Potential Antifertility Agents. 3. Substituted Dibenzothiophenecarboxylic Acids and Derivatives[1]

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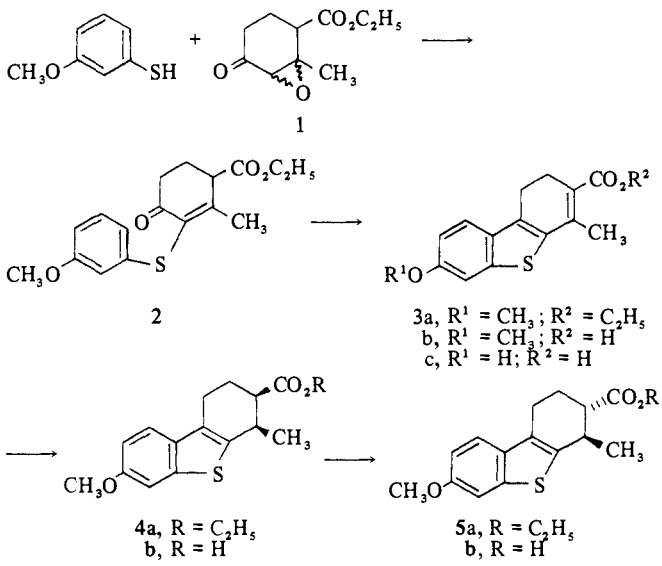
Syntheses and biological activities are reported for 37 derivatives of 4-methyldibenzothiophene-3-carboxylic acid. The most active compounds prevented pregnancy in rats at 1 mg/kg. In certain postcoital dosing regimens, compounds **4b** and **17** were considerably more active in preventing or terminating pregnancy in the rat than would be predicted on the basis of their estrogenicity in immature rats.

A synthetic sequence which we reported earlier for the preparation of the thiophene isostere of equilenin[2] suggested to us an analogous synthesis for the tetrahydrodibenzothiophenecarboxylic acids **4b** and **5b** (Scheme I). We considered these compounds to be of interest as potential antifertility agents because of structural resemblances with *cis*-bisdehydrodoisynolic acid methyl ether[3,4] and with 2-methyl-3-ethyl-4-phenylcyclohex-4-enecarboxylic acid,[5] compounds which have attracted attention as postcoital antifertility agents.

Scheme I



Chemistry. Alkaline hydrogen peroxide oxidation of the readily available ethyl 2-methyl-4-oxo-2-cyclohexenecarboxylate (Hagemann's Ester) yielded the epoxide **1**. Condensation of **1** with *m*-methoxythiophenol in refluxing DMF, or in hexamethylphosphoric triamide, produced the ketoester **2**. Cyclization of **2** in polyphosphoric acid at 55°, or with $AlCl_3$ in CH_2Cl_2, gave **3a**. Catalytic reduction of **3a** produced one pure isomer, assigned as the cis structure **4a**. (All structures assigned as cis or trans represent racemates.) Treatment of **4a** with base produced the more thermodynamically stable isomer, assigned as the trans structure **5a**. The isomers are readily distinguishable on vpc analysis or by the nmr chemical shift of the doublet attributable to the C-4 methyl protons, the doublet of the cis compounds (**4a**, **4b**) showing resonance at higher field than that of the corresponding trans isomers (**5a**, **5b**).

The biological activities of **4b** and **5b** warranted synthesis of a number of derivatives (*cf.* tables). The alcohols **20** and **26** were prepared by LAH reduction of the corresponding esters **4a** and **5a**, respectively. Again, the C-4 methyl doublet for the cis isomer (**20**) absorbed at higher field (δ 1.22 ppm, $CDCl_3$) than that of the trans isomer (**26**) (δ 1.37 ppm, $CDCl_3$). Demethylation of **20** and **26** with BBr_3 in CH_2Cl_2[6] yielded the phenolic alcohols **17** and **27**. The acids **4b** and **5b** were similarly demethylated to yield the phenolic acids **6** and **25**.

The acyl derivatives were prepared from the appropriate hydroxy compounds by standard procedures using the following reaction media: (a) pyridine-Ac_2O (**7**, **18**, **19**); (b) $CHCl_3$-Et_3N-acyl chloride (**22**, **23**, **24**); (c) DMF-NaH-acyl chloride (**9**, **10**, **21**). For each set of reaction conditions, evidence was obtained to ensure that epimerization had not occurred. For example, acetyl derivatives **7** and **22** were hydrolyzed back to the starting materials (**6** and **17**, respectively) which were shown to be pure cis. Aliquots of the disodium salt of **6** in DMF which were removed prior to addition of the acylating agent showed that no epimerization had occurred in this system. Ester **15**, formed by alkylation of the sodium salt of **4b** in DMF, proved to be pure cis. The aminoester **16**, formed by heating the acid chloride of **4b** in *N,N*-diethylaminoethanol, was a mixture of epimers.

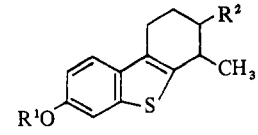
The ketone **28** was prepared by treatment of **4a** with methylsulfinyl carbanion.[7] Also isolated from the reaction was a small amount of the fully aromatized relative **33** (Table II). The nmr spectrum of **28** showed overlapping doublets for the C-4 methyl resonances. This pattern suggests a mixture of C-3 diastereoisomers, although the additional asymmetric center introduced by the sulfoxide group makes provisional any stereochemical assignment for **28** on the basis of nmr data alone. The methyl ketone obtained from treatment of **28** with Al(Hg)[7] also showed two C-4 methyl doublets (δ 1.18 and 1.31 ppm, $CDCl_3$), thus providing further support that **28** was a mixture of C-3 diastereoisomers. Recrystallization of the methyl ketone gave one pure isomer which, having only the C-4 methyl doublet centered at δ 1.31 ppm, was assigned as the trans structure **29**.

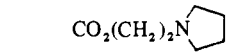
Reduction of **29** with $NaBH_4$ in EtOH gave a mixture of epimeric alcohols from which one pure isomer (**30**) was isolated; the second epimer could not be separated from **30**, so was screened in biological assays as a mixture (**31**). The ethynyl alcohol **32** was prepared from **29** and lithium acetylide-ethylenediamine complex in dioxane.[8]

The dibenzothiophene **34** was prepared by aromatization of **3a** with chloranil in xylene; basic hydrolysis of **34** yielded **35**.

Biological Activity. Compounds in this series were assayed for estrogenic and antifertility activities in female mice and rats. In general, the cis isomers (Table I) were more active in both assays than were the trans isomers. The fully aromatized derivatives (Table II) were inactive in both assays as were the intermediates **2**, **3b**, and **3c**. Detailed discussion of biological activities will be limited to compounds **4b** and **17** which appeared to be the most promising members of the series for postcoital antifertility activity.

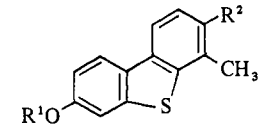
Table I. Substituted 4-Methyl-1,2,3,4-tetrahydrodibenzothiophenes[a]



No.	Isomer	R^1	R^2	Mp, °C	Crystn solvent[b]	Formula	Analyses[c]
4a	Cis	CH_3	CO_2Et	103.5–105	A	$C_{17}H_{20}O_3S$	C, H, S
4b	Cis	CH_3	CO_2H	233.5–235	A	$C_{15}H_{16}O_3S$	C, H, S
5a	Trans	CH_3	CO_2Et	75.5–76.5	A	$C_{17}H_{20}O_3S$	C, H, S
5b	Trans	CH_3	CO_2H	223.5–225	E	$C_{15}H_{16}O_3S$	C, H, S
6	Cis	H	CO_2H	211–213	B	$C_{14}H_{14}O_3S$	C, H, S
7	Cis	CH_3CO	CO_2H	213–215	F	$C_{16}H_{16}O_4S$	C, H
8	Cis	CH_3CO	CO_2Me	75.5–79	G	$C_{17}H_{18}O_4S$	C, H, S
9	Cis	$CH_3(CH_2)_5CO$	CO_2H	172.5–175	A	$C_{21}H_{26}O_4S$	C, H
10	Cis	$CH_3(CH_2)_{10}CO$	CO_2H	160–162	A	$C_{26}H_{36}O_4S$	C, H, S
11	Cis		CO_2Me	118–119.5	G	$C_{20}H_{24}O_3S$	C, H
12	Cis		CO_2H	201–202.5	A	$C_{19}H_{22}O_3S$	C, H, S
13	Cis		CO_2Me	193–196	A	$C_{21}H_{27}NO_3S \cdot HCl$	C, H
14	Cis		CO_2H	258–261	A	$C_{20}H_{25}NO_3S \cdot HCl$	C, H, N, S
15	Cis	CH_3		81–84	BD	$C_{21}H_{27}NO_3S$	C, H,[d] S
16	Mixture	CH_3	$CO_2(CH_2)_2NEt_2 \cdot HCl$	193–195	B	$C_{21}H_{29}NO_3S \cdot HCl$	C, H, N
17	Cis	H	CH_2OH	183–186.5	BD	$C_{14}H_{16}O_2S$	C, H
18	Cis	CH_3CO	$CH_2O_2CCH_3$	73–75	A	$C_{18}H_{20}O_4S$	C, H, S
19	Cis	CH_3	$CH_2O_2CCH_3$	114–116.5	B	$C_{17}H_{20}O_3S$	C, H, S
20	Cis	CH_3	CH_2OH	132.5–134.5	B	$C_{15}H_{18}O_2S$	C, H, S
21	Cis	C_6H_5CO	CH_2OH	114–116	B	$C_{21}H_{20}O_3S$	C, H
22	Cis	CH_3CO	CH_2OH	80–83	AD	$C_{16}H_{18}O_3S$	S
23	Cis	$CH_3(CH_2)_5CO$	CH_2OH	Wax		$C_{21}H_{28}O_3S$	S
24	Cis	$CH_3(CH_2)_{10}CO$	CH_2OH	58–60	A	$C_{26}H_{38}O_3S$	S
25	Trans	H	CO_2H	190–194	B	$C_{14}H_{14}O_3S$	C, H, S
26	Trans	CH_3	CH_2OH	118.5–120.5	A	$C_{15}H_{18}O_2S$	C, H, S
27	Trans	H	CH_2OH	164–170		$C_{14}H_{16}O_2S$	C, H[e]
28	Mixture	CH_3	$COCH_2S(O)CH_3$	110.5–116	B	$C_{17}H_{20}O_3S_2$	C, H, S
29	Trans	CH_3	$COCH_3$	105–107	H	$C_{16}H_{18}O_2S$	C, H, S
30	3,4-Trans	CH_3	$CH(OH)CH_3$	135–136.5	A	$C_{16}H_{20}O_2S$	C, H
31	3,4-Trans	CH_3	$CH(OH)CH_3$[f]	117–125	A	$C_{16}H_{20}O_2S$	C, H
32	3,4-Trans	CH_3	$CH(OH)C{\equiv}CH$	Oil[g]		$C_{18}H_{20}O_2S$	C, H, S

[a] All compounds had ir and nmr spectra consistent with assigned structure. [b] A, EtOH; B, MeCN; C, DMF; D, H_2O; E, abs EtOH; F, $PhCH_3$; G, MeOH; H, methylcyclohexane. [c] Analytical results obtained for the elements listed were within ±0.4% of the theoretical values unless otherwise indicated. [d] Calcd: C, 67.53; H, 7.29. Found: C, 68.42; H, 7.33. [e] Calcd: C, 67.72; H, 6.50. Found: C, 67.27; H, 6.57. [f] Mixture of epimeric alcohols. [g] Purified by chromatography on alumina; elution with $PhCH_3$–abs EtOH (99:1).

Table II. Substituted 4-Methyldibenzothiophenes[a]



No.	R^1	R^2	Mp, °C	Crystn solvent[b]	Formula	Analyses[c]
33	CH_3	$COCH_2S(O)CH_3$	161–165	A	$C_{17}H_{16}O_3S_2$	C, H, S
34	CH_3	CO_2Et	149–151.5	B	$C_{17}H_{16}O_3S$	C, H, S
35	CH_3	CO_2H	273–298[d]	CD	$C_{15}H_{12}O_3S$	C, H, S

[a–c] See corresponding footnotes, Table I. [d] Mp unchanged by additional recrystallization.

Estrogenic activity was assayed by determining the increase in uterine weight following administration of the compounds to immature, 21-day-old mice and rats. The animals were dosed orally for 3 days and autopsied on day 4. Wet weights of the uteri were obtained following expression of any luminal fluid. The doses reported are the total amount of drug administered per animal over the 3-day period.

In the mouse, both **4b** and **17** were weakly estrogenic.† Shallow dose-response lines with slopes significantly different from those of ethinyl estradiol (EE) were obtained. A 10-μg dose of either **4b** or **17** produced uterine weights approximately equivalent to 0.1 μg of EE, but the dose of **4b** and **17** had to be increased to 100 μg to approximate the response obtained with only 0.3 μg of EE. In addition, the 100-μg dose of **4b** and **17** gave the maximal response for these compounds in mice. At higher doses (1000 μg), no further increment in uterine weight was obtained.

The assay results with **4b** and **17** in the immature rat‡

†Data are based on two to eight assays at each dose level mentioned; three to five mice per group were used in each assay.

‡Five rats per group at each dose level.

were quite similar to those in the mouse. The major difference was the absence of a "ceiling" effect in the rat, as each dose examined (6 doses ranging from 10 to 1000 μg) continued to produce a further increase in uterine weight. As in the mouse, the slopes of the dose-response lines were not parallel to EE. To achieve the uterine weights produced by EE at 0.2 and 1.0 μg required doses of 20 and 1000 μg of **17**. Essentially the same dose-response curve relative to EE was seen with **4b**. Thus, at lower doses in both the mouse and the rat **4b** and **17** possess approximately 1% the estrogenicity of EE, while at higher doses the figure decreases to ≤0.1% EE.

Although EE is considerably more potent when administered subcutaneously as opposed to the oral route, no such difference was observed with either **4b** or **17**.

Antifertility assays involved postcoital oral dosing of the compounds employing varying schedules of administration in mice and rats.§ Administration of **4b** or **17** to mated mice on days 1-5 post coitum at 4-8 mg/kg per day resulted in contraceptive action. EE at 0.05 mg/kg per day produced an equivalent effect. In other dosing regimens the activity ratios of **4b** and **17** to EE remained relatively constant. Thus, in the mouse, the minimal dose of **4b** or **17** required for contraception is approximately that which would be predicted from their minimum utereotropic doses and the compounds offer no advantage over EE.

In the rat, different results were obtained. Using the dosing regimen covering days 1-5 post coitum, both **4b** and **17** had an MED_{100} of 1 mg/kg per day, compared to 0.1 mg/kg per day for EE. When mated rats were dosed on days 8-12, **17** was still completely effective at 1 mg/kg per day, whereas EE was not effective at 0.5 mg/kg per day. These results were compared to controls in which the pregnancy rate was 91%.

Thus, both **4b** and **17** exhibited greater contraceptive activity in the rat than could be anticipated from their level of estrogenicity. Whereas both compounds were ≥100 times less estrogenic than EE in the immature rat assay, they required doses of only 2--10 times EE for contraceptive activity. It appears, therefore, that in the rat, **4b** and **17** afford a theoretical advantage over EE in regard to contraceptive activity *vs.* estrogenicity.

However, the contraceptive activity of **4b** and **17** nevertheless may be related to their estrogenic activity. Mature, ovariectomized (10 days) rats were dosed daily for 5 days with **17** at 1 mg/kg per day, or EE at 0.1 mg/kg per day, their respective contraceptive doses. The uterine weights were determined 24 hr after the last dose. It was found that the mean uterine weights were 96.7 mg for controls, 267.1 mg for **17**-treated animals, and 309.7 mg for animals receiving EE. Thus, the contraceptive dose of **17** resulted in pronounced uterine stimulation, comparable to that achieved with an equivalently contraceptive dose of EE.

These latter data emphasize the danger that exists in the comparative pharmacological evaluation of antifertility compounds. Specifically, estrogenic data obtained from immature animals may not truly reflect the activity of the compounds in another estrogenic animal model that is somewhat closer related to the antifertility model.

Experimental Section

General Comments. Melting points are capillary and are uncorrected. All compounds had consistent ir and nmr spectra for assigned structures. Nmr spectra were obtained using a Varian Associates A-60 spectrometer. Where elemental analyses are indicated by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Ethyl 2,3-Epoxy-2-methyl-4-oxocyclohexanecarboxylate (1). A cold soln of aqueous 4 *N* NaOH (27 ml, 0.11 mole) contg 30% aqueous H_2O_2 (14 ml, 0.11 mole) was added over 8 min to a soln of ethyl 2-methyl-4-oxo-2-cyclohexenecarboxylate (20.00 g, 0.11 mole, Aldrich Chemical Co.) in MeOH (215 ml) cooled in an ice-salt bath. During the addition an exothermic reaction (to 13°) occurred. The soln was stirred at 0° for 40 min and then was worked up by pouring onto ice (75 g) and satd brine soln (90 g), followed by extn into $CHCl_3$. Distn gave 1 (13.61 g, 63%), bp 73-85° (0.05 mm); nmr indicated the presence of about 20% methyl ester. When EtOH was substituted for MeOH in the procedure to eliminate the exchange with solvent, less satisfactory results were obtained. An analytical sample had bp 85° (0.05 mm). *Anal.* ($C_{10}H_{14}O_4$) C, H.

Ethyl 3-(*m*-Methoxyphenylthio)-2-methyl-4-oxo-2-cyclohexenecarboxylate (2). To hexamethylphosphoric triamide (45 ml), preheated to 108°, there was added in succession *m*-methoxythiophenol (18.1 g, 0.13 mole) and the epoxide 1 (25.5 g, 0.13 mole). The mixt was stirred under nitrogen at 108° for 1 hr, and then was cooled and dild with Et_2O, and the resultant soln washed several times with H_2O. Evapn of the Et_2O left 37.06 g of oil. Distn gave 29.5 g (bp 174-182°, 0.05 mm) of 2 contaminated with *m*-methoxyphenyl disulfide. An analytical sample of 2 was prepd by chromatography of 3.26 g of the distillate on acid-washed alumina (80 g) using $PhCH_3$-Skellysolve B (1:1) followed by $PhCH_3$: yield of 2, 2.46 g (75% recovery; on this basis, the 29.5 g of distillate represents 54% yield). *Anal.* ($C_{17}H_{20}O_4S$) C, H, S.

Ethyl 1,2-Dihydro-7-methoxy-4-methyldibenzothiophene-3-carboxylate (3a). A mixt of $AlCl_3$ (2.00 g, 0.015 mole) and 2 (2.39 g, 0.0075 mole) in CH_2Cl_2 (45 ml) was stirred at 28° for 17 hr. The syrup was poured onto ice (55 g) and 6 *N* HCl (26 ml), and then was extd into $CHCl_3$. Evapn gave cryst 3a (100% yield): recrystn (MeCN) gave mp 122-122.5°; uv max (EtOH) 276 (log ε 4.02), 282 (4.03), 357 nm (4.30); nmr ($CDCl_3$) δ 2.47 ppm (s, 3, C-4 methyl protons). *Anal.* ($C_{17}H_{18}O_3S$) C, H, S.

Hydrolysis of 3a with aqueous KOH-EtOH gave the acid 3b (yield, 79%): mp 226-226.5° (aqueous DMF). *Anal.* ($C_{15}H_{14}O_3S$) C, H, S.

Demethylation of 3b (1.33 g, 4.86 mmoles) with BBr_3 (2.43 g, 9.72 mmoles) in CH_2Cl_2[6] gave the phenolic acid 3c (0.76 g, 60%): mp 182-185° (aqueous EtOH). *Anal.* ($C_{14}H_{12}O_3S$) C, H, S.

cis-7-Methoxy-4-methyl-1,2,3,4-tetrahydrodibenzothiophene-3-carboxylic Acid (4b). Hydrogenation of 3a (18.8 g) in EtOAc (300 ml) contg 10% Pd/C (5 g) under initial pressure of 50 psi resulted in uptake of 1 equiv of H_2 after 16 hr: yield of 4a, 16.5 g (88%); mp 103.5-105° (EtOH); homogeneous by vpc analysis.# *Anal.* ($C_{17}H_{20}O_3S$) C, H, S.

A soln of 4a (5.00 g, 0.0165 mole) in EtOH (27 ml) and H_2O (5.5 ml) contg KOH pellets (1.20 g) heated under reflux for 18 hr yielded, after acidification, the acid 4b (4.31 g, 95%): mp 229.5-232°; recrystn (EtOH) gave mp 233.5-235°; nmr ($CDCl_3$, DMSO-d_6) δ 1.25 ppm (d, 3, C-4 methyl protons); homogeneous by vpc analysis (after CH_2N_2 treatment). *Anal.* ($C_{15}H_{16}O_3S$) C, H, S.

trans-7-Methoxy-4-methyl-1,2,3,4-tetrahydrodibenzothiophene-3-carboxylic Acid (5b). A soln of 4a (1.79 g, 0.006 mole) in abs EtOH (50 ml) contg NaOEt (0.005 mole) was heated at reflux for 4.5 hr. Nmr and vpc# analysis of the crude product (1.78 g, 99%) indicated 85-90% epimerization. Recrystn (EtOH) gave 5a, mp 75.5-76.5°, contg <5% 4a. *Anal.* ($C_{17}H_{20}O_3S$) C, H, S.

Hydrolysis by the procedure described above gave pure trans acid 5b (yield, 94%): mp 223.5-225.5° (abs EtOH); nmr ($CDCl_3$, DMSO-d_6 in same proportions used above for data on 4b) δ 1.37 ppm (d, 3, C-4 methyl protons); shown to be homogeneous and different from 4b by vpc (after CH_2N_2 treatment). *Anal.* ($C_{15}H_{16}O_3S$) C, H, S.

cis-3-Hydroxymethyl-7-methoxy-4-methyl-1,2,3,4-tetrahydrodibenzothiophene (20). A soln of the ester 4a (20.00 g, 0.066 mole) in Et_2O (800 ml) was added over 1.5 hr to a refluxing suspension of LAH (2.50 g, 0.066 mole) in Et_2O (200 ml). The mixt was refluxed an addnl 2.5 hr and then was worked up in the usual manner to yield 20 (14.17 g, 82%): mp 131.5-133.5°; recrystn (MeCN) gave mp 132.5-134.5°. *Anal.* ($C_{15}H_{18}O_2S$) C, H, S.

§ Five to twenty animals tested at each dose level.

#Vpc analyses obtained in a glass column, 6 ft × 4 mm i.d., packed with 1% butane-1,4-diol succinate polyester on Gas-Chrom Q (Applied Science Laboratories, Inc.), at 220° isothermally, flow rate of 40 ml of helium/min. Retention times were 9.25 and 10.40 min for 5a and 4a, respectively.

The trans isomer **26** was similarly prepd from LAH reduction of **5a**.

Ethyl 7-Methoxy-4-methyldibenzothiophene-3-carboxylate (34). A soln of the ester **3a** (3.54 g, 0.017 mole) and chloranil (2.92 g, 0.019 mole) in xylene (175 ml) was heated under reflux for 3.5 hr. The solvent was removed, and the residue was triturated under Et_2O. The residual solid was dissolved in $CHCl_3$, and the soln was washed with aq 1 *N* NaOH (2 × 50 ml) and then with H_2O. Evapn of the dried $CHCl_3$ soln gave **34** (2.88 g, 81%): mp 147–150°; recrystn (MeCN) gave mp 149–151.5°. *Anal.* ($C_{17}H_{16}O_3S$) C, H, S.

7-Methoxy-4-methyldibenzothiophene-3-carboxylic Acid (35). Basic hydrolysis of **34** (2.40 g, 0.008 mole) by the procedure described for **4b** yielded the acid **35** (1.96 g, 90%): mp 271–278°; recrystn (aqueous DMF) gave mp 273–298°; mp unchanged after addnl recrystn (DMSO–Me_2CO); nmr (DMSO-d_6) δ 2.80 (s, 3, CH_3), 3.90 (s, 3, OCH_3), 7.1–8.5 ppm (m, 5, arom). *Anal.* ($C_{15}H_{12}O_3S$) C, H, S.

cis-**7-Cyclopentyloxy-4-methyl-1,2,3,4-tetrahydrodibenzothiophene-3-carboxylic Acid (12).** A mixt of **6** (2.00 g, 7.65 mmoles) and NaH (0.65 g of 57% dispersion in oil; 15.3 mmoles of NaH) in DMF (15 ml) was stirred at 70° for 30 min. Cyclopentyl bromide (1.14 g, 7.65 mmoles) in DMF (5 ml) was added, and the mixt was stirred at 72° for 12 hr.

The cooled mixt was poured onto ice, acidified with 1 *N* aqueous HCl, and then extd with Et_2O. The Et_2O was washed several times with H_2O. Drying and evapn of the Et_2O soln gave 2.55 g of a mixt of **6** and **12**. Recrystn (EtOH) gave **12** (0.51 g, 20%): mp 201–202.5°; nmr ($CDCl_3$, DMSO-d_6) δ 1.25 ppm (d, 3, C-4 methyl protons). *Anal.* ($C_{19}H_{22}O_3S$) C, H, S.

The methyl ester **11** was prepd by treatment of **12** in Et_2O with CH_2N_2: mp 118–119.5° (MeOH). *Anal.* ($C_{20}H_{24}O_3S$) C, H.

cis-**4-Methyl-7-[2-(1-pyrrolidyl)ethoxy]-1,2,3,4-tetrahydrodibenzothiophene-3-carboxylic Acid Hydrochloride (14).** A soln of 5.52 g (20.0 mmoles) of the methyl ester of **6** (prepd by treatment of **6** with 1 equiv of CH_2N_2 in Et_2O; the crude ester, mp 162–169°, was used without further purification since nmr analysis indicated >95% purity) in DMF (75 ml) was treated with NaH (0.86 g of 56% dispersion in oil; 20.0 mmoles of NaH). The mixt was stirred at 25° until cessation of gas evolution (about 30 min) and then a soln of *N*-(2-chloroethyl)pyrrolidine (3.46 g, 26.0 mmoles) in DMF (20 ml) was added. The mixt was stirred at 70° for 18 hr.

The mixt was concd at 1 mm to remove most of the DMF, and then was dild with Et_2O. The Et_2O was extd twice with aqueous 0.25 *N* HCl. The combined acid exts were extd with $CHCl_3$ (4 × 100 ml). Drying and evapn of the $CHCl_3$ exts gave a residue which was triturated under Me_2CO to yield the ester **13** (5.10 g, 63%): mp 188–191°; recrystn (EtOH) gave mp 193–196°; nmr ($CDCl_3$) δ 1.23 ppm (d, 3, C-4 methyl protons). *Anal.* ($C_{21}H_{27}NO_3S \cdot HCl$) C, H.

A soln of **13** (2.32 g, 5.67 mmoles) in EtOH (75 ml) and H_2O (15 ml) contg KOH pellets (0.74 g) was heated under reflux for 17 hr. The cooled soln was neutralized with aqueous 1 *N* HCl (14 ml) and the insol zwitterion was collected by filtration; the product was dissolved in EtOH (75 ml) and treated with 1 equiv (5.67 ml) of 1 *N* aqueous HCl. The soln was evapd and the residue was triturated under Me_2CO to yield **14** (1.94 g, 86%): mp 258–260°; recrystn (EtOH) gave mp 258–261°; nmr (DMSO-d_6) δ 1.22 ppm (d, 3, C-4 methyl protons). *Anal.* ($C_{20}H_{25}NO_3S \cdot HCl$) C, H, N, S.

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Antiandrogens. 2′,3′α-Tetrahydrofuran-2′-spiro-17-(1,2α-methylene-4-androsten-3-ones)†

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The syntheses of several 1,2α-methylene steroids containing a spirotetrahydrofuran ring at the 17 position are described. These compounds are effective antiandrogens with minimal other hormonal activity. *tert*-Butyl chromate oxidation of the spirotetrahydrofuran XIII affords the corresponding spirolactone XIV in high yield.

The aldosterone antagonist 3′-(7α-acetylthio-17β-hydroxy-3-oxo-4-androsten-17α-yl)propionic acid lactone,‡,[2] I, has been used effectively in cases of hyperaldosteronism for many years. Clinical investigators[3] have noted that this compound under prolonged high-dosage use produces an infrequent gynecomastia as well as decreased libido in males. Both of these effects disappear on withdrawal of the drug. Until recently there has been no published explanation for these phenomena. Steelman, *et al.*,[4] in these laboratories have found that spironolactone is a reasonably potent antiandrogen. This fact could explain the clinical observations noted above.

In 1963, a publication[5] appeared describing a series of steroidal 17-spiroethers which are aldosterone antagonists. One of these compounds 2′,3′α-tetrahydrofuran-2′-spiro-17-(7α-acetylthio-4-androsten-3-one), II, spiroxasone, has also been found[4] to be an antiandrogen. These findings stimulated a modest synthetic effort to prepare a more potent antiandrogen based on the spirolactone and spiroether structures.

The high antiandrogenic activity of 17α-acetoxy-6-chloro-1,2α-methylene-4,6-pregnadiene-3,20-dione,§,[6] III, led us to explore the effect of a 1,2α-methylene function on the androgen antagonist activity of the 17-spiroethers. The 1,2α-methylene derivative VII of spiroxasone was prepared in three steps from the dienone IV.[5] Dehydrogenation of IV with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gave the trienone V. This compound on reaction with dimethylsulfoxonium methylide[7] led selectively to 2′,3′α-tetrahydrofuran-2′-spiro-17-(1,2α-methylene-4,6-androstadien-3-one), VI, as has been reported in analogous cases.[8,9] Addition of thiolacetic acid to VI resulted in a mixture of 7α- and 7β-acetylthio derivatives from which the 7α isomer VII could be isolated.

Reaction of the 1,2α-methylene-4,6-dien-3-one (VI) with *m*-chloroperbenzoic acid gave the corresponding 6,7-epoxide (VIII) which with hydrogen chloride in chloroform at

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‡Spironolactone.

§Cyproterone acetate.