by passing the solution through a column of the weakly basic anion-exchange resin, Dowex AG 3-X4, in the chloride cycle. No avian depressor activity was detected in the deionized solution. The volume of the solution was reduced to approximately 40 ml by evaporation in a rotary evaporator, and the concentrated solution was put onto a column of Sephadex G-25 (100–200 mesh), which had been equilibrated with lower phase of the solvent system water(containing 3.5% acetic acid and 1.5% pyridine)–1-butanol–benzene (8:6:1),. The upper phase of this system was used for elution and one hundred 10-ml. fractions were collected. Folin–Lowry color values[27] of aliquots from every second fraction were plotted, and fractions corresponding to a peak having its maximum at fraction 55 (R_f ~0.2) were pooled, concentrated, and lyophilized, to give 41 mg, $[\alpha]^{21}D$ −24.0° (*c* 0.5, 1 *N* acetic acid).

Anal. Calcd for $C_{42}H_{65}N_{11}O_{11}S_2$: C, 52.3; H, 6.80; N, 16.0. Found: C, 52.3; H, 6.88; N, 15.7.

A sample of this material was hydrolyzed in 6 *N* HCl at 110° for 22 hr and was analyzed on a Beckman/Spinco amino acid analyzer,[28] operating the short column at 30° to effect separation of the methylamine and the ammonia. The molar ratios obtained, taking aspartic acid as 1, were: aspartic acid 1.0, glutamic acid 1.0, proline 1.0, cystine 0.95, isoleucine 1.0, leucine 1.0, tyrosine 0.9, ammonia 2.0, methylamine 1.0.

Acknowledgments.—The authors are indebted to the following members of this laboratory for their help in the course of the work: Dr. W. D. Cash for advice during the synthesis of *N*-carbobenzoxy-*S*-benzyl-L-cysteinyl-L-prolyl-L-leucine methylamide, Mr. Joseph Albert for the elemental microanalyses, Mr. Roger Sebbane for the amino acid analyses, and Mrs. Sherilyn Goodwin, Mrs. Marilyn Rippe, and Miss Margitta Wahrenburg, under the direction of Dr. W. Y. Chan, for the biological assays.

(27) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, **193**, 265 (1951).

(28) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

Mammalian Antifertility Agents. III. 1-Aryl-2-phenyl-1,2,3,4-tetrahydro-1-naphthols, 1-Aryl-2-phenyl-3,4-dihydronaphthalenes, and Their Derivatives[1]

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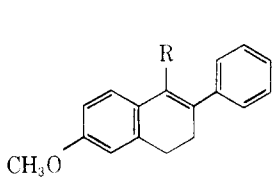
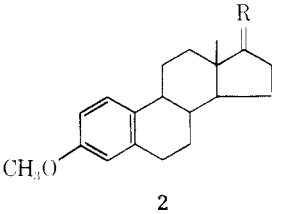
The preparation of a series of 1-aryl-2-phenyl-1,2,3,4-tetrahydro-1-naphthols and the corresponding 3,4-dihydronaphthalenes from 6-methoxy-2-phenyl-1-tetralone is described. The results of assays of these compounds as antifertility agents are reported. Biologic characterization showed that this activity in most cases be ascribed to the uterotropic activity of the compounds.

The preparation and structure–activity relationships of a series of diphenylindenes[2] and diphenylcoumarins[1] as antifertility agents have been previously reported. The sensitivity of the potency of given compounds of the previous series to structural modifications led us to investigate the naphthalene ring system (**1**) as a possibility for a further series of biologically active compounds. The resemblance of such a system to the A–B rings of the natural steroidal estrogens (**2**) lent further encouragement to these efforts.[3]



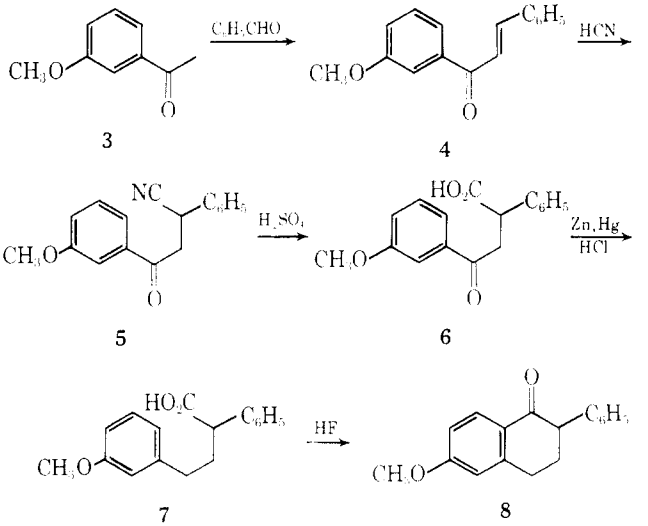
1



2

Preparation of 6-Methoxy-2-phenyl-1-tetralone.—The tetralone (**8**) upon which this series of compounds was based was originally prepared by a modification of Scheme I, first reported by Newman.[4,5]

SCHEME I



3 4 5 6 7 8

The cyanide addition and Clemmensen reduction proved difficult to carry out on large scale. The alternate route to **8** shown in Scheme II proved more convenient for scale up. Each of the steps went in a straightforward manner in workable yields.

1-Aryl-2-phenyl-1,2,3,4-tetrahydro-1-naphthols.—Reaction of the tetralone **8** with the appropriate aro-

(1) Previous paper in this series: D. Lednicer, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **8**, 725 (1965).

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

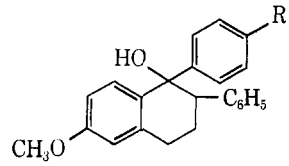
(3) Subsequent to the completion of this work a paper describing the preparation and biological activities of 6-deoxy-1,2-diphenyl-3,4-dihydronaphthalenes has appeared: W. L. Benezc, L. I. Barsky, W. P. Sopchak, A. A. Renzi, N. Howie, and J. J. Chart, *ibid.*, **8**, 213 (1965).

(4) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 2947 (1938).

(5) D. Lednicer, J. C. Babcock, S. C. Lyster, and G. W. Duncan, *Chem. Ind.* (London), 408 (1963).

TABLE I

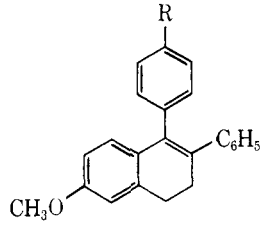
1-ARYL-6-METHOXY-2-PHENYL-1,2,3,4-TETRAHYDRO-1-NAPHTHOLS

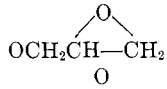
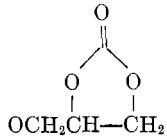


No.	R	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
14	H	38	113–116	$C_{23}H_{22}O_2$	83.60	82.98	6.96	6.93
15	CH_3	39	108–111	$C_{24}H_{24}O_2$	83.69	83.67	7.02	7.12
16	F	54	130–132.5	$C_{23}H_{21}FO_2$	79.29	79.65	6.08	6.41

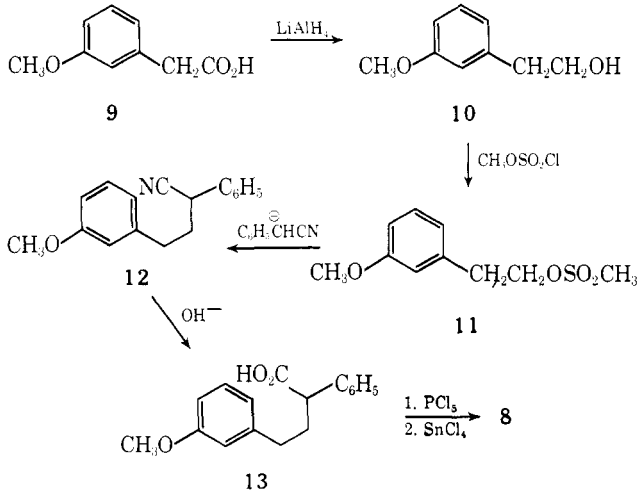
TABLE II

1-ARYL-6-METHOXY-2-PHENYL-3,4-DIHYDRONAPHTHALENES



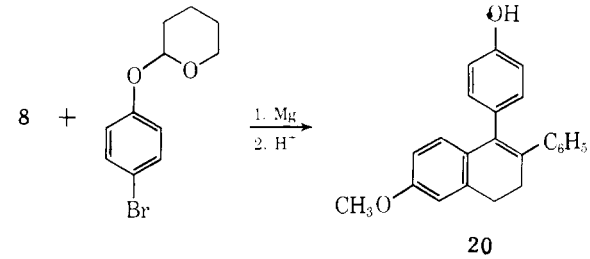
No.	R	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
17	H	90–92	$C_{23}H_{20}O$	88.42	87.99	6.45	6.78
18	CH_3	100–103	$C_{24}H_{22}O$	88.31	88.33	6.79	7.06
19	F	99–101	$C_{23}H_{19}FO$	83.61	83.82	5.80	5.82
20	OH	161–163	$C_{23}H_{20}O_2$	84.12	83.99	6.14	6.17
21	$OC(CH_3)_2CO_2C_2H_5$	107–111	$C_{29}H_{30}O_4$	78.70	78.69	6.83	7.06
22	$OC(CH_3)_2CO_2H$	136–137	$C_{27}H_{26}O_4$	78.24	78.13	6.32	6.62
23	$OCH_2CHOHCH_2OH$	106–108	$C_{26}H_{25}O_4$	77.59	77.13	6.51	6.49
24		114–117	$C_{26}H_{24}O_3$	81.22	81.35	6.29	6.55
25		158–160	$C_{27}H_{24}O_5$	75.68	75.72	5.65	5.66

SCHEME II



matic Grignard Reagent afforded the carbinols listed in Table I.

1-Aryl-2-phenyl-3,4-dihydronaphthalenes.—Heating the naphthols obtained above in toluene in the presence of *p*-toluenesulfonic acid afforded the olefins. In order to obtain the phenol **20**, the tetralone was condensed with the Grignard reagent from *p*-bromophenyl tetrahydropyranyl ether.[6] Mild acid hydrolysis led directly to the phenolic dihydronaphthalene. The carbinol was not isolated in this case, either as a result of this acid treatment or perhaps because the presence of two oxygenated functions *para* to the diarylcarbinol makes this system unusually labile. Alkylation of the phenol



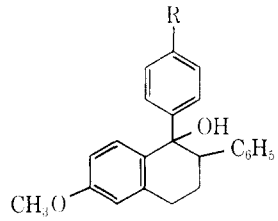
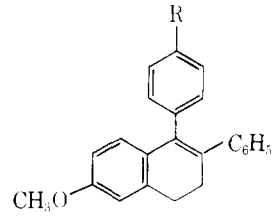
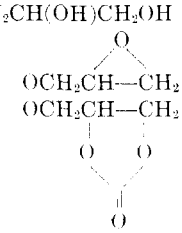
20 with the appropriate halides gave the compounds **21**, **23**, and **24**. The acid **22** was obtained by saponification of **21**. Reaction of **23** with ethyl chloroformate followed by base gave **25** (see Table II).

Biological Activity.—The compounds above were tested for antifertility activity in the rat in the manner

(6) W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948).

TABLE III

ANTIFERTILITY ACTIVITIES

Compd	R	MED_{100},[a] mg/rat/day
1-Aryl-6-methoxy-2-phenyl-1,2,3,4-tetrahydro-1-naphthols		
		
14	H	0.01
15	CH_3	0.2
16	F	0.01
1-Aryl-6-methoxy-2-phenyl-3,4-dihydronaphthalenes		
		
17	H	0.005
18	CH_3	0.2
19	F	0.05
20	OH	0.025
21	$OC(CH_3)_2CO_2C_2H_5$	10
22	$OC(CH_3)_2CO_2H$	>10[b]
23	$OCH_2CH(OH)CH_2OH$	0.05
24		1.0
25		1.0

[a] Minimal daily oral dose at which none of the animals showed implants. [b] Inactive at the maximum screening dose used in this study.

described previously.[2] The results of these assays are summarized in Table III.

The uterotropic effect of the more potent compounds was evaluated in 55-g bilaterally ovariectomized rats treated orally for 7 days. Uterine weight increases comparable to those induced by subcutaneous estradiol treatment occurred except following administration of the glyceryl ether (**23**) (Table IV). This compound induced the impeded uterine response previously reported for the basic ethers of diphenylindenes[7] and dihydronaphthalenes.[8] When **23** was administered concomitantly with estradiol an inhibition of the anticipated estrogen-dependent response occurred. It thus appears that with the notable exception of **23**, the antifertility potency of this series closely parallels the uterotropic potency.

It is known[9] that in the diethylstilbesterol family of synthetic estrogens, the presence of a *p*-hydroxyl function is necessary for maximum activity. It is

TABLE IV

ORAL UTEROTROPIC ACTIVITY[a]

Without concomitant estradiol			With concomitant estradiol (0.04 μg, sc)		
No.	Daily dose, μg	Av uterine wt, mg	No.	Daily dose, μg	Av uterine wt, mg
				0	145
14	5	142	14	250	168
	100	143		500	164
16	1	104	17	0	123
	5	144		10	152
17	2.5	147		100	153
				200	149
18	20	95			
	80	112	18	0	106
				40	112
20	0.4	39		160	103
	0.8	59			
	1.6	86	20	0	113
				5	114
23	10	49			
	20	56	23	0	109
	40	57		5	91
				10	106
Estradiol (sc)	0.00	25		160	76
	0.01	39			
	0.02	58			
	0.06	121			

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

thus of interest that in the present series, the compound which shows the highest potency as an antifertility agent (**17**) is devoid of substitution in that position. Indeed the incorporation of a hydroxyl group at that position decreases the potency by a factor of 5. When metabolic hydroxylation of that position is blocked by fluorine, as in **19**, the compound retains half the activity of the hydroxylated analog.

Introduction of the glyceryl ether side chain (**23**) has the net effect of producing an antifertility agent which elicits a modest uterotropic response *per se* but which will antagonize the response of a concomitantly administered estrogen. This type of activity has hitherto been associated with the basic ether grouping.[2,3,10]

Experimental Section[11]

3′-Methoxychalcone (4).—A solution of 45.0 g of *m*-methoxyacetophenone in 75 ml of 95% ethanol was added to a cooled solution of 16.0 g of NaOH in 140 ml of water. The mixture was then placed in an ice bath and 31.8 g of benzaldehyde was added at such a rate as to keep the temperature below 20°. The mixture was stirred for an additional 30 min in the cold and then for 27 hr at room temperature. The resulting clear two-phased solution was extracted with ether. The extracts were washed with brine, percolated through $MgSO_4$, and taken to dryness *in vacuo*. The residual oil was distilled to afford 50.9 g of 3′-methoxychalcone, bp 180–185° (4 mm) (yield, 70%; a small lower boiling forerun was discarded).

2-Phenyl-4-(*m*-methoxyphenyl)-4-ketobutyronitrile (5).—A solution of 27.8 g of KCN in 50 ml of water was added to a mixture of 50.9 g of 3-methoxychalcone, 13.0 g of AcOH, and 100 ml of 95% ethanol over 10 min. Cooling was provided to keep the temperature below 45°. The turbid mixture was stirred for

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

(8) G. W. Duncan, S. C. Lyster, J. J. Clark, and D. Lednicer, *ibid.*, **112**, 439 (1963).

(9) See J. A. Hogg and J. Korman, "Medicinal Chemistry V," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1956, p 34.

(10) L. J. Lerner, F. J. Holthaus, Jr., and C. R. Thompson, *Endocrinology*, **83**, 295 (1958).

(11) All melting points were obtained on a Thomas–Hoover melting point apparatus. Elemental analyses were performed by the Department of Physical and Analytical Chemistry of The Upjohn Co.

6 hr and then allowed to stand in the cold overnight. The crystals which separated were removed by filtration and washed with 80 ml of ice-cold 50% aqueous ethanol and then water. A single recrystallization of the crude product from ethanol afforded 49.22 g of the nitrile: mp 96–101°; ν_{max} 2200, 1660, 1580 cm^{-1} (yield 86.5%).

2-Phenyl-4-(*m*-methoxyphenyl)-4-ketobutyric Acid (6).—A suspension of 49.22 g of the nitrile **5** in a mixture of 140 ml of concentrated H_2SO_4 and 125 ml of water was heated on the steam bath with vigorous stirring for 4 hr. Upon cooling, the mixture was diluted with ice water and the solid was collected on a filter. This product was recrystallized once from aqueous ethanol and then from benzene to yield 29.5 g of **6**, mp 140–145°. The analytical sample, mp 143–145°, was obtained by one further crystallization from benzene.

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.10; H, 5.74.

6-Methoxy-2-phenyl-1-tetralone (8). A.—Mossy zinc (300 g) was washed briefly with 2.5 *N* HCl and then water. The metal was covered with a solution of 6.7 g of $HgCl_2$ in 500 ml of water, and this mixture was allowed to stand for 30 min with occasional shaking. The liquid phase was decanted and the amalgamated metal was washed well with water. To the amalgamated zinc there was added 29.3 g of 2-phenyl-4-(*m*-methoxyphenyl)-4-ketobutyric acid and 400 ml of HCl. The mixture was cautiously brought to reflux. At the end of 5 and 10 hr, 100-ml portions of HCl were added. After a total heating period of 20 hr, the liquid was decanted from the residual metal. The latter was washed well with ether. The former was extracted with ether and these extracts were combined with the washes. The organic extract was washed with water and brine, percolated ($MgSO_4$), and taken to dryness *in vacuo*. There was obtained 26.2 g of 2-phenyl-4-(*m*-methoxyphenyl)butyric acid as a viscous oil, λ_{max} 1705 cm^{-1}. This material was used in the next step without further purification (yield 94.5%).

Hydrogen fluoride (150 ml) was added to 26.2 g of 2-phenyl-4-(*m*-methoxyphenyl)butyric acid with good swirling. The solution was allowed to stand at room temperature for 3 days. The residue was dissolved in CH_2Cl_2 and poured onto concentrated aqueous K_2CO_3. The organic layer was separated, washed with water and saturated NaCl solution, and taken to dryness. The residual solid was dissolved in 2 l. of 7.5% acetone in Skellysolve B and passed through a column of 500 g of Florisil prewashed with the same solvent. The product (17.0 g) was recrystallized twice from cyclohexane to afford 13.38 g of the tetralone, mp 113–116° (yield 55%).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.08; H, 6.35.

B. Scheme II.—A solution of 100 g of *m*-methoxyphenylacetic acid in 600 ml of ether was added to a mechanically stirred suspension of 34 g of $LiAlH_4$ in 30 ml of ether at such a rate as to produce a vigorous reflux. Following this, the mixture was heated under reflux for 30 min, and then cooled in an ice bath. The excess reagent was then cautiously decomposed with 50 ml of water. There was then added in turn 500 ml of saturated aqueous NH_4Cl and 300 ml of 2.5 *N* HCl. The organic layer was separated, washed twice with water, once with brine, and dried (Na_2SO_4). The oil (91.1 g) which remained when the solvent was removed under vacuum was distilled through a short Vigreux column. There was obtained 84.5 g of *m*-(methoxy)phenethyl alcohol, bp 99–102°.

A solution of 15.2 g of the alcohol was cooled in an ice–methanol bath. Over the period of 10 min 15.2 g of methanesulfonyl chloride was added to the solution with good stirring. Following an additional hour of stirring in the cold, the mixture was diluted to 600 ml with ice and water. The precipitated oil was extracted with ether, and this last solution was in turn washed with water, 2.5 *N* HCl, water, and brine. The solvent was removed to afford 22.27 g of the mesylate as a viscous oil which appeared to be homogeneous by tlc. The infrared spectrum showed the OH to be gone and exhibited strong bands at 1360 and 1165 cm^{-1}.

To an ice-cooled, well-stirred solution of 11.7 g of phenylacetonitrile in 50 ml of dry DMF and 25 ml of dry toluene there was added 4.50 g of NaH (53% in mineral oil). Following 1 hr of stirring under nitrogen, there was added 22.27 g of the mesylate in 30 ml of toluene. The mixture was then allowed to stir overnight at room temperature. The bulk of the solvent was removed *in vacuo* and water and ether were added. The organic layer was washed with water and brine and dried by percolation (Na_2SO_4). The oil which remained when the solvent was removed was distilled at 1–2 mm through a Vigreux column. There was obtained 6.03 g of forerun, bp 52–170° (mainly 54–64°) and 18.79 g of the nitrile **12**, bp 170–190°.[12]

A mixture of 18.79 g of 4-(*m*-methoxyphenyl)-2-phenylbutyronitrile and 20 g of KOH in 200 ml of ethylene glycol was heated overnight at reflux. The resulting solution was allowed to cool, diluted with 600 ml of water, and extracted once with ether. This ether was discarded. The aqueous layer was then acidified with concentrated HCl and extracted well with ether. These last extracts were washed once with water and brine and dried by percolation (Na_2SO_4). The solution was taken to dryness *in vacuo*, the residue was dissolved in dry benzene, and the solution again was taken to dryness. The acid (16.29 g) was obtained as a clear amorphous gum.

A solution of 16.29 g of 4-(*m*-methoxyphenyl)-2-phenylbutyric acid and 12.7 g of PCl_5 was heated under reflux for 1 hr. The solution was then cooled in ice and 7.15 ml of $SnCl_4$ was added with stirring. Following 2.5 hr of stirring at room temperature, the two-phased mixture was poured into 250 ml of 2.5 *N* HCl. Following 0.5 hr of stirring, the organic layer was separated and washed in turn with 2.5 *N* HCl, water, saturated aqueous $NaHCO_3$, water, and brine. A crystalline solid remained when the solution was taken to dryness. This was recrystallized from methanol to afford 11.34 g of the tetralone, mp 113–116°, mmp (with authentic material) 113.5–117°. The over-all yield, based on *m*-methoxyphenylacetic acid was 41.4%.

Grignard Condensation of Tetralone 8.—In a typical experiment a solution of 5.04 g of the tetralone **10** in 75 ml of THF was added to the stirred, ice-cooled Grignard reagent prepared from 34.4 g of *p*-bromotoluene and 4.90 g of Mg in 200 ml of ether. Following 17 hr standing at room temperature, 25 ml of water was added. The gel which formed was removed by filtration and washed well with ether. The combined filtrates were washed with water and brine and taken to dryness *in vacuo*. The residual gum was chromatographed over 800 ml of Florisil (elution with ligroin followed by 4% acetone in ligroin). The product thus obtained was recrystallized twice from ligroin to give 2.68 g of **15**, mp 108–111°.

Dehydration of the Carbinols.—A solution of 1.68 g of **15** and 170 mg of *p*-toluenesulfonic acid in 170 ml of toluene was heated at reflux under a Dean–Stark trap for 5 hr. The solvent was removed at reduced pressure and the residue was dissolved in ether. This solution was washed with aqueous $NaHCO_3$ and water. The gum which remained when the solvent was removed was chromatographed over 200 ml of Florisil. The crystalline fractions were combined and recrystallized twice from methanol to afford 0.97 g of **18**, mp 100–103°.

6-Methoxy-1-(*p*-hydroxyphenyl)-2-phenyl-3,4-dihydronaphthalene (20).—To a solution of the Grignard reagent prepared from 52.5 g of *p*-(2-tetrahydropyranyloxy)bromobenzene and 4.83 g of Mg in 500 ml of THF, there was added in the cold 10.0 g of the tetralone **8** in 100 ml of THF. Following 17 hr of standing at room temperature the reaction mixture was worked up as above. A mixture of the crude product was dissolved in 300 ml of methanol and 100 ml of 2.5 *N* HCl was added. Following 2 hr of stirring at room temperature, the bulk of the solvent was removed *in vacuo*. The residue was dissolved in ether–methylene chloride, and the organic layer was extracted thoroughly with 5% aqueous NaOH. The solid which was obtained on acidification was chromatographed on Florisil (elution with 4% acetone in ligroin). The crystalline fractions were combined and recrystallized from acetone–cyclohexane to afford 2.97 g of **20**, mp 160–163°.

Ethyl 2-[*p*-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthyl)-phenoxy]-2-methylpropionate (21).—Sodium hydride (0.35 g, 53% in mineral oil) was added to 2.50 g, of the phenol in 13 ml of DMF and 65 ml of benzene. When effervescence had ceased 1.50 g of ethyl bromoisobutyrate in 15 ml of benzene was added, and the mixture was heated under reflux for 17 hr. The mixture was allowed to cool, washed with water and brine, and taken to dryness. The residual gum was chromatographed over Florisil (5% acetone in ligroin) to afford 1.94 g of crude **21** and 0.71 g of recovered phenol. The former was recrystallized from ligroin to give 1.82 g of the ether, mp 107–111°.

(12) This material cannot conveniently be characterized since it is admixed with mineral oil from the sodium hydride. This in part accounts for the wide boiling range. It is, however, not necessary to separate the oil since it is disposed of in the next step.

2-[*p*-(3,4-Dihydro-6-methoxy-2-phenyl-1-naphthyl)phenoxy]-2-methylpropionic Acid (22).—A solution of 1.42 g of the ethyl ester and 3 ml of 50% aqueous KOH in 50 ml of methanol was heated under reflux for 5 hr. The solvent was then removed *in vacuo*, the residual solid was suspended in water, and this mixture was made strongly acidic with 2.5 *N* HCl. The precipitate was collected on a filter and recrystallized twice from aqueous methanol. There was obtained 1.04 g of product, mp 136–137°.

1-[*p*-(2,3-Dihydroxypropoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene (23).—To a suspension of 2.97 g of phenol in 50 ml of methanol there was added 2.1 ml of 4.55 *N* $NaOCH_3$ in methanol. When the solid had completely dissolved, 1.0 g of 1-chloropropane-2,3-diol was added. The mixture was heated for 20 hr under reflux and the solvent was removed *in vacuo*. The residue was dissolved in ether and water. The organic layer was washed with 5% aqueous NaOH, water, and brine and taken to dryness. Chromatography of the residue over Florisil (4% acetone in ligroin and then 100% acetone) gave the glycol in the last fraction. The solid was recrystallized twice from aqueous methanol to give 1.33 g of **23**, mp 106–108°.

1-[*p*-(2,3-Dihydroxypropoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene Cyclic Carbonate (25).—Ethyl chloroformate (3 ml) was added dropwise to an ice-cooled solution of 2.81 g of the glycol in 28 ml of pyridine. At the end of 1 hr the mixture was diluted with ether and the precipitated oil was dissolved in ether. The organic layer was washed with ice-cold 2.5 *N* HCl and water and taken to dryness. The residual gum was again dissolved in pyridine (28 ml), treated with ethyl chloroformate, and worked up as above. The gummy product was dissolved in 300 ml of benzene and heated under reflux with 300 mg of NaH for 2 hr. The mixture was allowed to cool, 25 ml of saturated aqueous NH_4Cl was added, and the organic layer was separated. The gum which remained when the solvent was removed was chromatographed on Florisil (10% acetone in ligroin and then 100% acetone) to give 0.21 g of crude carbonate and 1.07 g of recovered glycol. The former was recrystallized several times from methanol to afford 0.16 g of product, mp 158–160°.

1-[*p*-(2,3-Epoxypropoxy)phenyl]-2-phenyl-6-methoxy-3,4-dihydronaphthalene (24).—The phenol (**20**) (5.0 g) was alkylated with 1.85 g of epichlorohydrin by means of 0.69 g of NaH in 25 ml of DMF and 125 ml of benzene in exactly the same manner used to obtain **21**. The product was worked up in the same way and then chromatographed (10% acetone) to yield the epoxide. This material was recrystallized from cyclohexane to yield 3.08 g, mp 114–117°.

α,β-Diphenyl-α-trifluoromethyl-2-pyridineethanol and Related Compounds as Synthetic Estrogens

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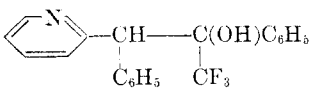
A series of substituted α,β-diphenyl-α-trifluoromethyl-2-pyridineethanols and some related compounds were synthesized. Many were potent estrogens.

α,β-Diphenyl-α-trifluoromethyl-2-pyridineethanol (**1**) was prepared and unexpectedly found to be a potent



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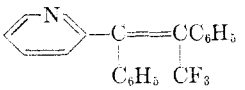

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estrogen. To our knowledge this is the first example of a synthetic estrogen of this type. Addition of selected substituents gave a series of compounds with decreased estrogenic activity that varied over a wide range.

The compounds were synthesized by adding an aralkylpyridine anion to the appropriately substituted trifluoroacetophenone. Since two asymmetric centers were generated in this reaction, two pairs of diastereoisomers were possible. In many cases (Table I) the pairs of isomers were separated by fractional crystallization.[1]

Dehydration to the corresponding stilbene derivative proved difficult. Starting material was recovered from several runs using various techniques such as heating with iodine, potassium hydrogen sulfate, 85% phosphoric acid, or *p*-toluenesulfonic acid in xylene. α-(2-Pyridyl)-α′-(trifluoromethyl)stilbene (**2**) was finally obtained by using thionyl chloride in pyridine.

Substituted 2,2,2-trifluoroacetophenones have been reported by several authors. Most commonly these preparations involved a Friedel–Crafts reaction. Although this reaction was successful in a few cases, it was not generally applicable. The addition of an arylorganometallic derivative to trifluoroacetonitrile or trifluoroacetic acid anhydride[2] was successful for difficult cases and provided the most consistent and usable synthesis.

A small amount of an anomalous compound was obtained from the reaction of α-phenethylmagnesium bromide and trifluoroacetophenone. The product was homogeneous by vapor phase and thin layer chromatography. Since unreacted magnesium had been present during the addition, a pinacol condensation was suspected. Indeed, reaction of trifluoroacetophenone with a mixture of magnesium and magnesium bromide[3] in ether gave a better yield of the unknown compound than the original reaction conditions. However, the infrared spectrum showed strong carbonyl adsorption in addition to hydroxyl adsorption. Microanalyses and molecular weight determinations were in agreement with a dimeric structure but with two fluorine atoms less than expected. Analysis of the 2,4-dinitrophenylhydrazine derivative also agreed with this empirical formula.

The compound was hydrogenated catalytically and slightly more than 1 molar equiv of hydrogen was

(1) It is likely that a mixture was formed in all of the reactions and that the mixture was separable given a large enough supply of starting material and sufficient patience. Since the stereochemistry is unknown, the pairs of diastereoisomers were simply designated as the high-melting form and the low-melting form. This carries no implication that all of the high-melting or low-melting forms belong to the same stereoisomeric series.

(2) M. S. Newman and W. T. Booth, Jr., *J. Am. Chem. Soc.*, **67**, 154 (1945). Addition of ferric chloride, as suggested by W. C. Percival, R. B. Wagner, and N. C. Cook, *ibid.*, **75**, 3731 (1953), did not affect the yield.

(3) M. Gomberg and W. E. Bachmann, *ibid.*, **49**, 236 (1927).