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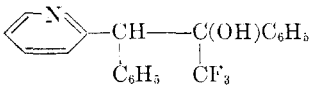
A series of substituted α,β-diphenyl-α-trifluoromethyl-2-pyridineethanols and some related compounds were synthesized. Many were potent estrogens.

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



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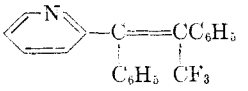

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estrogen. To our knowledge this is the first example of a synthetic estrogen of this type. Addition of selected substituents gave a series of compounds with decreased estrogenic activity that varied over a wide range.

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

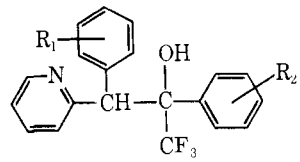
(1) It is likely that a mixture was formed in all of the reactions and that the mixture was separable given a large enough supply of starting material and sufficient patience. Since the stereochemistry is unknown, the pairs of diastereoisomers were simply designated as the high-melting form and the low-melting 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).

TABLE I

α,β-DIPHENYL-α-TRIFLUOROMETHYL-2-PYRIDINEETHANOLS

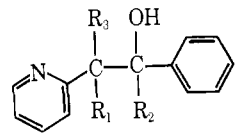


				% Carbon		% Hydrogen		% Nitrogen		
R_1	R_2	Mp, °C	Formula	Calcd	Found	Calcd	Found	Calcd	Found	ES[a]
H	H	190–190.5	$C_{20}H_{16}F_3NO$	69.96	70.03	4.70	4.85			236
H	H	159.5–160	$C_{20}H_{16}F_3NO$	69.96	70.18	4.70	4.91			113
2-OCH_3	H	145–146.5	$C_{21}H_{18}F_3NO_2$	67.55	67.30	4.86	5.00	3.76	3.95	3.5
2-OCH_3	H	110–112	$C_{21}H_{18}F_3NO_2$	67.55	67.58	4.86	4.93	3.76	3.91	14
4-CH_3	H	193–195	$C_{21}H_{18}F_3NO$	70.57	70.58	5.08	5.46	3.92	4.19	1.0
4-Cl	H	174–175	$C_{20}H_{15}ClF_3NO$	63.57	63.82	4.00	4.26	3.71	3.87	62
H	2-Cl	157–158	$C_{20}H_{15}ClF_3NO$	63.57	63.56	4.00	4.10	3.71	3.76	185
H	2-Cl	133–134.5	$C_{20}H_{15}ClF_3NO$	63.57	63.39	4.00	4.21	3.71	3.61	20.8
H	3-Cl	169–170	$C_{20}H_{15}ClF_3NO$	63.57	63.78	4.00	4.17	3.71	3.74	25
H	4-Cl	159–161	$C_{20}H_{15}ClF_3NO$	63.57	63.70	4.00	4.23	3.71	3.79	30.2
H	4-CH_3	141–142	$C_{21}H_{18}F_3NO$	70.57	70.42	5.08	5.24	3.92	4.07	3.9
H	4-CH_3	180–182	$C_{21}H_{18}F_3NO$	70.57	70.45	5.08	5.37	3.92	4.14	2.8
H	4-OCH_3	113–115	$C_{21}H_{18}F_3NO_2$	67.56	67.73	4.86	4.96	3.76	3.81	51.3
H	4-OCH_3	152–153	$C_{21}H_{18}F_3NO_2$	67.56	67.44	4.86	5.13	3.76	3.93	65.6
H	4-C_6H_5	183–184	$C_{26}H_{20}F_3NO$	74.46	74.74	4.81	5.02			

[a] Estrogenic potency was measured as the number of micrograms of diethylstilbestrol required to give the same biological effect as 1 mg of test compound. Thus, diethylstilbestrol would have a rating of 1000.

TABLE II

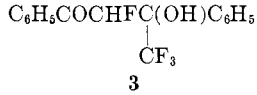
β-PERFLUOROALKYL-β-PHENYL-2-PYRIDINEETHANOLS



					% Carbon		% Hydrogen		% Nitrogen		
R_1	R_2	R_3	Mp, °C	Formula	Calcd	Found	Calcd	Found	Calcd	Found	ES[a]
H	CF_3	H	151–153	$C_{14}H_{12}F_3NO \cdot HCl$	55.36	55.26	4.31	4.57	4.61	4.52	0.9
H	CF_3	CH_3	138–140	$C_{15}H_{14}F_3NO$	64.07	63.99	5.01	5.40	4.98	5.09	4.4
H	CF_3	$CH_2CH_2CH_3$	129–130	$C_{17}H_{18}F_3NO$	66.01	66.26	5.87	6.08	4.53	4.44	1.0
H	C_2F_5	C_6H_5	166–167	$C_{21}H_{16}F_5NO$	64.12	64.15	4.10	4.14	3.56	3.86	22.0
H	C_2H_5	C_6H_5	151–153	$C_{21}H_{16}F_5NO$	64.12	64.12	4.10	4.28	3.56	4.33	
CH_3	CF_3	C_6H_5	137–137.5	$C_{21}H_{18}F_3NO$	70.57	70.55	5.08	5.25	3.92	3.96	0.8

[a] Estrogenic potency was measured as the number of micrograms of diethylstilbestrol required to give the same biological effect as 1 mg of test compound. Thus, diethylstilbestrol would have a rating of 1000.

adsorbed. The product showed no carbonyl band in the infrared. Treatment of the unknown with aqueous sodium hydroxide gave approximately 1 molar equiv of benzoic acid. The nmr spectrum dictated structure **3**, which is consistent with the rest of the data. In



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addition to ten aromatic protons there was one unsplit hydroxyl proton and one proton split by the fluorine into a doublet with peaks at 5.80 and 6.58 ppm.

Pharmacology.—The compounds were tested for estrogenic activity using the vaginal-smear technique.[4] Tests on selected compounds using the increase in uterine weight method[5] gave comparable results. These data are recorded in Tables I and II. Substitution had a deleterious effect on the estrogenic potency. This was surprising since substitution in the stilbene series of synthetic estrogens gives a striking increase in potency.

Experimental Section

Melting points were determined in open capillary tubes using the Thomas–Hoover apparatus equipped with a thermometer calibrated against known standards.

2′-Chloro-2,2,2-trifluoroacetophenone.—Excess trifluoroacetonitrile[6] was added over 45 min to the Grignard reagent prepared from 100 g of 3-bromochlorobenzene, 13 g of magnesium, and 400 ml of dry ether. The temperature was maintained at 0° and a Dry Ice condenser was used to contain the trifluoroacetonitrile. The mixture was allowed to stand at 0° for at least 3 hr and was decomposed with ice and dilute H_2SO_4. The ether layer was washed with water, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residue was distilled twice through a 10-cm Vigreux column at 77–80° (20 mm); yield of colorless liquid, 22 g (20%).

Anal. Calcd for $C_8H_4ClF_3O$: C, 46.06; H, 1.93. Found: C, 46.05; H, 2.18.

(4) C. W. Emmens, *Methods Hormone Res.*, **2**, 65 (1962).

(5) C. W. Emmens, *ibid.*, **2**, 93 (1962).

(6) Obtained from Columbia Organic Chemicals.

3′-Chloro-2,2,2-trifluoroacetophenone,[7] bp 76–78° (19 mm), was prepared in the same manner in 30% yield.

4′-Methoxy-2,2,2-trifluoroacetophenone.—The Grignard reagent prepared from 125 g of *p*-bromoanisole, 17 g of Mg, and 350 ml of anhydrous ether was cooled to 0° and added dropwise to a solution at −70° of 273 g of trifluoroacetic anhydride in 250 ml of anhydrous ether. The mixture was maintained at −60 to −70° for 16 hr and then decomposed with ice and HCl. The ether layer was washed with cold aqueous Na_2CO_3 solution until neutral, then water and dried ($MgSO_4$). After two distillations using a 10-cm Vigreux column 27.8 g (20% yield) of a colorless oil, bp 108–112° (23 mm), was obtained.

Anal. Calcd for $C_9H_7F_3O_2$: C, 52.95; H, 3.46. Found: C, 53.00; H, 3.91.

4′-Chloro-2,2,2-trifluoroacetophenone.[8]—Using the procedure given above, 4′-chloro-2,2,2-trifluoroacetophenone, bp 80–84° (19 mm), was synthesized in 34% yield.

α,β-Diphenyl-α-trifluoromethyl-2-pyridineethanol (1).—To the blood red solution of phenyllithium prepared from 10 g of lithium ribbon, 67 ml of bromobenzene, and 500 ml of anhydrous ether was added dropwise, at reflux temperature, 98 g of 2-benzylpyridine (Reilly Chemical) in 200 ml of ether. The mixture turned dark orange. α,α,α-Trifluoroacetophenone (100 g, Columbia Organic Chemicals) in 200 ml of ether was added dropwise. The mixture was stirred at reflux for 3.5 hr and decomposed by adding 500 ml of water. The heavy precipitate which formed was collected by filtration and washed with cold ethanol; yield 139 g, mp 153–163°. Evaporation of the ether layer gave a dark residue which was crystallized from ethanol; yield 5 g, mp 178–180° (over-all crude yield 72%). Repeated fractional crystallization gave 24 g of high-melting isomer, mp 190–190.5°, and 28 g of low-melting isomer, mp 159.5–160°. Substituted α,β-diphenyl-α-trifluoromethyl-2-pyridineethanols and related compounds prepared by the above method are listed in Tables I and II.

α,β-Diphenyl-α-trifluoromethyl-3-pyridineethanol.—Sodium diisopropylamide was prepared by the method of Raynolds and Levine[9] from 0.2 mole of isopropylamine. To this mixture at 5–15°, was added slowly 35 g of 3-benzylpyridine in 35 ml of benzene. After 30 min, 17.5 g of α,α,α-trifluoroacetophenone in 17 ml of benzene was added slowly. The mixture was stirred for 1 hr after the addition was complete and decomposed by the addition of a mixture (1:1) of benzene–isopropyl alcohol. A dry nitrogen atmosphere was maintained throughout the reaction. Hydrochloric acid was added to pH 1 and the layers were separated. The acidic aqueous layer was washed twice with benzene and then made alkaline by means of 20% NaOH. The aqueous layer was decanted from a brown thick oil and was extracted several times with ether. The ether extracts were combined with the brown oil, dried ($MgSO_4$), and evaporated. The residue was crystallized from ethanol–heptane with charcoal and then three times from methanol; yield 1.5 g, mp 222–223°. Estrogenic potency was 5.5 (see footnote *a*, Table I for an explanation of this value).

Anal. Calcd for $C_{20}H_{16}F_3NO$: C, 69.97; H, 4.70; N, 4.08. Found: C, 69.83; H, 4.64; N, 4.12.

α,β-Diphenyl-α-trifluoromethyl-4-pyridineethanol.—Following the above procedure, there was obtained 2.0 g of colorless crystals, mp 211–212°. Estrogenic potency was 19.8 (footnote *a*, Table I).

Anal. Calcd for $C_{20}H_{16}F_3NO$: C, 69.97; H, 4.70; N, 4.08. Found: C, 69.91; H, 4.71; N, 4.28.

A lower melting form was also isolated but a constant melting point was not obtained.

α-(2-Pyridyl)-α′-(trifluoromethyl)stilbene (2).—To a solution at 35° of 140 g of α,β-diphenyl-α-trifluoromethyl-2-pyridineethanol (1) in 1 l. of pyridine was added 288 ml of $SOCl_2$ over a 3-hr period. The mixture was allowed to stand overnight; it gave a dark solution and a black tar. The solution was decanted and evaporated *in vacuo*. This residue and the tar obtained from the reaction were treated with hot saturated $NaHCO_3$ solution containing about 25% ethanol. This solution was diluted with water until no further precipitation occurred and the black precipitate was extracted several times with ethyl acetate and water. Insoluble material was discarded. The ethyl acetate extracts were evaporated *in vacuo* and taken up in several portions of ether. The combined ether extract was evaporated and the dark oil was crystallized twice with charcoal from 95% denatured ethanol containing a few drops of water; yield of off-white solid, 14.7 g, mp 81–83°. Two crystallizations of a small portion yielded an analytical sample, mp 87–88.5°.

Anal. Calcd for $C_{20}H_{14}F_3N$: C, 73.84; H, 4.34; N, 4.31. Found: C, 73.68; H, 4.59; N, 4.17.

2,4,4,4-Tetrafluoro-3-hydroxy-3-phenylbutyrophenone (3). To 14.4 g of Mg turnings suspended in 200 ml of dry ether was added dropwise 24 g of bromine at a rate to maintain gentle reflux. A solution of 50 g of trifluoroacetophenone in 50 ml of ether was added dropwise to the heterogenous mixture. The reaction was mildly exothermic. After being allowed to stand overnight the mixture was decomposed with ice and HCl. The layers were separated and the aqueous layer was extracted with ether. The combined organic extract was dried ($MgSO_4$) and evaporated in a rotary evaporator. Vacuum distillation yielded 20.4 g of unreacted trifluoroacetophenone, bp 50–55° (18 mm), and a brown semisolid residue. By repeated extractions of the brown residue with boiling cyclohexane followed by concentration of the combined extracts there was obtained a tan solid. The solid was crystallized from cyclohexane with charcoal to yield 5.0 g of white crystals, mp 105–106°. The compound was homogeneous by thin layer chromatography on silica gel in several solvents. The infrared spectrum showed strong hydroxyl absorption at 3270 cm^{-1} and carbonyl absorption at 1707 cm^{-1} (KBr disk). The nmr[10] spectrum showed 10 aromatic protons at 7.1–7.8 ppm, one hydroxyl proton at 4.65 ppm, and one proton split into a doublet with maxima at 5.80 and 6.58 ppm.

Anal. Calcd for $C_{16}H_{12}F_4O_2$: C, 61.52; H, 3.88; F, 24.33; mol wt, 312. Found: C, 61.43; H, 4.24; F, 23.93; mol wt (Rast), 299.

2,4-Dinitrophenylhydrazone derivative.

Anal. Calcd for $C_{22}H_{16}F_4N_4O_5$: C, 53.66; H, 3.28; F, 15.48; N, 11.39. Found: C, 53.42; H, 3.36; F, 15.45; N, 11.52.

Hydrogenation of 3.—A sample (188 mg) of **3** was hydrogenated at 1.5 atm pressure using PtO_2 catalyst, and 110% of the theoretical amount of hydrogen was adsorbed. The product was an oil which could not be induced to solidify. The carbonyl band in the infrared spectrum had completely disappeared.

Treatment of 3 with Alkali.—Treatment of 250 mg of **3** with 10 ml of 1 *N* NaOH solution at 90° for 1 hr gave a drop of oil. The oil was extracted into ether and the ether solution was washed with 1 *N* NaOH solution. The combined basic extract was acidified with HCl and extracted with ether. From the ether extract there was obtained 80 mg (calcd, 97 mg) of benzoic acid, mp 121° alone and mixed with an authentic sample.

Acknowledgment.—The estrogenic assays were carried out by Dr. Fred Armstrong of the Bioassay Department, Parke, Davis and Co. We appreciate his courtesy in allowing us to publish these data. Microanalyses were by Mr. C. Childs and his associates and spectra were by Dr. John Vandenbelt and Mr. R. B. Scott and their associates.

(7) J. D. Parke, H. A. Brown, and J. R. Lacher, *J. Am. Chem. Soc.*, **73**, 709 (1951), prepared this compound by a different route.

(8) A. Kaluszyner, S. Reutner, and E. D. Bergmann, *ibid.*, **77**, 4164 (1955), used another route to this compound.

(9) S. Raynolds and R. Levine, *ibid.*, **82**, 472 (1960).

(10) Nmr spectra were taken in $CDCl_3$ solution using a Varian A-60 instrument. Tetramethylsilane was used as an internal standard.