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)†


G. H. Rasmusson,* A. Chen, G. F. Reynolds, D. J. Patanelli, A. A. Patchett, and G. E. Arth

*Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07065.*

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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.

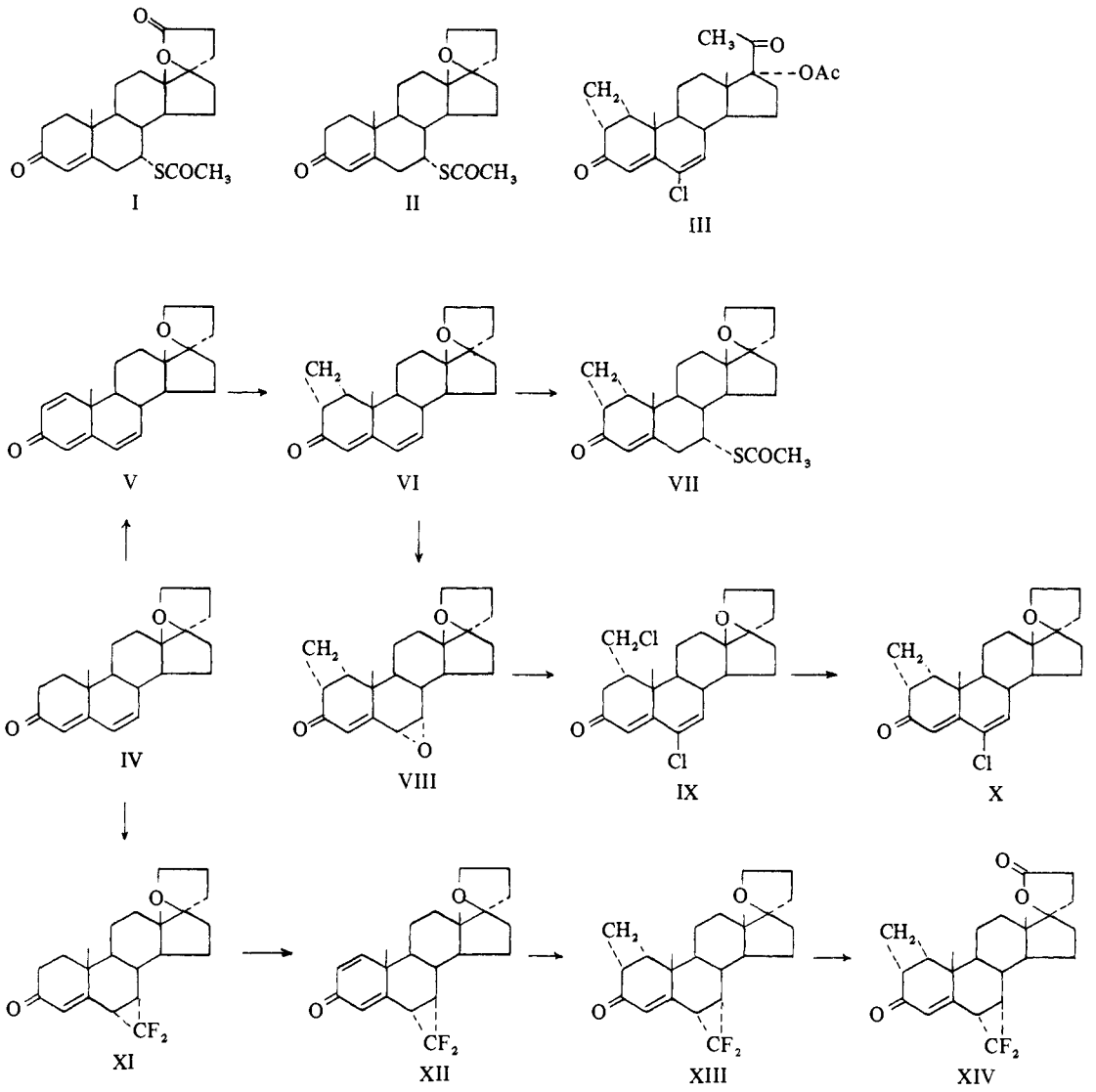
The high antiandrogenic activity of 17α-acetoxy-6-chloro-1,2α-methylene-4,6-pregnadiene-3,20-dione,§,[6] III, led us to explore the effect of a 1,2α-methylene function on the androgen antagonist activity of the 17-spiroethers. The 1,2α-methylene derivative VII of spiroxasone was prepared in three steps 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

†A portion of this work was presented at the 163rd National Meeting of the American Chemical Society.[1]

‡Spironolactone.

§Cyproterone acetate.




room temperature was converted smoothly to the dichloro steroid IX, in analogy with reactions previously described by Krakower and Van Dine.[9] The 1,2α-methylene ring was reconstructed by refluxing a collidine solution of IX, affording 2′,3′α-tetrahydrofuran-2′-spiro-17-(1,2α-methylene-6-chloro-4,6-androstadien-3-one), X.

The 6,7α-difluoromethylene compound, XI, prepared by the addition of difluorocarbene[10] to the dienone, IV, was also found to have elevated androgen antagonist activity. Dehydrogenation of XI with DDQ gave the corresponding $\Delta^1$ derivative XII which on reaction with dimethylsulfoxonium methylide afforded 2′,3′α-tetrahydrofuran-2′-spiro-17(6,7α-difluoromethylene-1,2α-methylene-4-androsten-3-one), XIII. Attempts to prepare XIII by reaction of VI with difluorocarbene were less successful.

The assignment of stereochemistry to the 1,2-methylene and 6,7-difluoromethylene groups in these compounds is based on their mode of formation and molecular rotational ($M_D$) differences previously discussed in closely related cases.[9,10] Mass spectra of the spiroethers all gave an intense fragment at *m/e* 97 which is attributed to the ion XV. The


XV

formation of this ion is analogous to that observed with 17-ketone ethylene ketals.[11] This indicates that the spiroether ring was stable to the various reaction conditions in the preparation of these compounds.

It was desirable to have a means of converting the spiroether ring directly into a spirolactone ring. In other work[12] it has been found that the spiroether ring is particularly susceptible to oxidation with *tert*-butyl chromate. Indeed, when the spiroether XIII was heated in carbon tetrachloride with this reagent a high yield of the spirolactone XIV was obtained with no detectable side-product formation.

**Biological Data.** The antiandrogenic activity of these compounds was determined in immature male castrate rats treated with testosterone enanthate. The ability of the compounds to antagonize the androgen-stimulated weight gain of the seminal vesicle and ventral prostrate serves as a measure of their activity. These data are shown in Table I. The order of antiandrogenic potency of the analogs tested is approximately III ≥ XIII ≅ XIV > X > XI ≅ VII > I ≅ II. Compounds XIII and X are marginally active as aldosterone antagonists but display no progestational, antiprogestational, estrogenic, antiestrogenic, or antigonadotropin activities# at doses where significant antiandrogenic activ-

#We are grateful to Drs. S. L. Steelman, J. R. Brooks, and M. S. Glitzer and to Mr. E. R. Morgan of the Merck Institute for Therapeutic Research for the endocrinological information here discussed.

Table I

| Compound | Daily dose,[a] mg | Body weight change, g | Seminal vesicle mg | Seminal vesicle "P" value | Ventral prostate mg | Ventral prostate "P" value |
|---|---|---|---|---|---|---|
| Sesame oil | 0.2 ml | +39.6 | 7.7 | | 11.1 | |
| T.E. | 0.5 | +40.7 | 32.7 | | 43.0 | |
| I | 1.0 | +41.2 | 15.7 | <0.01, >0.001 | 30.5 | <0.05, >0.02 |
| | 3.0 | +37.3 | 12.0 | <0.01, >0.001 | 24.3 | <0.01, >0.001 |
| II | 0.3 | +38 | 22 | N.S. | 39 | <0.3, >0.2 |
| | 1.0 | +34 | 19 | <0.1, >0.05 | 39 | <0.2 |
| III | 0.1 | +40.4 | 14.2 | <0.01, >0.001 | 25.0 | <0.01, >0.001 |
| | 0.3 | +39.3 | 11.0 | <0.001 | 18.2 | <0.001 |
| VII | 2.0 | +40.0 | 12.3 | <0.001 | 24.5 | <0.01, >0.001 |
| X | 0.3 | +49.0 | 18.5 | <0.3, >0.2 | 40.3 | <0.01, >0.001 |
| | 1.0 | +43.8 | 14.7 | <0.05, >0.02 | 32.0 | <0.01, >0.001 |
| XI | 0.15 | +36.7 | 25.3 | <0.2, >0.1 | 40.5 | <0.05, >0.02 |
| | 1.35 | +38.0 | 20.5 | <0.05, >0.02 | 31.5 | <0.01, >0.001 |
| XIII | 0.1 | +46.2 | 16.8 | <0.1, >0.05 | 39.5 | <0.02 |
| | 0.3 | +42.2 | 13 | <0.001 | 21.3 | <0.001 |
| XIV | 0.15 | +34.8 | 12.2 | <0.05, >0.02 | 20.0 | <0.05, >0.02 |
| | 0.45 | +35.3 | 9.5 | <0.001 | 17.3 | <0.001 |

[a] All groups received 0.5 mg of testosterone enanthate in one single dose, except controls.

ity is found. In a further demonstration of its antiandrogenic potency, XIII has been found to be capable of effectively reducing prostate size in aged dogs.[13]

## Discussion

The antiandrogenic activity associated with the tetrahydrofuran-2′-spiro-17-androstenones I and II has thus been increased by addition of a 1,2α-methylene function and by incorporation of either a 6-chloro-$\Delta^6$ or 6,7α-difluoromethylene group to the basic steroid skeleton.

The biological activity of these compounds resembles that of 17α-methyl-*B*-nortestosterone[14] in their specificity of action but is in direct contrast with III which is a potent progestogen, antiestrogen, and gonadotropin inhibitor.[15] The latter also causes adrenal atrophy in test animals,[15] not an unexpected property in view of its close structural relationship to the adrenocorticoids.

## Experimental Section**

**Antiandrogenic Assay.** Carworth Farm male albino rats weighing 50–55 g were castrated at about 22 days of age and treated the following day. Testosterone enanthate (0.5 mg) was administered subcutaneously in 0.2 ml of sesame oil in one single dose to all groups except controls. The test compounds, dissolved in sesame oil, were given by the subcutaneous route daily for 7 days. On day 8, the animals were sacrificed, and seminal vesicles and prostates were secured and weighed.

**2′,3′α-Tetrahydrofuran-2′-spiro-17-(1,4,6-androstatrien-3-one) (V).** A soln of the dienone IV (5.00 g, 0.015 mole) and DDQ (3.83 g, 0.017 mole) in 40 ml of $C_6H_6$ was refluxed for 2.5 hr and then stirred at room temp for 16 hr. The pptd hydroquinone was removed by filtration, and the filtrate was concd to leave an amber oil. Elution of this material adsorbed on 250 g of basic $Al_2O_3$ with $C_6H_6$ with increasing concns of $Et_2O$ (up to 100%) afforded 3.25 g of crystalline trienone V. Recrystn of this material from $C_6H_{14}$ contg $CH_2Cl_2$ gave 2.95 g of V: mp 161–162°; [α]D −63.3°; $\lambda_{max}^{MeOH}$ 302 (ε 12,900), 257 mμ (9300). *Anal.* ($C_{22}H_{28}O_2$) C, H.

**2′,3′α-Tetrahydrofuran-2′-spiro-17-(1,2α-methylene-4,6-androstadien-3-one (VI).** A soln of dimethylsulfoxonium methylide was prepd from trimethylsulfoxonium iodide (3.30 g, 0.015 mole) and NaH (320 mg, 0.013 mole) in 20 ml of DMSO under $N_2$. To the clear soln was added the trienone V (1.500 g, 4.64 mmoles) as a solid. The mixt was stirred under $N_2$ for 1.5 hr. The reaction mixt was treated with $H_2O$, and the solid was sepd by filtration. The solid was rinsed well with $H_2O$ and air-dried. Crystn from MeOH gave VI as heavy prisms. Recrystn from $C_6H_{14}$ afforded 1.023 g of VI: mp 142–144°; [α]D +158.7°; $\lambda_{max}^{CH_3OH}$ 283 mμ (ε 19,800). *Anal.* ($C_{23}H_{30}O_2$) C, H.

**2′,3′α-Tetrahydrofuran-2′-spiro-17-(1,2α-methylene-7α-acetylthio-4-androsten-3-one) (VII).** A soln of the diene VI (400 mg, 0.913 mmole) in 8 ml of thiolacetic acid was heated at 100° for 1 hr. The mixt was neutralized with satd aqueous $NaHCO_3$ soln, and the product isolated by $Et_2O$ extn. The organic layer was washed, dried ($Na_2SO_4$), and concd to leave a pale yellow residue. This material was eluted from 25 g of silica gel with increasing concns of $Et_2O$ in $C_6H_6$. The colorless material obtained amounted to 420 mg: mp 170–194°; [α]D +106.3°. *Anal.* ($C_{25}H_{34}O_3S$) C, H, S. The nmr spectrum of this material indicated two acetylthio compds in a ratio of about 2:1 (acetyl singlets at τ 7.68 and 7.71, respectively). The major isomer, mp 201–209°, [α]D +63.4°, could be isolated by repeated crystns from heptane or as the first product eluted by fractional chromatography on a mixt of Stahl silica gel G†† and diatomaceous earth (6:5) eluting with 4% $Et_2O$ in $C_6H_6$. This compd had nmr absorption at τ 9.07 (18-$CH_3$, s), 8.71 (19-$CH_3$, s), 7.68 (-$COCH_3$, s), 7.13 (7β-CH), 6.2 (O-$CH_2$), and 4.52 (4-CH, narrow). The 7α configurational assignment is based on a comparison of the $M_D$ change with that observed for 2′,3′α-tetrahydrofuran-2′-spiro-17-(7α-acetylthio-4-androsten-3-one)[5] and the similarity of the nmr absorption around τ 7 for these two compds.

**2′,3′α-Tetrahydrofuran-2′-spiro-17-(6-chloro-1,2α-methylene-4,6-androstadien-3-one) (X).** A soln of the dienone VI (300 mg, 0.89 mmole) and *m*-$ClC_6H_4CO_3H$ (660 mg, 3.82 mmoles) in 12 ml of $CHCl_3$ was allowed to stand at room temp for 16 hr. The mixt was dild with $CH_2Cl_2$ and washed with 5% $NaHCO_3$, $H_2O$, 5% KI, $H_2O$, 5% $NaHCO_3$, $H_2O$, and satd NaCl. The soln was dried ($Na_2SO_4$) and concd to give VIII as a pale yellow oil which moved as a single spot on thin-layer chromatography (silica gel, 4:1 $C_6H_6$–EtOAc). Trituration with $CH_3OH$ induced the material to cryst but attempts to recryst it were fruitless.

A soln of the above crude epoxide in 5 ml of $CHCl_3$ was added to 5 ml of a satd soln of anhyd HCl in $CHCl_3$. The vessel was stoppered and allowed to stand at room temp for 16 hr. The soln was treated with $H_2O$, and the organic layer worked up to give 330 mg of crude, cryst IX. A quick recrystn from EtOH gave needles: mp 201–205°; $\lambda_{max}^{MeOH}$ 289 mμ (ε 20,700); nmr (100 MHz) τ 9.02 (18-$CH_3$, s), 8.70 (19-$CH_3$, s), 5.26 ($CH_2O$; $CH_2Cl$, m) and 3.69 (4 and 7 CH, narrow). *Anal.* ($C_{23}H_{30}Cl_2O_2$) C, H, Cl.

A soln of 330 mg of the crude 1α-chloromethyl intermediate IX in 8 ml of redistd collidine was heated at reflux for 3 hr under $N_2$. The soln was then acidified with 2.5 *N* HCl, and the product was isolated by extn into $Et_2O$. The organic layer was washed with $H_2O$, dried ($Na_2SO_4$), and concd to give about 250 mg of cryst residue. Recrystn from MeOH afforded 165 mg of X: mp 170–175°. An addnl recrystn gave material: mp 173–174°; [α]D +154.6°;

**Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra are in accord with the assigned structures and were taken either as Nujol mulls or as chloroform solutions. Nuclear magnetic resonance spectra were determined in deuteriochloroform solutions with a Varian Associates Model A-60A spectrometer unless otherwise noted. Rotational data were obtained on 1% chloroform solutions. Mass spectra were run on either a CEC Model 21-110 or an LKB Type 9000 spectrometer by the direct probe technique.

††E. Merck, A. G., Darmstad, Germany. Distributed by Brinkmann Instrument Co., Catiague Road, Westbury, N. Y. 11590.

$\lambda_{max}^{MeOH}$ 283 mμ (ε 16,700). The mass spectrum exhibits mol ions at *m/e* 372, 374, and major fragments at 339 and 97. *Anal.* ($C_{23}H_{29}ClO_2$) C, H.

**2',3'α-Tetrahydrofuran-2'-spiro-17-(6,7α-difluoromethylene-4-androsten-3-one) (XI).** A soln of the dienone IV (1.00 g, 3.06 mmoles) in 5 ml of redistd triglyme was treated dropwise at 195–200° over a 2-hr period with a soln of 6.0 g of anhyd sodium chlorofluoroacetate in 50 ml of triglyme. The reaction mixt was poured on ice and then was extd with $Et_2O$. The $Et_2O$ layers were washed with $H_2O$, then dried ($Na_2SO_4$) and concd. The crude product was eluted from 100 g of silica gel with $C_6H_6$ and $C_6H_6$ with increasing concns of $Et_2O$ up to 5% $Et_2O$. The cryst material was separated from heptane to give 628 mg (55.3%) of XI: mp 130–132°; [α]D +33.7°; $\lambda_{max}^{CH_3OH}$ 247.5 (ε 14,900). *Anal.* ($C_{23}H_{30}F_2O_2$) C, H, F.

**2',3'α-Tetrahydrofuran-2'-spiro-17-(6,7α-difluoromethylene-1,4-androstadien-3-one) (XII).** A soln of XI (625 mg, 1.66 mmoles) and DDQ (497 mg, 2.19 mmoles) in 7 ml of $C_6H_6$ was refluxed for 4 hr. The mixt was cooled to room temp and the hydroquinone largely recovered by filtration. The filtrate was applied directly to a silica gel (6 g) column and partial purification was accomplished by eluting the desired product with 5% $Et_2O$ in $C_6H_6$ to pure $Et_2O$. The colored material so obtained was chromatographed on basic alumina (100:1) to give the desired product, 382 mg, eluted with 10% $Et_2O$ in $C_6H_6$. Recrystn from heptane gave XII: mp 158–159°; [α]D −45°; $\lambda_{max}^{MeOH}$ 245 mμ (ε 14,800). *Anal.* ($C_{23}H_{28}F_2O_2$) C, H, F.

**2',3'α-Tetrahydrofuran-2'-spiro-17-(6,7α-difluoromethylene-1,2α-methylene-4-androsten-3-one) (XIII).** A soln of dimethylsulfoxonium methylide was prepd from a suspension of NaH (40 mg of a 55% dispersion in mineral oil) and 220 mg of trimethylsulfoxonium iodide in 2 ml of anhydrous DMSO with vigorous stirring over 60 min. The clear soln was treated with a soln of 100 mg (0.266 mmole) of the diene XII in 2 ml of DMSO at room temp under $N_2$. After standing 17 hr, $H_2O$ was added and the solid was isolated by filtration. This material was adsorbed on a silica gel column (100:1). The desired product XIII was eluted with increasing concns of $Et_2O$ in $C_6H_6$ up to 5%. Recrystn from $C_6H_{14}$ afforded 77.8 mg of XIII: mp 156–158°; [α]D +180°; $\lambda_{max}^{CH_3OH}$ 244 mμ (ε 11,500). *Anal.* ($C_{24}H_{30}F_2O_2$) C, H, F.

**3'-(6,7α-Difluoromethylene-1,2α-methylene-17β-hydroxy-3-oxo-4-androsten-17α-yl)propionic Acid Lactone (XIV).** A soln prepd from 200 mg of the spiroether XIII, 2.8 ml of *tert*-butyl chromate,[16] 0.8 ml of glacial HOAc, and 0.4 ml of $Ac_2O$ in 4.0 ml of $CCl_4$ was refluxed for 2.5 hr under $N_2$. The cooled reaction mixt was treated with 4 ml of a satd aqueous soln of oxalic acid. The organic layer was dild with $CCl_4$ and was sepd from the aqueous layer. The organic layer was washed with $H_2O$, dried, and concd to an amber oil which ran as a single spot on thin-layer chromatography on silica gel. Chromatography of this material on 20 g of silica gel with increasing concns of EtOAc in $C_6H_6$ gave, initially, fractions of a dark oil. Continued elution gave the desired product XIV (140 mg) as a clear oil which readily crystd. Recrystn from aqueous $CH_3OH$ afforded a colorless solid: mp 183–185°; [α]D +162.6°; $\lambda_{max}^{CH_3OH}$ 243 mμ (ε 11,600); mol wt 402 (mass spectrum). *Anal.* ($C_{24}H_{28}F_2O_3$) C, H, F.

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# Azaindole Anthelmintic Agents


Michael H. Fisher,* George Schwartzkopf, Jr., and Dale R. Hoff

*Merck Sharp and Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07065.*

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A series of 2-substituted azaindoles, isosteric with analogous anthelmintic benzimidazoles related to thiabendazole, was synthesized. The most promising of these, 2-(4-thiazolyl)-6-azaindole, proved to be effective against the abomasal parasite *Haemonchus contortus* in sheep at 100 mg/kg but lacked the breadth of spectrum of thiabendazole.


2-(4-Thiazolyl)benzimidazole, thiabendazole, reported from these laboratories in 1961,[1] has gained wide acceptance as a safe, broad-spectrum anthelmintic agent. In a continuing attempt to extend this activity to other heterocyclic systems,[2] a series of azaindoles of related structure was synthesized for biological testing.

**Chemistry.** The chemistry of azaindoles has recently been reviewed by Willette.[3] Azaindoles prepared are listed in Tables I, II, and III. Intermediates are shown in Tables IV and V. Synthetic procedures, generalized where possible, are described in the Experimental Section.

2-Phenyl-4-, 5-, 6-, and 7-azaindoles (**16**, **1**, **9**, and **15**) were prepared by cyclization of the appropriate *o*-benzamidopicolines, using the standard Madelung procedure.[4] However, the strongly basic conditions and high temperatures necessary in this reaction made it unsuitable for the synthesis of azaindoles bearing sensitive substituents. New azaindole syntheses were devised to provide the required compounds.

2-(2-Thiazolyl)-6-azaindole (**14**) was obtained from ethyl 6-azaindole-2-carboxylate (**5**)[5] by a series of straightforward chemical manipulations *via* compounds **6**, **7**, and **8**.

There have been several reports[6] describing the formation of 5-membered heterocycles *via* nitrene intermediates