of chlorine (**12j**) or a methyl group (**12i**) greatly decreased the potency. The same trend can be seen in the similarly substituted compounds lacking the 6-methoxyl group (**12b**, **c**, and **e**). Replacing the diethylamino group of **12g** with piperidino (**12m**) or 2,2-dimethylpyrrolidino groups (**12n**) had no appreciable effect on potency. The morpholino analog **12p** showed a marked decrease in potency. Unexpectedly, incorporation of the pyrrolidine moiety led to a fourfold increase in potency, so that **12n** was active in the rat at a daily dose of 25 γ.

Thus we have found several potent mammalian antifertility agents in this class of compounds. Extensive biological characterization of a representative compound (**12g**)[13] in this series showed it to exhibit estrogen-antagonistic properties, which may be related to the observed antifertility efficacy.

Experimental[14]

The experimental procedures given below are representative for all compounds prepared in Tables I through IV.

2-(*p*-Fluorophenyl)-3-phenylpropionic Acid.—To a solution of potassium amide prepared from 7.82 g. of the metal in 200 ml. of liquid ammonia there was added a solution of 15.4 g. of *p*-fluorophenylacetic acid in 100 ml. of ether. Over the period of 10 min. a solution of 14.0 g. of benzyl chloride in 50 ml. of ether was added to the mixture, followed by an additional 2 ml. of the halide 20 min. later. At the end of 2 hr. a small amount (5–10 g.) of ammonium chloride was added, and the ammonia was allowed to evaporate. Ether and water were then added to the residue. The aqueous layer was separated, filtered through Celite, and acidified. The crude product which precipitated was collected on a filter, dried, and recrystallized twice from methylene chloride–ligroin. There was obtained 17.0 g. of acid, m.p. 91–94°. One further crystallization afforded the analytical sample, m.p. 93.5–95° (see Table I).

2-(*p*-Fluorophenyl)-1-indanone. Cyclization by Means of Hydrofluoric Acid.—2-(*p*-Fluorophenyl)-3-phenylpropionic acid (16.8 g.) was dissolved in 120 ml. of liquid HF and the solution allowed to stand for 16 hr. The residue was taken up in ether and this solution was washed with water, saturated aqueous sodium bicarbonate, and finally 5% aqueous KOH. The ethereal solution was percolated through anhydrous sodium sulfate and taken to dryness *in vacuo*. The residual solid (12.2 g.) was recrystallized twice from ligroin to afford 10.56 g. of the indanone, m.p. 55.5–58°. One further crystallization from the same solvent afforded a sample, m.p. 55.5–58° (see Table II).

6-Methoxy-2-phenyl-1-indanone. Cyclization of the Acid Chloride with Aluminum Chloride.—A mixture of 4.80 g. of 3-(*p*-methoxyphenyl)-2-phenylpropionic acid and 4.16 g. of phosphorus pentachloride was heated at reflux until the evolution of gas ceased (45 min.). The mixture was taken to dryness *in vacuo*, redissolved in 50 ml. of benzene, and again taken to dryness. The dark residue was dissolved in 80 ml. of benzene. Over the period of 10 min., a slurry of 2.65 g. of aluminum chloride in 20 ml. of benzene was added to the solution of acid chloride. Following 17 hr. stirring at room temperature, the mixture was poured onto 250 ml. of ice and 100 ml. of HCl. This was stirred for 1 hr. The organic layer was separated and washed in turn with 2.5 *N* HCl, brine, 4% aqueous KOH, and again with brine. The organic solution was then taken to dryness to afford the crude ketone as a gum (4.30 g.). Chromatography on Florisil (elution with 5% acetone in ligroin) followed by two crystallizations from acetone–ligroin afford 1.04 g. of product, m.p. 151–154° (Table II).

***p*-(2-Piperidinoethoxy)bromobenzene.**—To a solution of 17.3 g. (0.10 mole) of *p*-bromophenol in 100 ml. of ethanol was added 22.4 g. of 25% sodium methoxide in methanol. Following 10 min. stirring, 16.1 g. of N-(2-chloroethyl)piperidine (used directly as obtained by neutralization of the corresponding hydrochloride) in the same volume of ethanol was added to the mixture. The mixture was stirred under reflux for 16 hr., allowed to cool, and filtered through Celite. The filtrate was concentrated *in vacuo*, taken up in ether, and washed with water. The residue which remained when the ether was removed was distilled through a short Vigreux column at 1.5 mm. There was obtained 4.32 g. of viscous forerun, b.p. 85–127°, and 22.45 g. of product, b.p. 127–133°.

2-(*p*-Fluorophenyl)-3[*p*-(2-diethylaminoethoxy)phenyl]indene Hydriodide.—Magnesium (1.12 g.) was placed in a three-necked flask and dried with a flame under a stream of nitrogen. Several milliliters of tetrahydrofuran (distilled over lithium aluminum hydride) and 4 drops of methyl iodide were added. Then was added 12.4 g. of *p*-(2-diethylaminoethoxy)bromobenzene in 120 ml. of tetrahydrofuran and the mixture was stirred under reflux until the magnesium had been consumed (1 hr.). A solution of 10.36 g. of 2-(*p*-fluorophenyl)-1-indanone in 100 ml. of tetrahydrofuran was added, and the mixture was heated at reflux for 16 hr. At the end of this time the mixture was allowed to cool and treated with a small amount of water. The resulting gel was removed by filtration. Ether was added to the filtrate; the mixture was washed well with water and taken to dryness. The residue was taken up in ether and extracted with 0.5 *N* HCl. The acid solution was extracted with methylene chloride. The residue which remained when the latter was taken to dryness was dissolved in 200 ml. of benzene and heated for 2 hr. at reflux in the presence of 200 mg. of *p*-toluenesulfonic acid under a Dean–Stark trap. On cooling, the benzene solution was washed with saturated aqueous sodium bicarbonate. The product was partitioned between the benzene, 10% hydriodic acid, and methylene chloride as above. The solid which remained when the last solution was taken to dryness was recrystallized twice from methylene chloride–benzene. There was obtained 4.70 g. of product, m.p. 181–183° (see Table III).

2-Phenyl-5-hydroxy-1-indanone.—Solid anhydrous aluminum chloride (1.33 g., 0.01 mole) was added to a solution of 1.20 g. (0.005 mole) of 2-phenyl-5-methoxy-1-indanone in 25 ml. of benzene. The green mixture was stirred under reflux for 3 hr. The mixture was allowed to cool and poured onto 120 ml. of 1:1 ice–concentrated HCl. Methylene chloride was added and the mixture was stirred until no more solid remained. The organic layer was separated, washed with water, and extracted with 200 ml. of 5% NaOH in 3 portions. The solid which was obtained on acidification of the alkaline extracts (1.0 g., m.p. 192–198°) was recrystallized twice from aqueous methanol to give 0.90 g. of the phenol, m.p. 197.5–199°.

2-Phenyl-3-[*p*-(2-diethylaminoethoxy)phenyl]-6-hydroxyindene.—A heterogeneous mixture of 2.24 g. of the phenol, 5 ml. of dihydropyran, and 50 mg. of *p*-toluenesulfonic acid in 50 ml. of benzene and 100 ml. of ether was stirred at room temperature for 3 hr. Methylene chloride was added, and the solution was washed with aqueous sodium bicarbonate and brine. The gummy solid which remained when the solvent was removed *in vacuo* was dissolved in 100 ml. of tetrahydrofuran and added to 0.01 mole of *p*-(2-diethylaminoethoxy)phenyl-

(13) G. W. Duncan, J. C. Stucki, S. C. Lyster, and D. Lednicer, *Proc. Soc. Exptl. Biol. Med.*, **109**, 163 (1962).

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

magnesium bromide in 25 ml. of tetrahydrofuran. The reaction was run, and the product was isolated in the usual manner. The first aqueous acid extract was in this case allowed to stand for 2 hr. The product was dehydrated as above. The benzene solution was washed with sodium bicarbonate solution and taken to dryness. The residue was recrystallized twice from methanol to give 0.39 g. of the aminophenol, m.p. 154–155.5° (see Table IV).

Studies in Alkyl–Oxygen Heterolysis. Some 4-Alkoxypiperidines Related to Reversed Esters of Pethidine

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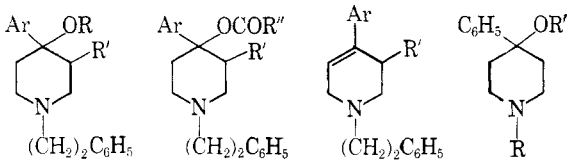
The preparation and pharmacological activity in the hot plate test of some 4-alkoxy-4-arylpiperidines is reported, and structure–activity relationships in this class of analgesics are discussed. Study has been made of the influence of the 4-aryl group upon alkyl–oxygen heterolysis in esters of 4-piperidinols.

A series of 4-alkoxy-4-(2-furyl)piperidines (**1a**, R = lower alkyl) has been reported previously, certain members being significantly active as analgesics in mice.[1] The results of a detailed study of the most active compound, 4-ethoxy-4-(2-furyl)-3-methyl-1-phenethylpiperidine (**1a**, R = C_2H_5; R^1 = CH_3) (4.4 times as active as pethidine and 1.2 times as active as morphine in the hot plate test) showed that it could be classified as a morphine-type analgesic. The object of the present work was to prepare 4-aryl analogs of the active 4-(2-furyl) ethers **1a** (R = CH_3 or C_2H_5) as part of a study of structure–activity relationships in this class of analgesics.



1 **2** **3** **4**

a, Ar = 2-C_4H_3O (2-furyl)
b, Ar = C_6H_5
c, Ar = *o*-$CH_3C_6H_4$
d, Ar = *p*-$CH_3C_6H_4$
e, Ar = *m*-$CH_3C_6H_4$
f, Ar = *m*-$CH_3OC_6H_4$
g, Ar = *p*-$CH_3OC_6H_4$
h, Ar = 2-(5-$CH_3C_4H_2O$) [2-(5-methylfuryl)]
i, Ar = *p*-$NO_2C_6H_4$
j, Ar = *p*-FC_6H_4

Since Williamson procedures (*e.g.*, reaction between lithium salts of 4-phenyl-4-piperidinols and alkyl halides) failed to give the desired ethers, resort was made to acid-catalyzed etherification reactions. Esters of 4-(2-furyl)-4-piperidinols give good yields of ethers (together with alkenes as by products) when treated in the cold with a molar excess of hydrogen chloride in a lower unbranched alcohol, transformations that have been interpreted as proceeding *via* carbonium ions generated by acid-catalyzed alkyl–oxygen fission of the ester groups.[2] The facile nature of these reactions was attributed to the high electron-releasing power of the 4-(2-furyl) substituent. Investigation was made previously of acid conditions necessary to induce carbonium ion reactions in analogous alcohols and esters containing a 4-phenyl substituent, an aryl group that less readily releases electrons.[2] Such compounds were stable in cold methanol containing up to 6% HCl or 16% sulfuric acid, but at the reflux temperature were converted, in these solvents, to methyl ethers. When methanol was replaced by ethanol or 1-propanol containing 16% sulfuric acid, elimination products were isolated, results indicating that, at high acid concentrations, the small unfavorable steric factors introduced by the latter change in nucleophile size are sufficient to make proton loss the predominant carbonium ion fate. Since esters of benzoic acid undergo alkyl–oxygen heterolysis more readily than those of saturated carboxylic acids,[3] the ethanolysis of 4-benzoyloxy-4-phenylpiperidines was investigated in the expectation that reaction could be induced at acid concentrations low enough to render elimination a minor pathway. Treatment of the 4-benzoyloxypiperidine **2b** (R′ = H; R″ = C_6H_5) with 9% sulfuric acid in ethanol at the reflux temperature, conditions which had no effect on the corresponding 4-acetoxy analog,[4] gave the ethyl ether **1b** (R = C_2H_5; R′ = H); the critical acid concentration for reaction was found to be between 2.4 and 1.4%. The 4-benzoyloxy-3-methylpiperidine **2b** (R′ = CH_3; R″ = C_6H_5) was recovered after treatment with hot 9% sulfuric acid in ethanol, while use of 13% acid gave the alkene **3b** (R′ = CH_3).[5] Unchanged substrate was also recovered when the corresponding 4-*p*-nitrobenzoyloxy-3-methylpiperidine was treated with 9% sulfuric acid in ethanol. These results are in contrast to the successful methanolysis of 3-methyl-4-phenyl-4-piperidinols and their esters[2] and illustrate the sensitivity of the described alkyl–oxygen heterolyses to steric factors in both substrate and nucleophile. 1-Benzyl-4-ethoxy-4-phenylpiperidine **4** (R′ = C_2H_5; R = $CH_2C_6H_5$) was debenzylated reductively and the resultant secondary amine was converted to the 1-methyl derivative **4** (R′ = C_2H_5; R = CH_3) by reductive methylation, the 1-(2-benzoylethyl) derivative **4** [R′ = C_2H_5; R = $(CH_2)_2COC_6H_5$] by a Mannich base exchange process,[6] and the 1-(3-*p*-fluorobenzoylpropyl) deriva-

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(2) A. F. Casy, A. H. Beckett, and N. A. Armstrong, *Tetrahedron*, **16**, **85** (1961).

(3) V. R. Stimson, *J. Chem. Soc.*, 4020 (1955); G. J. Harvey and V. R. Stimson, *ibid.*, 3629 (1956).

(4) N. A. Armstrong, Ph.D. Thesis, University of London, 1962.

(5) The structure of the alkene was confirmed by n.m.r. spectroscopy, the key signals supporting the formulation **3b** (R′ = CH_3), being an unresolved triplet at τ 4.19 (vinylic proton at C-5) and a doublet at 8.98, J = 7 c.p.s. (3 protons of 3-methyl substituent) (solvent, CCl_4).

(6) E. M. Fry and E. L. May, *J. Org. Chem.*, **24**, 116 (1959).