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Potential Antifertility Agents. 1. Substituted Diaryl Derivatives of Benzo[*b*]thiophenes, Benzo[*b*]furans, 1*H*-2-Benzothiapyrans, and 2*H*-1-Benzothiapyrans[1]

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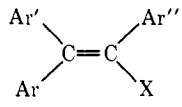
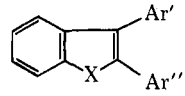
Syntheses and biological activities are reported for 24 of the title compds. The most active compds were 6-methoxy-3-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-2-phenylbenzo[*b*]thiophene (**3m**) and 3,4-dihydro-7-methoxy-3-phenyl-4-hydroxy-4-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-1*H*-2-benzothiapyran (**11a**). In addition to the title compds, a dibenzo[*b*,*e*]thiepin (**20**) containing some of the structural features of **11a** is reported; this structural modification resulted in loss of activity. Both **3m** and **11a** afford complete protection against pregnancy in rats at doses of 0.1 mg/kg. The compds exhibit a rapidly plateauing uterotropic activity in the rat which does not approach the maxima seen with known potent estrogens.

A number of triaryl ethylene derivatives of the general structure I are potent antifertility agents in rodents



I



II

a, X = CH_2 e, X = S
b, X = CH_2CH_2 f, X = O
c, X = NH g, X = CH_2S
d, X = OCH_2 h, X = SCH_2

owing to their estrogenic and/or estrogen antagonist activities. Among these are derivatives in which X is H, alkyl, halo, CN, and NO_2.[2,3] A similar type of activity, often with increased potency, has been demonstrated with compounds of structural type II, which may be viewed as "cyclized" triaryl ethylenes.[3] For example, Lednicer and associates have reported a series of variously substituted 2,3-diarylindenes (IIa)[4] and 1,2-diaryl-3,4-dihydronaphthalenes (IIb)[5] as potent antifertility agents. Showing similar biological activities, but with lowered potency, have been 2,3-diarylindoles (IIc)[6] and 3,4-diarylchromenes (IId) and derivatives.[7] In a research program started several years ago in these laboratories, we sought structures of type II containing S and O (IIe–IIh).[1] We now report synthesis and biological properties of compounds of type IIe–IIh and related structures.

(1) Some of these compds have been described in the following patents: (a) R. R. Crenshaw, U. S. Patent 3,413,305 (1968); (b) R. R. Crenshaw, U. S. Patent 3,394,125 (1968); (c) R. R. Crenshaw, U. S. Patent 3,332,956 (1967); (d) R. R. Crenshaw, U. S. Patent 3,321,483 (1967).

(2) For a comprehensive review of estrogenic di- and triaryl ethylenes prior to 1956 *cf.* J. A. Hogg and J. Korman in "Medicinal Chemistry," Vol. II, F. F. Blicke and C. M. Suter, Ed., Wiley, New York, N. Y., 1956, Chapter 2.

(3) For a recent review *cf.* D. Lednicer in "Contraception: The Chemical Control of Fertility," D. Lednicer, Ed., Marcel Dekker, Inc., New York, N. Y., 1969, Chapter 5.

(4) (a) D. Lednicer, J. C. Babcock, S. C. Lyster, J. C. Stucki, and G. W. Duncan, *Chem. Ind. (London)*, 2098 (1961); (b) D. Lednicer, J. C. Babcock, P. E. Marlatt, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **8**, 52 (1965).

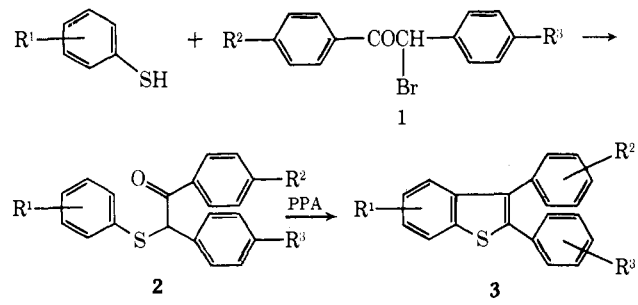
(5) (a) D. Lednicer, J. C. Babcock, S. C. Lyster, and G. W. Duncan, *Chem. Ind. (London)*, 408 (1963); (b) D. Lednicer, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **10**, 78 (1967).

(6) (a) J. K. Landquist and C. J. Marsden, *Chem. Ind. (London)*, 1032 (1966); (b) R. N. Iyer and R. Gopalchari, *Indian J. Chem.*, **4**, 520 (1966).

(7) (a) R. W. Carney, W. L. Bencze, J. Wojtkunski, A. A. Renzi, L. Dorfman, and G. DeStevens, *J. Med. Chem.*, **9**, 516 (1966); (b) K. Irmscher, J. Kramer, H. Kraft, and H. Kieser, U. S. Patent 3,471,520 (1969); (c) R. Gopalchari and R. N. Iyer, *Indian J. Chem.*, **4**, 331 (1966).

Chemistry.—The benzo[*b*]thiophene nucleus was formed for most of the compounds as outlined in Scheme I.[8] The requisite α-bromo ketones **1** were prepared in

SCHEME I



essentially quantitative yield using $CuBr_2$ with the corresponding deoxybenzoins according to King and Ostrum.[9] Reaction of **1** with arylthiolate anions produced the α-arylthio-substituted ketones **2** which were cyclized in polyphosphoric acid to the benzo[*b*]thiophenes **3a–3g** (Table I). These then were elaborated further through alkylation, or demethylation followed by alkylation, to produce the substituted benzo[*b*]thiophenes **3m–3q**. No identifiable benzo[*b*]thiophenes could be isolated from attempted cyclization of the ketones **2h–2j** (Table II).

An alternative route was used for formation of the benzo[*b*]thiophene nucleus containing a 5-NO_2 substituent (Scheme II). The activated chloro group of **4** was displaced by α-toluenethiol to yield **5** which was cyclized with KO-*tert*-Bu to the 5-nitrobenzo[*b*]thiophene **3h**. The NO_2 group then was modified through reduction and subsequent acylation to yield benzo[*b*]thiophenes **3i–3j**. Scheme II is related to work by Middleton in which 2-carboxy-substituted benzo[*b*]thiophenes were prepared from the reaction of mercaptoacetic acid with 2-chloro-5-nitrobenzophenone followed by cyclization.[10] It was hoped that the 5-aminobenzo[*b*]thiophene **3i** might serve as a precursor to the 5-OH-substituted relative which had proved

(8) Similar syntheses of benzo[*b*]thiophenes have been reported previously. *Cf.* (a) K. Rabindran and B. D. Tilak, *Curr. Sci.*, **20**, 207 (1951); (b) J. E. Banfield, W. Davies, N. W. Gamble, and S. Middleton, *J. Chem. Soc.*, 4791 (1956), and ref cited therein; (c) E. Campaigne, A. Dinner, and E. S. Neiss, *J. Heterocycl. Chem.*, **7**, 695 (1970).

(9) L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).

(10) S. Middleton, *Aust. J. Chem.*, **12**, 218 (1959).

TABLE I

2,3-DIARYLBENZO[*b*]THIOPHENES

Compd	R¹	R²	R³	Mp, °C	Recrystn solvent[a]	Formula[b]	Anal.
3a	6-OCH_3	*p*-OH	H	177–179	*c*	$C_{21}H_{16}O_2S$	C, H, S
3b	H	H	H	110–111[d]	A–B	$C_{20}H_{14}S$	
3c	6-OCH_3	*p*-OCH_3	H	141.5–142.5	A–B	$C_{22}H_{18}O_2S$	C, H, S
3d	6-OCH_3	H	H	135–136	A–B	$C_{21}H_{16}OS$	C, H, S
3e	H	*p*-OCH_3	H	124–125	C	$C_{21}H_{16}OS$	C, H, S
3f	6-OCH_3	*p*-OCH_3	*p*-OCH_3	141.5–142.5	A–B	$C_{23}H_{20}O_3S$	C, H, S
3g	6-CH_3	*p*-OCH_3	H	175–176	C	$C_{22}H_{18}OS$	C, H, S
3h	5-NO_2	*p*-OCH_3	H	146–148	*c*	$C_{21}H_{15}NO_3S$	C, H, N, S
3i	5-NH_2·HCl	*p*-OCH_3	H	244 dec	*c*	$C_{21}H_{17}NOS$·HCl	C,[e] H, Cl, N, S
3j	5-CH_3CONH	*p*-OCH_3	H	168–170	D–E	$C_{23}H_{19}NO_2S$	C,[f] H, N
3k	6-OH	*p*-OH	H	269–271	*c*	$C_{20}H_{14}O_2S$	C, H, S
3l	6-OH	H	H	172.5–174	F	$C_{20}H_{14}OS$	C, H, S
3m	6-OCH_3	*p*-$O(CH_2)_2$N⟨⟩·HCl	H	207–208	*c*	$C_{27}H_{27}NO_2$·HCl	C, H, N
3n	6-OCH_3	*p*-$O(CH_2)_2$—N⟨⟩=O	H	128–130	D	$C_{27}H_{25}NO_3S$	C, H, N, S
3o	6-OCH_3	*p*-$O(CH_2)_2N(CH_3)_2$·HCl	H	230	G–H	$C_{25}H_{25}NO_2S$·HCl	C, H, N, S[g]
3p	6-$O(CH_2)_2$N⟨⟩·HCl	H	H	220 dec	I–H	$C_{26}H_{25}NOS$·HCl	C, H, N, S
3q	6-$O(CH_2)_2$N⟨⟩·HCl	*p*-$O(CH_2)_2$N⟨⟩·HCl	H	133–136	J–E	$C_{32}H_{36}N_2O_2S$·2HCl	C,[h] H, Cl, N

[a] A, Me_2CO; B, Skellysolve B; C, *n*-BuOH; D, EtOH; E, H_2O; F, C_6H_6; G, CH_2Cl_2; H, EtOAc; I, $CHCl_3$; J, *i*-PrOH. [b] Anal. results for indicated elements are within ±0.4% of the theor values unless otherwise noted. [c] *Cf.* Experimental Section. [d] Lit. mp 114–115° [H. Standinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 840 (1920)]. [e] C: Calcd, 68.56; found, 69.19. [f] C: Calcd, 73.97; found, 74.45. [g] Calcd as monohydrate. [h] C: Calcd, 65.63; found, 64.83.

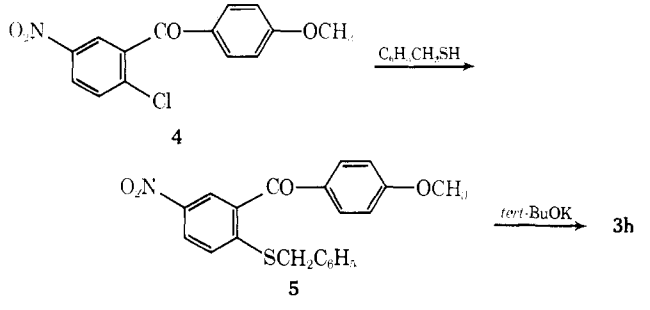
TABLE II

α-ARYLTHIODEOXYBENZOINS

Compd	R_1	R_2	R_3	Mp, or bp (mm), °C	Recrystn solvent[a]	Formula[b]	Anal.
2a	*m*-CH_3O	OH	H	142–143	A–B	$C_{21}H_{18}O_3S$	C, H
2b	H	H	H	78–79.5[c]	A	$C_{20}H_{16}OS$	C, H, S
2c	*m*-CH_3O	OCH_3	H	Oil[d]		$C_{22}H_{20}O_3S$	C;[e] H
2d	*m*-CH_3O	H	H	50–51.5	C	$C_{21}H_{18}O_2S$	C, H, S
2e	H	OCH_3	H	69–71	A	$C_{21}H_{18}O_2S$	C, H, S
2f	*m*-CH_3O	OCH_3	OCH_3	Oil[d]		$C_{23}H_{22}O_4S$	
2g	*m*-CH_3	OCH_3	H	Oil[d]		$C_{22}H_{20}O_2S$	
2h	*m*-HO	OCH_3	H	104.5–106	D	$C_{21}H_{18}O_3S$	C, H, S
2i	*p*-CF_3	OCH_3	H	97–99	A	$C_{22}H_{17}F_3O_2S$	C, H
2j	*p*-HO	OCH_3	H	Oil[d]		$C_{15}H_{18}O_3S$	

[a] A, EtOH; B, H_2O; C, MeOH; D, C_6H_6. [b] Anal. results for indicated elements are within ±0.4% of the theor values unless otherwise noted. [c] Lit. mp 81° [W. A. Mitchel and S. Smiles, *J. Chem. Soc.*, 1529 (1933)]. [d] Consistent spectral data; used crude for cyclization step. [e] C: Calcd, 72.51; found, 71.78.

SCHEME II



inaccessible from cyclization of the ketone **2j**. However, treatment of the diazonium salt of **3i** with aq H_2SO_4 gave a mixture of unidentified products from which none of the desired 5-OH-substituted benzo[*b*]thiophene was isolated.

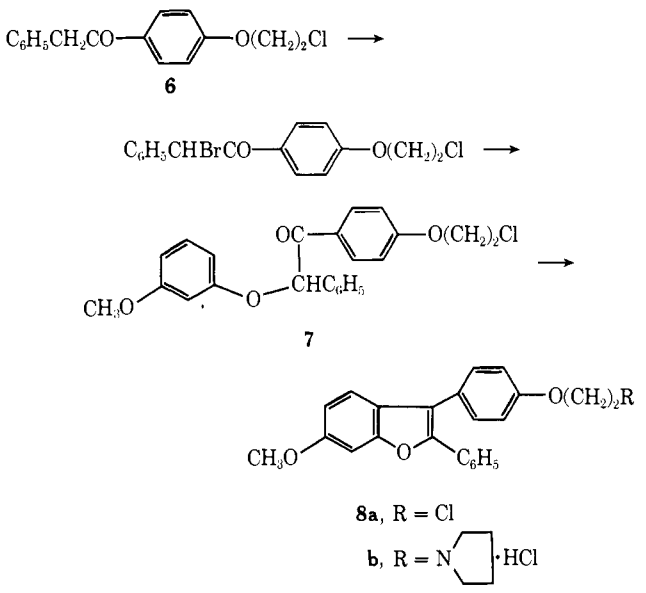
A series of 2,3-diarylbenzo[*b*]furans has been reported by Grover, *et al.*,[11] to possess antifertility activity. A similar series of compounds was synthesized independently in these laboratories[1b] using a synthetic approach (*cf.* Scheme III) different from that used by Grover. The most potent compound in our series was **8b**.

The 1*H*-2 and 2*H*-1 benzothiapyran derivatives were prepared as outlined in Schemes IV and V, resp. The biologically active alcohol derivatives **11** and **16** appear to be homogeneous (tlc, free bases; mp unchanged by repeated recrystallizations) and, if so, represent only one of two possible diastereoisomeric forms.

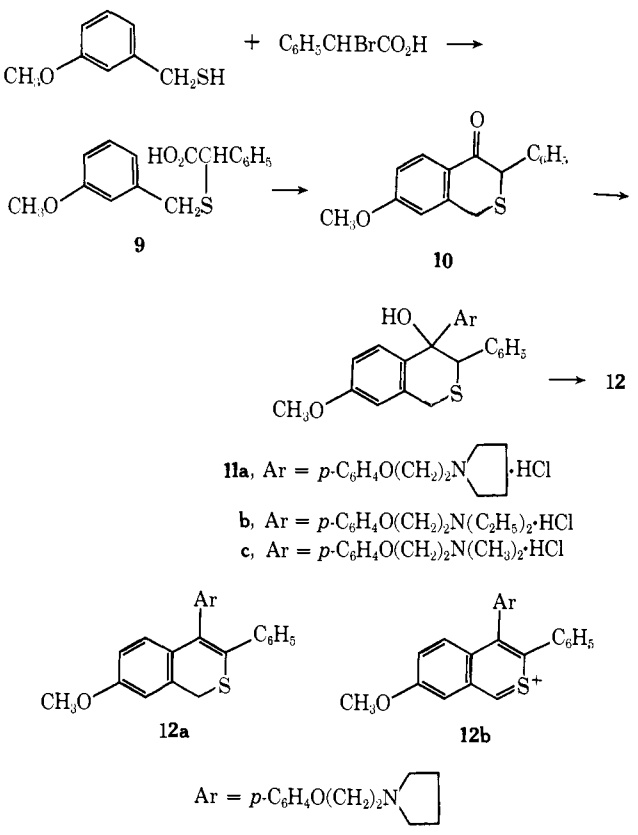
The alcohols **11** and **16** in both series were formed in low yields. For **11** the low yield was shown to result

(11) (a) P. K. Grover, H. P. S. Chawla, N. Anand, V. P. Kamboj, and A. B. Kar, *J. Med. Chem.*, **8**, 720 (1965); (b) H. P. S. Chawla, P. K. Grover, N. Anand, V. P. Kamboj, and A. B. Kar, *ibid.*, **13**, 54 (1970).

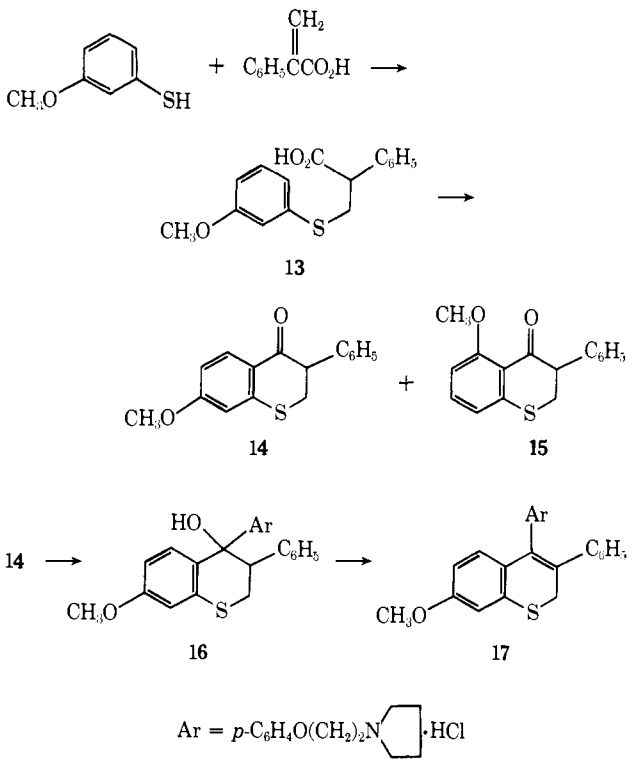
SCHEME III



SCHEME IV



SCHEME V



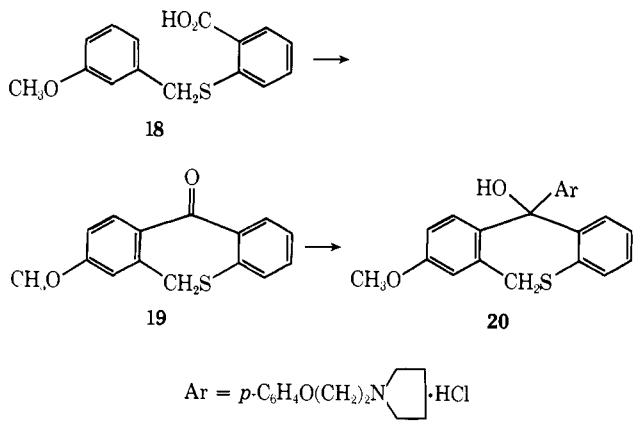
from acidity of the ketone **10**, rather than from steric hindrance, on the basis of an experiment in which the Grignard adduct of **10** was decomposed with D_2O. Nmr analysis of the unreacted ketone **10** which was recovered showed 75% incorporation of D α to C=O; additionally, *N*-(2-phenoxyethyl)pyrrolidine which was isolated showed no evidence (nmr) for *p*-D incorporation.

Dehydration of the 2*H*-1 benzothiapyran derivative **16** with HCl in EtOH yielded the expected product **17**. In contrast, treatment of the 1*H*-2 derivative **11a** under the same conditions gave a product **12** which has not been unequivocally established as having structure **12a**.

Although elemental analyses, ir, uv, and mass spectral data were consistent for **12a**, 100-MHz nmr spectra showed anomalies (*cf.* Experimental Section). However, an nmr spectrum of the product **12** in F_3CCO_2D is consistent for the cationic structure **12b** which could be expected to arise from treatment of a structure such as **12a** with strong acid.[12,13] The uv spectrum of **12** after treatment with F_3CCO_2H is likewise consistent for a transformation of **12a** to **12b** with absorption extending into the visible region.[13]

The potent antifertility activity shown by **11a** suggested synthesis of the dibenzothiepin **20** which has some structural similarities with **11a**. Synthesis of **20** proceeded without difficulty (Scheme VI), but the

SCHEME VI



compound proved devoid of activity.

Biological Activity.—All of the compounds reported herein were initially screened for antifertility activity

(12) *Cf.* E. R. DeWaard, W. J. Vloon, and H. O. Huisman, *Chem. commun.*, 841 (1970).

(13) *Cf.* T. E. Young and C. R. Hamei, *J. Org. Chem.*, **35**, 816 (1970).

in mice. The dosing regimen entailed oral administration of the drug for 9 days over an 11-day period. The dosing schedule involved both pre- and postcoital administration. All antifertility doses reported represent daily doses. Estrogenic and antiestrogenic activities were determined by uterine weight responses in immature 21-day-old mice and rats. The animals were dosed orally for 3 days and were autopsied on day 4. In the antiestrogenic assays, the dosing regimen was the same with the exception that the compounds were given together with ethynyl estradiol (EE). For both the estrogenic and antiestrogenic assays, the doses reported represent the total amount of drug per animal for the 3-day period. Gonadotropin inhibition was determined by oral administration of the compounds to 28-day-old male rats for 7 days. The weights of the testes, ventral prostate, and seminal vesicles were used as the end points for gonadotropin inhibition. Hypocholesteremic activity was ascertained in mature male rats after a 4-day or 30-day oral dosing schedule. It is our intent to present data for the representative compounds.

Estrogenic and Antiestrogenic Activities.—In the mouse, **3a** and **3d** exhibit doubling of uterine weight at 1000 μg/animal. Compound **3h** appears to be inactive. In the rat these compounds are less estrogenic than in the mouse. In the same series addition of the basic side chain (**3m**) produces a compound that exhibits potent uterotropic activity in the mouse. At 1 μg/mouse **3m** has activity approximating that of 1 μg of EE. At 0.1 μg, **3m** is less potent than 0.1 μg of EE. At higher doses (10 and 100 μg), **3m** exhibits autoinhibitory properties, with lower uterine weights seen at these higher doses than with lower doses of **3m**. In the mouse the compound has definite antiestrogenic properties with resultant uterine weights following concomitant **3m** (100 μg) and EE (1 μg) administration being lower than one observes with the same dose of **3m** alone. In the immature female rat, doubling of uterine weight is seen at 10 μg/animal of **3m**. No further increases in uterine weight are seen at doses 200-fold higher. This compound is also a potent antiestrogen in rats. Unlike the situation observed in the mouse, in the rat concomitant dosing of EE and **3m** gave no inhibition of uterine weight below that produced by the antagonist **3m** alone.

In the mouse uterine weight assay, **11a** administered at 10 μg produces weights equivalent to 1 μg of EE. Its antiestrogenic activity in the mouse is similar to that of **3m**. In the rat estrogenic and antiestrogenic assays, activity of **11a** parallels that of **3m**. Product **12** in the mouse is only weakly estrogenic and produces doubling of uterine weight at 100 μg.

Compound **8b** is weakly uterotropic in both mice and rats, significant increases in the mouse occurring at 100 μg and in the rat at 1000 μg. Compared to **3m** and **11a**, it does not exhibit antiestrogenic activity in the rat.

Compound **16** doubles mouse uterine weight at 10 μg/mouse. In the rat doubling of uterine weight occurs at 100 μg. Chemical dehydration to yield **17** lowered estrogenicity considerably both in the mouse and the rat. Compound **20** was not estrogenic in either mice or rats up to 1000 μg.

Antifertility Activity.—The antifertility activity of compounds in this series closely parallels their estrogenicity with the exception of **3h**. Compounds **3a, 3d, 3h, 3l, 3n,** and **3q** were active in mice at 50 mg/kg but not at lower doses. The two most active compounds were **3m** and **11a**. In mice, the MED_{100} for **3m** was 0.1 mg/kg and for **11a** was 0.25 mg/kg. These doses are essentially the same for a postcoital dosing schedule (days 1–5 of pregnancy). In the rat both of these compounds are effective at 0.1 mg/kg in postcoital assays.

In mice, an MED_{100} of 10 mg/kg was seen with **8b** and **16**. Compounds **12**, **17**, and **20** gave incomplete protection in mice at 10 mg/kg.

Gonadotropin Inhibition.—Compound **3m** was tested for its gonadotropin inhibitory activity in immature (28-day-old) male rats. At 5 mg/kg and a dosing schedule of 7 days there was a nonsignificant reduction in testes weights, whereas the ventral prostate and seminal vesicles were significantly reduced in weight. No dose–response could be established because toxicity was encountered at 20 mg/kg. In our assays, the gonadotropin inhibition and toxicity of this compound are of the same order as that of the corresponding 3,4-dihydronaphthalene (nafoxidine·HCl).[14] Compound **11a** produced a nonsignificant depression of testes, ventral prostate, and seminal vesicles weights. In doses of up to and including 40 mg/kg, no dose–response relationship could be established. No toxicity was observed at the doses employed.

Hypocholesteremic Activity.—Serum cholesterol values were determined in mature male rats dosed with **3m** for 4 or 30 days. Rats dosed for 4 days exhibited a significant depression (−46% $p < 0.001$) of serum cholesterol levels at 2.5 mg/kg. This depression was not accompanied by changes in weight of the testes or the accessory sexual organs. In the 30-day study no significant effect was observed at the dose of 5.0 mg/kg. These data suggest a possible biphasic effect of **3m** on serum cholesterol that has been previously reported by Uchida, *et al.*,[15] for a number of estrogens.

Experimental Section[16]

A. Benzo[*b*]thiophenes. 4-Hydroxyphenyl α-Bromobenzyl Ketone (1, R^2 = OH; R^3 = H).—A mixt of 4-hydroxyphenyl benzyl ketone (22.0 g, 0.104 mole) and $CuBr_2$ (46.6 g, 0.208 mole) in $CHCl_3$ (105 ml) and EtOAc (130 ml) was stirred under reflux for 2 hr.[9] The mixt was filtered and the filtrate was evapd. Trituration of the residue under Skellysolve B gave the title compd, 27.9 g (93%), mp 162–163.5°; the nmr spectrum ($CDCl_3$, DMSO-d_6) exhibited a singlet (1 H) for CHBr at δ 6.7 with no evidence for nuclear bromination, α-dibromination, or unchanged starting material.

4-Hydroxyphenyl α-(3-Methoxyphenylthio)benzyl Ketone (**2a**).—A soln of 4-hydroxyphenyl α-bromobenzyl ketone (15.0 g, 0.052 mole) in $CHCl_3$ (50 ml) and THF (35 ml) was added to a soln of *m*-methoxythiophenol (7.6 g, 0.054 mole) in abs EtOH (25 ml) contg NaOEt (0.054 mole). The mixt was heated at reflux for 3 hr. The solvent was replaced by Et_2O and the resultant soln washed with aq NaOH and H_2O. Evapn yielded

(14) 3,4-Dihydro-6-methoxy-2-phenyl-1-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}naphthalene·HCl; *cf.* ref 5b.

(15) K. Uchida, M. Kadowaki, K. Miyata, and T. Miyake, *Endocrinol. Jap.*, **16**, 211 (1969).

(16) Melting points are capillary and are uncorrected. All compds had consistent ir and nmr spectra for assigned structures. Routine nmr spectral data were obtained using a Varian A-60 spectrometer. Nmr data reported for **11a** and **12** were obtd on a Varian HA-100 spectrometer. Mass spectral data was obtd on a LKB 9000 mass spectrometer. Where elemental analyses are indicated by symbols of the elements, anal. results were within ±0.4% of the theor values.

2a: 15.2 g (84%); mp 142–143° after recrystn (aq EtOH). *Anal.* ($C_{21}H_{18}O_3S$) C, H.

6-Methoxy-3-(*p*-hydroxyphenyl)-2-phenylbenzo[*b*]thiophene (3a).—A mixt of the ketone **2a** (12.3 g) and PPA[17] (256 g) was heated at 90° for 1 hr. It was then poured onto ice and extd with $CHCl_3$. The exts were washed with H_2O, dried, and then evapd to give solid **3a** (8.3 g, 71%). An anal. sample (C_6H_6) had mp 177–179°. *Anal.* ($C_{21}H_{16}O_2S$) C, H, S. Similarly prepared were **3b–3g**; reaction condns in PPA: **3b** (190°/3.5 hr); **3c**, **3d**, **3f** (90–100°/1 hr); **3e** (180°/3.5 hr); **3g** (135–150°/2.5 hr).

6-Methoxy-3-{*p*-[2-(*N*-pyrrolidyl)ethoxy]phenyl}-2-phenylbenzo[*b*]thiophene·HCl (3m).—NaH (0.21 mole) dispersion in oil was added to **3a** (64.1 g, 0.19 mole) in DMF (720 ml) at 4°. The mixt was stirred at 34° for 2 hr, and then a soln of *N*-(β-chloroethyl)pyrrolidine (32.4 g, 0.24 mole; freshly prepd from the HCl salt) in DMF (140 ml) was added. The resultant mixt was stirred at 55–60° for 1 hr, and then at 25° for 16 hr. A few ml of EtOH was added and the DMF was then removed at 5 mm. The solid obtained was triturated under 1 *N* HCl (245 ml). The mixt was then extd with $CHCl_3$ which was washed with H_2O and dried. Evapn of the $CHCl_3$ left a solid which was recrystd from CH_2Cl_2 (275 ml)–EtOAc (400 ml): yield of **3m**, 64.0 g (71%); mp 204–207°. A second recrystn gave mp 207–208°. *Anal.* ($C_{27}H_{27}NO_2S\cdot HCl$) C, H, N.

The same general method of alkylation was used for prepg **3n–3q**. The pyrrolidone **3n** was purified by chromatog on silica gel.

6-Hydroxy-3-(*p*-hydroxyphenyl)-2-phenylbenzo[*b*]thiophene (3k) was prepd from **3a** (11.00 g, 0.033 mole) and BBr_3 (16.70 g, 0.066 mole) using the method of McOmie, *et al.*:[18] yield, 7.9 g (74%); mp 269–271° (*p*-dioxane). *Anal.* ($C_{20}H_{14}O_2S$) C, H, S. Compd **3l** was prepd similarly from **3d**.

2-Benzylthio-5-nitro-4′-methoxybenzophenone (5).—A mixt of 2-chloro-5-nitro-4′-methoxybenzophenone[19] (16.40 g, 0.056 mole), α-toluenethiol (6.98 g, 0.56 mole), and KOH (3.15 g) in EtOH (140 ml) was refluxed 3 hr. The product obtained was chromatogd (alumina; elution with Skellysolve B–C_6H_6) to yield 8.05 g of **5**; recrystn (EtOH) gave mp 123–125°. *Anal.* ($C_{21}H_{17}NO_4S$) C, H, S.

3-(*p*-Methoxyphenyl)-5-nitro-2-phenylbenzo[*b*]thiophene (3h).—KO-*tert*-Bu (4.30 g) was added to a refluxing soln (3.75 g) in dry *tert*-BuOH (140 ml). The mixt was heated under reflux for 25 min, and then was stirred at 25° for 12 hr. Dilution with H_2O gave 2.70 g. (79%) of **3h** which was recrystd (*i*-PrOH) to const mp 146–148°. *Anal.* ($C_{21}H_{15}NO_3S$) C, H, N, S.

5-Amino-3-(*p*-methoxyphenyl)-2-phenylbenzo[*b*]thiophene·HCl (3i).—A suspension of **3h** (1.54 g) and Raney Ni (2 g) in *i*-PrOH (55 ml) contg 85% hydrazine hydrate (2 ml) was refluxed 1 hr. The hot soln was filtered, and the filtrate was acidified with 1 *N* HCl and evapd to leave **3i** (1.00 g); recrystn (MeOH–Et_2O) gave mp 244° dec. *Anal.* ($C_{21}H_{17}NOS\cdot HCl$) C, H, Cl, N, S.[20]

B. Benzo[*b*]furans. Benzyl *p*-(2-Chloroethoxy)phenyl Ketone (6).—A mixt of NaOH (3.46 g), benzyl *p*-hydroxyphenyl ketone (15.93 g), and 2-chloroethyl *p*-toluenesulfonate (20.3 g) in PhMe (150 ml) was stirred under reflux for 15 hr with provision for removal of H_2O. The cooled mixt was washed in succession with aq caustic, H_2O, and satd brine soln. Evapn left 14.70 g of **6** (71%), mp 105–107.5° (PhMe). *Anal.* ($C_{16}H_{15}ClO_2$) Cl.

***p*-(2-Chloroethoxy)phenyl α-(*m*-Methoxyphenoxy)benzyl Ketone (7).**—A soln of *m*-methoxyphenol (4.05 g) in DMF (50 ml) was added to NaH dispersion (1 equiv) in DMF (50 ml). When H_2 evoln had ceased, a soln of α-bromobenzyl *p*-(2-chloroethoxy)phenyl ketone (11.50 g; from **6** and $CuBr_2$) in C_6H_6 (100 ml) was added and the mixt was heated under reflux for 16 hr. The solvent was removed, and the residue was dissolved in a mixt of C_6H_6 and Et_2O. The soln was washed with aq caustic and H_2O, and then was dried. Evapn, followed by removal of mineral oil by extn with Skellysolve B, yielded **7** as an oil, 12.90 g (99%). *Anal.* ($C_{23}H_{21}ClO_4$) Cl.

3-[*p*-(2-Chloroethoxy)phenyl]-6-methoxy-2-phenylbenzo[*b*]furan (8a).—A mixt of **7** (10.1 g) and PPA[15] (563 g) was stirred at 94–108° for 4 hr. The cooled mixt was poured onto ice and then was extd with C_6H_6. The C_6H_6 was washed with H_2O, dried, and evapd to yield **8a** monohydrate (7.6 g, 80%), mp 97.5–100° (MeCN). *Anal.* ($C_{23}H_{19}ClO_3\cdot H_2O$) Calcd: C, 69.61; H, 5.34; Cl, 8.93. Found: C, 69.28; H, 4.89; Cl, 8.48.

6-Methoxy-3-{*p*-[2-(*N*-pyrrolidyl)ethoxy]phenyl}-2-phenylbenzo[*b*]furan·HCl (8b).—A soln of **8a** (1.25 g) in pyrrolidine (10 ml) was heated under reflux for 3 hr. Excess pyrrolidine was removed and the residue was dissolved in C_6H_6. The C_6H_6 soln was extd with 1 *N* HCl, and the acid exts then were extd with $CHCl_3$. Drying and evapn of $CHCl_3$ left **8b** (1.12 g, 75%): mp 210–213° (*i*-PrOH); reported[11a] 209–210°. *Anal.* ($C_{27}H_{27}NO_3\cdot HCl$) C, H, N.

C. Isothiapyrans. α-(*m*-Methoxybenzylthio)phenylacetic Acid (9).—A soln of α-bromophenylacetic acid (54.8 g) and *m*-methoxy-α-toluenethiol (39.2 g) in EtOH (185 ml) contg 1 *N* aq NaOH (508 ml) was kept at 22° for 17 hr to yield **9** (68.8 g, 94%) as an oil. The product gave a cryst hydrated Na salt, mp 93–95° (dioxane–Et_2O). *Anal.* ($C_{16}H_{15}NaO_3S\cdot H_2O$) C, H.

7-Methoxy-3-phenyl-4-isothiochromanone (10).—A soln of $SnCl_4$ (18.8 ml) in C_6H_6 (48 ml) was added over 15 min to a soln at 0–5° of α-(*m*-methoxybenzylthio)phenylacetyl chloride (from 31.7 g of **9** and $SOCl_2$) in C_6H_6 (100 ml). The mixt was stirred at 0° an addnl 10 min, then was poured onto 36% HCl (165 ml) and ice. It was extd into Et_2O and the Et_2O was washed with aq $NaHCO_3$ and H_2O. The soln was dried, treated with charcoal, and evapd to an oil which was triturated under Skellysolve B to yield **10** (22.5 g, 76%), mp 70–73°. Recrystns (6:1 cyclohexane–Me_2CO) gave mp 85–86°. *Anal.* ($C_{16}H_{14}O_2S$) C, H, S.

3,4-Dihydro-7-methoxy-3-phenyl-4-hydroxy-4-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-1*H*-2-benzothiapyran·HCl (11a).—A mixt of Mg turnings (9.0 g, 0.37 g-atom) and *N*-[2-(*p*-bromophenoxy)ethyl]pyrrolidine (100.0 g, 0.37 mole) in THF (1 l.) was stirred under reflux until all Mg had reacted (1 hr). A soln of the ketone **10** (100.0 g, 0.37 mole) in THF (1 l.) was added rapidly, and the resultant soln was heated under reflux for 16 hr. H_2O (37 ml) was added slowly at 0°, and the salts were removed by filtration. The filtrate was concd at 15 mm to remove most of the THF, and then was dild with Et_2O. The Et_2O was extd with aq 0.5 *N* HCl (3 × 375 ml). The combined acid exts were extd with CH_2Cl_2. Drying and evapn of the CH_2Cl_2 gave a gum (40.0 g); recrystd from Me_2CO (200 ml) to yield **11a** (23.6 g, 13%), mp 170–172° dec. Further recrystn (CH_2Cl_2–EtOAc) gave mp 176–177° dec; uv max (EtOH) 228 nm (sh) (log ε 4.35), 275 (3.46), 282 (sh) (3.40); ir (Nujol) 3260 cm^{-1} (OH); nmr (Pyr-d_5) δ 1.85 (m, 4, $NCH_2(CH_2)_2CH_2$), 3.24 (m, 4, $NCH_2(CH_2)_2CH_2$), 3.45 (t, 2, J = 5 Hz, CH_2N), 3.66 (s, 3, CH_3O), 3.78 (d, 1, J = 16 Hz, 0.5 CH_2S), 4.44 (d, 1, J = 16 Hz, 0.5 CH_2S), 4.51 (t, 2, J = 5 Hz, OCH_2CH_2), 4.90 (s, 1, C_6H_5CH), 5.75 (br, OH + H_2O from Pyr), 6.8–7.6 (m, 12, arom; integral cor for undeuterated Pyr). A spectrum run in $CDCl_3$ showed resonance at δ 3.19 (s, 1, OH) exchangeable with D_2O; mass spect (70 eV) m/e (rel intensity) 461 (M^+) (2), 443 (2), 339 (11), 241 (25), 98 (24), 84 (100). *Anal.* ($C_{28}H_{31}NO_3S\cdot HCl$) C, H, N, S.

Similarly prepared using the ketone **10** and the appropriate Grignard reagent were the salts **11b** (mp 186.5–187.5° dec) and **11c** (mp 167–169° dec). *Anal.* for **11b** ($C_{28}H_{33}NO_3S\cdot HCl$) C, H, Cl, N, S. *Anal.* for **11c**·H_2O ($C_{26}H_{29}NO_3S\cdot HCl\cdot H_2O$) N, S.

Preparation of 12.—A suspension of **11a** (1.30 g) in abs EtOH (13 ml) was satd with HCl gas. The resultant soln was stored at 25° overnight and then was refluxed for 3 hr. Filtration of the cooled mixt gave **12** (0.28 g, 22%), mp 279–281° dec. Recrystn (aq *i*-PrOH) gave mp 285° dec; uv max (EtOH) 256 nm (log ε 4.19), 350 (3.76); ir (Nujol) shows no OH absorption; nmr (Pyr-d_5, D_2O) δ 1.98 (m, 4, $NCH_2(CH_2)_2CH_2$), 3.38 (m, 4, $NCH_2(CH_2)_2CH_2$), 3.52 (s, 3, CH_3O), 3.68 (t, 2, J = 5 Hz, OCH_2CH_2N), 4.51 (t, 2, J = 5 Hz, OCH_2CH_2), 4.66 (s, 1, unknown), 6.8–7.6 (m, 12, arom; integral corrected for undeuterated Pyr); nmr (F_3CCO_2D) δ 2.30 (m, 4), 3.2–4.1 (m, 6), 4.17 (s, 3), 4.44 (t, 2), 6.9–8.2 (m, 12), 10.5 (s, 1, CH=S^+).

Dissoln of 1.8 mg of **12** in a few ml of F_3CCO_2H, followed by diln with MeCN gave the following uv spectrum: 228 (log ε 5.85), 284 (5.77), 322 (sh) (5.12), 445 (4.69) nm. Essentially the same spectrum was seen upon dissoln of **12** in 70% $HClO_4$ and diln with MeCN.[13] *Anal.* for **12** ($C_{28}H_{29}NO_2S\cdot HCl$) Calcd: C, 70.05; H, 6.30; Cl, 7.39; N, 2.92; S, 6.68. Found: C, 69.90; H, 6.36; Cl, 7.17; N, 2.92; S, 6.88.

(17) FMC Corporation polyphosphoric acid (115% H_3PO_4).

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(20) See Table I, footnote *e*.

Treatment of **12** with aq NaOH gave the free base: mp 246–250°; nmr ($CDCl_3$) δ 1.83 (m, 4, $NCH_2(CH_2)_2CH_2$), 2.24 (s, 1, OH?; exchanged with D_2O), 2.65 (m, 4, $NCH_2(CH_2)_2CH_2$), 2.90 (t, 2, OCH_2CH_2N), 3.27 (s, 3, CH_3O?), 4.08 (t, 2, OCH_2CH_2), 4.14 (s, 1, unknown), 6.5–7.3 (m, 12, arom); mass spect (70 eV) *m/e* (rel intensity) 443 (M^+) (43), 442 (98), 345 (32), 98 (41), 84 (100). A mol wt detd in soln (DMF; Mechrolab osmometer) indicated that the free base was monomeric; tlc in several solvents indicated homogeneity. *Anal.* ($C_{28}H_{29}NO_2S$) calcd mol wt: 443. Found: 540 (osmometer).

D. Thiapyrans. 3-(*m*-Methoxyphenylthio)-2-phenylpropionic Acid (13).—A mixt of atropic acid (10.45 g, 0.07 mole) and *m*-methoxythiophenol (9.88 g, 0.07 mole) was heated under N_2 at 125° for 20 hr.

The product was dissolved in Et_2O and the resultant soln was washed with 0.1 *N* I_2–KI soln and then was extd with NaOH. Acidification of the basic exts gave an oil which was extd into Et_2O. Washing, drying, and subsequent evapn of the Et_2O gave the acid **13** (15.59 g, 77%) as an oil; nmr indicated the addn to have occurred on the β-C; the product was used directly in the next step without further characterization.

7-Methoxy-3-phenyl-4-thiochromanone (14) and 5-methoxy-3-phenyl-4-thiochromanone (15).—A mixt of the acid **13** (39.9 g) and PPA[15] (798 g) was heated at 80–86° for 1 hr. The mixt was poured onto ice and then was extd with $CHCl_3$. The $CHCl_3$ exts were washed with aq $NaHCO_3$. Drying and evapn left an oil; recrystn (THF–Skellysolve B) gave **14** (11.0 g), mp 147–150°; further recrystn (EtOAc–Skellysolve B) gave mp 151–152.5°; nmr (DMSO-d_6) shows a downfield ortho-coupled doublet (δ 7.7, J = 7 Hz), consistent for the C-5 H deshielded by the adjacent C=O in support of the structural assignment **14**. *Anal.* ($C_{16}H_{14}O_2S$) C, H; S: calcd, 11.86; found, 11.18.

Concn of the mother liquors yielded an addl 9 g of **14** (contaminated by **15** and other impurities). The product from the remaining mother liquors was chromatog (alumina; elution with PhMe) to yield a semisolid (6.2 g); recrystd several times (MeCN) to yield **15** (2.0 g), mp 128.5–132°; nmr arom multiplicity and absence of a downfield doublet in 7.5–8.0 region support the structural assignment **15**. *Anal.* ($C_{16}H_{14}O_2S$) C, H, S.

3,4-Dihydro-7-methoxy-3-phenyl-4-hydroxy-4-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-2*H*-1-benzothiapyran·HCl (16).—Prepd from **14** (9.35 g) and *N*-[2-(*p*-bromophenoxy)ethyl]pyrrolidine (9.35 g) as described above for **11a**: yield of **16**, 2.11 g (12%); mp 172–173° dec (CH_3OH–Et_2O); uv max (EtOH), 222 (log ε 4.62), 258 (4.21), 280 (sh) (3.92), 296 (sh) (3.63); ir (Nujol) 3320 cm^{-1} (OH). *Anal.* ($C_{28}H_{31}NO_3S$·HCl) C, H, N, S.

7-Methoxy-3-phenyl-4-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-2*H*-1-benzothiapyran·HCl (17).—The alcohol **16** (1.70 g) was dehydrated by the procedure used for **12**: yield of **17**, 1.05 g (64%); mp 224–226° (CH_2Cl_2–EtOAc); uv max (EtOH), 250 (log ε 4.49), 262 (sh) (4.46), 319 (4.10); ir (Nujol) shows no OH absorption. *Anal.* ($C_{28}H_{29}NO_2S$·HCl) C, H, Cl, N, S.

E. Dibenzothiepins.—2-(*m*-Methoxybenzylthio)benzoic acid (18) was obtained from equimolar amts of *m*-methoxybenzylchloride and *o*-mercaptobenzoic acid in refluxing aq EtOH contg 2 equiv of $NaHCO_3$; mp 199–201° (Me_2CO–Skellysolve B). *Anal.* ($C_{15}H_{14}O_3S$) C, H, S.

8-Methoxydibenzo[*b,e*]thiepin-11(6*H*)-one (19) was prepd from the acid **18** (18.3 g) following the procedure described above for the isothiochromanone **10**: yield, 12.2 g (72%); mp 110–111°. *Anal.* ($C_{15}H_{12}O_2S$) C, H, S.

8-Methoxy-11-hydroxy-11-{*p*-[2-(1-pyrrolidyl)ethoxy]phenyl}-6,11-dihydrodibenzo[*b,e*]thiepin·HCl (20) was prepd from the ketone **19** (4.80 g) and *N*-[2-(*p*-bromophenoxy)ethyl]pyrrolidine (5.05 g) as described above for **11a**: yield of **20**, 3.10 g (34%); mp 183° dec. *Anal.* ($C_{27}H_{29}NO_3S$·HCl) C, H, Cl, S.

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17α-Propadienyl-19-nortestosterone and Related Compounds. A New Series of Potent Orally Active Progestogens[1]

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The synthesis of a series of 17α-propadienyl (allenyl) steroids in the 19-nortestosterone and estradiol series is described. 17β-Hydroxy-17α-propadienylestr-4-en-3-one (**3a**) and its 18-Me homolog (**3c**), the most active compounds of the former group, show oral progestational potencies 10 and 12 times 17α-ethynyl-19-nortestosterone, respectively.

The 17α-ethynyl-19-norsteroids are the first progestationally active compounds to receive widespread acceptance as oral contraceptive agents.[3] Replacement of the 17α-ethynyl group in the 19-nortestosterone series by vinyl or allyl substituents leads to compounds with progestational activities comparable to their 17α-ethynyl counterparts. However, these latter substances also show androgenic and anabolic activity in experimental animals.[4] A number of other 17α substituents such as 17α-cyclopropyl,[5] 17α-haloethynyl,[6] 17α-trihalovinyl,[6] and 17α-butadiynyl[7] have been incorporated into the 19-nortestosterone molecule. The chloroethynyl grouping showed the greatest activity enhancement relative to the 17α-ethynyl substituent, the progestational potency of 17α-chloroethynyl-19-nortestosterone being 2–3 times the parent 17α-ethynyl-19-nortestosterone (norethindrone).[6] This paper describes the synthesis and biological activity of a variety of 17α-propadienyl steroids in the estradiol and 19-nortestosterone series.[8] The 17α-propadienyl-19-nor-

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