$c$ = 22.127 (4) Å and $d_{calcd}$ = 1.296 g cm$^{-3}$ for $Z$ = 4. The data were corrected for absorption ($\mu$(Cu K$\alpha$) = 20.0 cm$^{-1}$). Diffraction data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K$\alpha$ radiation, $\theta$–$2\theta$ scans, pulse height discrimination) using a crystal with the dimensions 0.10 × 0.20 × 1.0 mm.

Of the 3575 independent reflections for $\theta$ <57°, 2531 had intensities significantly greater than background [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[19] and was refined by block-diagonal least squares in which the matrix was partitioned into two blocks. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are $R$ = 0.114 and $wR$ = 0.127 for the 2531 observed reflections. The final difference map had no peaks greater than ±0.6 e A$^{-3}$.

(19) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

**Registry No. 10a**, 75802-23-2; **12a**, 75812-49-6; **13a**, 75802-24-3; 1-bromo-3-fluoro-4,6-dinitrobenzene, 400-91-9.

# Totally Synthetic Steroid Heterocycles. 9.[1] Straightforward and Stereocontrolled Synthesis of Stereoisomeric 16-Thia-*D*-homoestrane Derivatives

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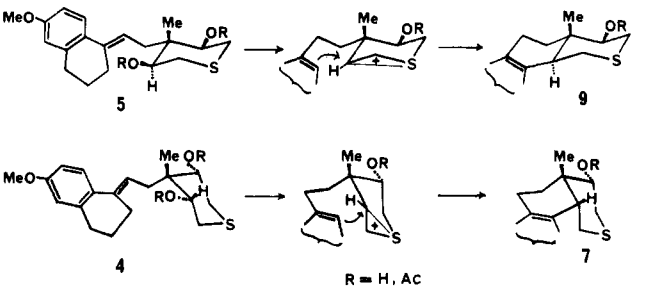
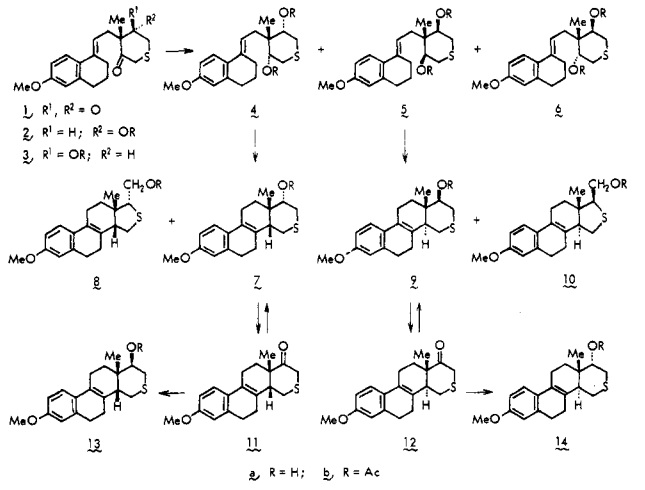
A simple preparative route for the total synthesis of stereoisomeric 16-thia-*D*-homoestrogens is described. The key step involves a novel annelation method utilizing a cationic cyclization reaction induced by sulfur participation. By this route, 16-thia-*D*-homoestradiol and 16-thia-*D*-homoestrone 3-methyl ethers are conveniently prepared in only four or five steps by starting from 2-methyl-5-thiacyclohexane-1,3-dione.

In a recent paper, we reported that seco compounds **4** and **5** under solvolytic conditions are capable of undergoing entirely stereospecific cyclization leading in a single step to cyclized products **7** and **9**, respectively, in good yield (Scheme I). The structures have been established by X-ray crystallographic analyses[2] with further chemical and spectroscopic evidence. This result undoubtedly suggests that the novel annelation process is based on cationic olefin cyclization reaction via sulfur participation. The stereochemical courses of both solvolytic cyclizations are thus illustrated as shown in Scheme I. This procedure provides a convenient preparative route to possible biologically interesting 16-thia-*D*-homoestrogens. In the present paper, we report a short stereocontrolled synthesis of 16-thia-*D*-homoestradiol and 16-thia-*D*-homoestrone 3-methyl ethers and their stereoisomers by this methodology.

Scheme I




Scheme II



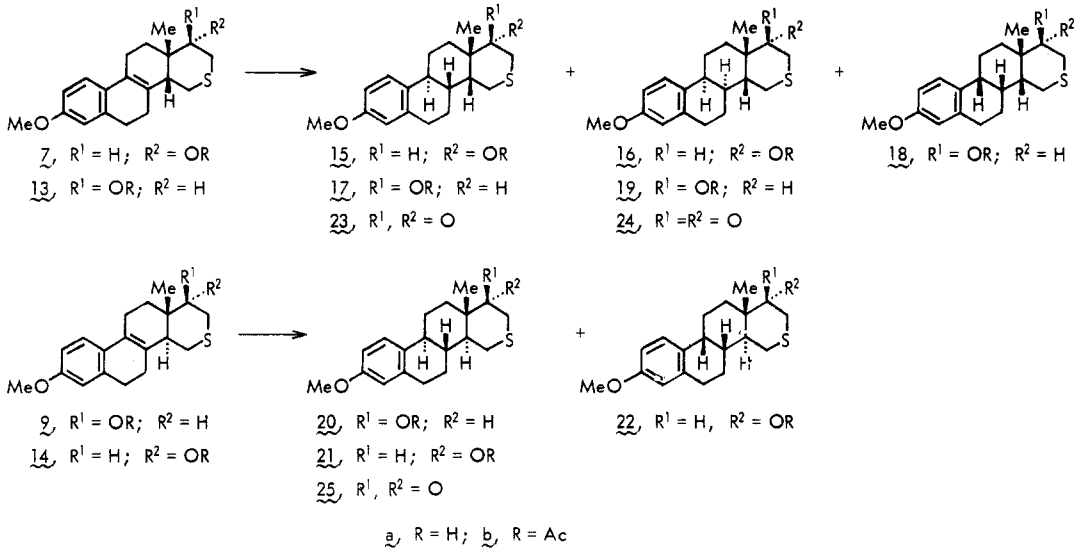

The key intermediate seco diols **4a** and **5a** were, in practice, prepared together by complete hydride reduction of the already known seco dione **1**,[3] readily available from 2-methyl-5-thiacyclohexane-1,3-dione and [(6-methoxy-1,2,3,4-tetrahydronaphthylidene)ethyl]isothiuronium acetate (Scheme II). Various aluminum hydrides were used for this reduction. However, the best method for producing both diols in high yields was reduction of **1** with sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) in benzene and then allowing the mixture to stand at room temperature for 7 h. The crude product was purified by preparative high-performance liquid chromatography (LC) on silica gel columns, giving about 40% each of **4a** and **5a** along with small amounts of **6a**. The stereochemistry assigned to these epimers was confirmed by identification with those derived from the previously established seco ketol derivatives **2** and **3** (see Experimental Section).

Treatment of **4a** with glacial acetic acid in the presence of 1 equiv of methanesulfonic acid (MsOH) at 55–60 °C for 2.5 h effected facile ring closure to afford C/D-cis

(1) Part 8: Terasawa, T.; Okada, T. *Tetrahedron Lett.* **1980**, *21*, 2549.
(2) Ultimately, X-ray analyses were undertaken on **14b** and its rearranged derivative, thereby confirming the assigned structures for the compounds of this series. The X-ray data will shortly be submitted for publication in *Cryst. Struct. Commun.*
(3) Terasawa, T.; Okada, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 576.

0022-3263/81/1946-0381$01.00/0 

Scheme III




tetracyclic acetates **7b** and **8b** in 72% and 6% yields, respectively. Similar acetolysis of **5b** was carried out at 100 °C, resulting in the formation of C/D-trans acetates **9b** (70%) and **10b** (2%). In either case, the desired major acetate was successfully isolated immediately as crystals from the reaction mixture, thereby minimizing the side reaction. The fact that the byproduct was formed reversibly from the major acetate as a result of successive skeletal rearrangement followed from equilibrating formolysis experiments with the corresponding alcohols, obtained on subsequent saponification or hydride reduction. When subjected to treatment with 100% formic acid at 100 °C for 2 h, the rearranged alcohols **8a** and **10a** were indeed reconverted partially to **7a** and **9a**, respectively, after alkaline hydrolysis. Thus, all the above acetolysis products proved useful for further transformations.

The remaining two epimeric alcohols **13a** and **14a** could alternatively be prepared via the corresponding ketones **11** and **12**. Oxidation of **7a** to **11** was achieved either by the Oppenauer procedure (60%) or with Fetizon's reagent[4] ($Ag_2CO_3$/Celite; 57%), whereas **9a** was successfully oxidized to **12** (52%) only when the latter reagent was utilized. Lithium aluminum hydride (LAH) reduction of **11** afforded **13a** (37%) and **7a** (35%) in comparable amounts. The product ratio in favor of the former unfortunately decreased to a great extent with SMEAH (1:2). On the other hand, analogous reduction of **12** with LAH predominated the formation of **14a** (67%) over **9a** (21%). A slight preference for the former was still observed with SMEAH (1.3:1).

Having obtained all the four possible homoestratetraenes, we then turned our attention to smooth reduction of the styryl double bonds. This was achieved by reduction with lithium in liquid ammonia irrespective of the use of aniline (Scheme III). Thus in the 14$\alpha$ series, **9a** led solely to the expected 16-thia-*D*-homoestradiol 3-methyl ether (**20a**) having the most thermodynamically stable trans-anti-trans configuration in 80% yield. In contrast, **14a** furnished *cis-anti-trans*-**22a** (35%) besides the major *trans-anti-trans*-**21a** (53%). In the 14$\beta$ series, both *trans-syn-cis*-**15a** and *cis-anti-cis*-**16a** were obtained in 36% and 28% yields, respectively, from Birch reduction of **7a**. However, analogous reduction of **13a** resulted in a complex mixture of homoestratrienes, from which *trans-syn-cis*-**17a** (7%), *cis-syn-cis*-**18a** (11%), and *cis-anti-cis*-**19a** (27%) were isolated by careful chromatography. The facts clearly suggest that the stereochemical course of the reduction is greatly influenced by the orientation of the 17a-hydroxyl group as well as the configuration at C-14. Alternatively, ionic hydrogenation with triethylsilane–trifluoroacetic acid in benzene or dichloromethane was also used for this reduction. Indeed, moderate yields were realized in the C/D-trans series. The simpler procedure, nevertheless, presented several difficulties in the C/D-cis series.

The B/C ring stereochemistry of the above isomeric homoestratrienes was based upon spectral and conformational considerations. The possible conformations for each stereoisomer were inspected in view of thermodynamic stability by Dreiding's model. As shown in Table I, these were compared in the light of the value observed for the downfield shift ($\Delta\delta H_1$–$H_4$) of the C-1 aromatic proton (NMR),[5] associated with the $H_1$–$H_{11}$ peri interaction, to determine the most probable conformation. The overall ring configuration[6] thus assigned was further ascertained in support of the orientation of the 17a-hydroxyl group, determined by the existence of the S···HO intramolecular hydrogen bonding (IR) or the signal pattern of the 17a-proton (NMR).

Finally, **20** was oxidized with Fetizon's reagent in refluxing toluene to the desired 16-thia-*D*-homoestrone 3-methyl ether (**25**) in 68% yield. In a similar manner, both isomeric ketones **23** and **24** were obtained from **15** and **16**, respectively, in 60–70% yield.

## Experimental Section

Melting points were determined on a calibrated Kofler hot-stage apparatus. Infrared spectra (IR) were recorded on a JASCO-

(4) (a) Fetizon, M.; Golfier, M. *C. R. Hebd. Seances Acad. Sci.* **1968**, *267*, 900. (b) Fetizon, M.; Golfier, M.; Mourgues, P. *Tetrahedron Lett.* **1972**, 4445.

(5) Nagata, W.; Terasawa, T.; Tori, K. *J. Am. Chem. Soc.* **1964**, *86*, 3746. See also: Terasawa, T.; Okada, T. *J. Heterocycl. Chem.* **1979**, *16*, 637.

(6) The stereochemical assignment in the 14$\beta$ series deserves comment. The 8$\alpha$,9$\alpha$ and 8$\beta$,9$\beta$ configurations for both B/C-cis compounds **16** and **18**, respectively, are deducible from the data listed in Table I. However, some uncertainty accompanies the assignment for the isomers **15** (8$\beta$,9$\alpha$), **17** (8$\beta$,9$\alpha$), and **19** (8$\alpha$,9$\alpha$). Conclusive evidence for these ring configurations was obtained by the following chemical transformations. LAH reduction of ketone **23**, which was obtained by oxidation of **15a**, reproduced **15a** along with **17a**, therefore proving the identity of both in the B/C ring configuration. On the other hand, the isomeric ketone **24** was similarly reduced to give a 1.5:1 mixture of **16a** and **19a**, thus confirming the 8$\alpha$,9$\alpha$ configuration (not 8$\alpha$,9$\beta$) of the latter.

Table I. Possible Conformers for Stereoisomeric Homoestratrienes

| B/C/D | 17a-OR | hydrogen bonding (S···HO) | peri interaction ($H_1$···$H_{11}$) | $\Delta\delta H_1$-$H_4$, ppm R = Ac | $\Delta\delta H_1$-$H_4$, ppm R = H |
|---|---|---|---|---|---|
| 14α,8β,9α | β(eq) | − | + | 0.56 | 0.58 (20) |
| | α(ax) | + | + | 0.57 | 0.58 (21) |
| 14α,8β,9β | β(eq) | − | + | | |
| | α(ax) | + | + | 0.57 | 0.62 (22) |
| 14α,8α,9α | β(eq) | − | − | | |
| | α(ax) | + | − | | |
| 14β,8β,9α | β(ax) | + | + | 0.57 | 0.58 (17) |
| | α(eq) | − | + | 0.57 | 0.58 (15) |
| 14β,8β,9β | β(ax) | + | + | | |
| | α(eq) | − | + | | |
| 14β,8β,9β | β(eq) | − | − | 0.43 | (18) |
| | α(ax) | + | − | | |
| 14β,8α,9α | β(ax) | + | − | | |
| | α(eq) | − | − | 0.47 | 0.49 (16) |
| 14β,8α,9α | β(eq) | − | + | 0.58 | 0.58 (19) |
| | α(ax) | + | + | | |
| 14β,8α,9β | β(eq) | − | + | | |
| | α(ax) | + | + | | |

DS-403G spectrophotometer. Ultraviolet spectra (UV) were obtained with a Hitachi 323 spectrophotometer. Nuclear magnetic resonance spectra (NMR) were taken on a Varian T-60A spectrometer using tetramethylsilane as an internal standard. Mass spectral analyses were carried out on a Hitachi RMU-6 mass spectrometer at 70 eV. Precoated TLC plates (silica gel 60 $GF_{254}$, 20 × 20 × 0.2 cm, Merck) were used for preparative thin-layer chromatography (TLC). Silica gel 60 (grain size 0.063–0.2 mm, Merck) was used for ordinary column chromatography. Preparative high-performance liquid chromatography (LC) was performed by using some prepacked silica gel columns. Usual workup means washing of the extracts with water and then brine, drying (sodium sulfate), filtration, and evaporation in vacuo.

**3-Methoxy-8,14-seco-16-thia-*D*-homoestra-1,3,5(10),9-(11)-tetraene-14,17a-diols (4a, 5a, and 6a).** (a) A 2.2 M benzene solution of SMEAH (20 mL, 44 mmol) was added dropwise to a stirred solution of 2.31 g (7 mmol) of **1** in 105 mL of dry benzene at 5–10 °C. Stirring was continued at room temperature for 7 h, and then the reaction was quenched with ice–water. The aqueous layer was separated and further extracted with ether–dichloromethane (3:1). The organic layers were combined and worked up as usual. The residue was purified by preparative high-performance LC [Micropak SI (10 μm, 8 mm × 250 mm, Varian) connected with Lichrosorb SI-60 (10 μm, 10 mm × 250 mm, Merck), *n*-hexane–MeOH (98:2)], affording as crystalline solids 992 mg (42.4%) of diol **4a** (mp 135–137 °C), 907 mg (38.7%) of **5a** (mp 123–127 °C), and 201 mg (8.6%) of **6a** (mp 103–105 °C). These materials were identical (IR, NMR) with the authentic samples prepared as below.

(b) Ketol acetate **2b** (106 mg, 0.283 mmol) was treated with 17 mg (0.449 mmol) of sodium borohydride in 4 mL of methanol and 0.5 mL of tetrahydrofuran under stirring at room temperature for 0.5 h. The mixture was poured into ice–water and extracted with ether. The oily residue, obtained after the usual workup, was purified by preparative TLC [benzene–ethyl acetate (20:1) with double development] which afforded two epimers (A, 57.5 mg, mp 164–168 °C; B, 26.5 mg, mp 112.5–114 °C) of possible diol monoacetate in a 2.2:1 ratio. Similarly, ketol acetate **3b** (150 mg, 0.4 mmol) was reduced with 21 mg (0.555 mmol) of sodium borohydride in 3 mL of methanol. After the usual extractive workup, the crude product was subjected to preparative TLC [benzene–ethyl acetate (20:1) with quadruple development] which separated additional two epimers (C, 58.2 mg, mp 136–137 °C; D, 21.7 mg, mp 113–115 °C) in a 2.7:1 ratio. On further hydride reduction with LAH, compounds A and D were converted to diols **4a** [mp 136–139 °C (ether–pentane)] and **5a** [mp 128.5–130 °C (ether–pentane)], respectively, while compounds B and C were led to an identical diol **6a**, mp 105–107 °C (ether–pentane). Acetylation with pyridine and acetic anhydride gave the corresponding diacetates **4b**, **5b**, and **6b** which had following data.

For **4b**: mp 150–151 °C (dichloromethane–ether); NMR ($CDCl_3$) δ 1.02 (s, 3 H, 13-Me), 2.07 (s, 6 H, OCOMe), 3.77 (s, 3 H, OMe), 4.90 (q, 2 H, *J* = 4.5 and 9 Hz, 14- and 17a-H), 6.00 (t, 1 H, *J* = 7 Hz, 11-H), 6.5–7.6 (m, 3 H, Ar H); IR ($CHCl_3$) 1740 $cm^{-1}$; UV (EtOH) 265 nm (ε 20 000). Anal. Calcd for $C_{22}H_{30}O_5S$: C, 66.00; H, 7.23; S, 7.66. Found: C, 65.73; H, 7.20; S, 7.70.

For **5b**: mp 131.5–133.5 °C (dichloromethane–ether); NMR ($CDCl_3$) δ 1.13 (s, 3 H, 13-Me), 2.03 (s, 6 H, OCOMe), 3.77 (s, 3 H, OMe), 4.97 (q, 2 H, *J* = 6 and 9 Hz, 14- and 17a-H), 5.85 (t, 1 H, *J* = 8 Hz, 11-H), 6.5–7.7 (m, 3 H, Ar H); IR ($CHCl_3$) 1736 $cm^{-1}$; UV (EtOH) 265.5 nm (ε 20 800). Anal. Calcd for $C_{22}H_{30}O_5S$: C, 66.00; H, 7.23; S, 7.66. Found: C, 65.78; H, 7.21, S, 7.68.

For **6b**: mp 115.5–117 °C (ether–pentane); NMR ($CDCl_3$) δ 1.08 (s, 3 H, 13-Me), 2.08, 2.11 (s, 3 H each, OCOMe), 3.78 (s, 3 H, OMe), 5.06 (q, 1 H, *J* = 3.5 and 5 Hz, 14-H), 5.25 (t, 1 H, *J* = 6 Hz, 17a-H), 5.80 (t, 1 H, *J* = 7 Hz, 11-H), 6.5–7.6 (m, 3 H, Ar H); IR ($CHCl_3$) 1740, 1735 $cm^{-1}$; UV (EtOH) 265.5 nm (ε 20 300). Anal. Calcd for $C_{22}H_{30}O_5S$: C, 66.00; H, 7.23; S, 7.66. Found: C, 65.89; H, 7.18; S, 7.71.

**3-Methoxy-16-thia-*D*-homo-14β-estra-1,3,5(10),8-tetraen-17aα-ol Acetate (7b) and 3-Methoxy-17α-(acetoxymethyl)-16-thia-14β-estra-1,3,5(10),8-tetraene (8b).** (a) A solution of 1.17 g (3.5 mmol) of **4a** in 60 mL of acetic acid containing 404 mg (4.2 mmol) of methanesulfonic acid was stirred at 55–60 °C for 2.5 h; meanwhile a crystalline product began to precipitate after 1 h or so. The mixture was chilled and filtered to afford 810 mg (64.5%) of **7b**, mp 209–210 °C. The filtrate was concentrated and extracted with dichloromethane. The extract was washed with aqueous sodium bicarbonate and worked up as usual. The residue was purified by preparative high-performance LC [Lichrosorb SI-60 (10 μm, 10 mm × 250 mm), *n*-hexane–dichloromethane (7:3) plus 0.5% ethyl acetate] which gave an additional 98.5 mg (7.9%) of **7b** (mp 210–211 °C) and 76.5 mg (6.1%) of **8b**, mp 96–98 °C. Both analytical samples were obtained by recrystallization from dichloromethane–ether. The major acetate **7b** had the following: mp 211–211.5 °C; NMR ($CDCl_3$) δ 1.00 (s, 3 H, 13-Me), 2.07 (s, 3 H, OAc), 3.79 (s, 3 H, OMe), 4.99 (q, 1 H, *J* = 4.5 and 10.5 Hz, 17a-H), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1739, 1725 $cm^{-1}$; UV (EtOH) 277 nm (ε 20 300); mass spectrum, *m/e* 358 ($M^+$). Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.13; H, 7.30; S, 8.78. The minor acetate **8b** had the following: mp 99–101 °C; NMR ($CDCl_3$) δ 1.11 (s, 3 H, 13-Me), 2.06 (s, 3 H, OAc), 3.78 (s, 3 H, OMe), 3.9–4.6 (m, 2 H, $CH_2O$), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1737 $cm^{-1}$; UV (EtOH) 277 nm (ε 16 900); mass spectrum, *m/e* 358 ($M^+$). Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.19; H, 7.40; S, 9.02. The corresponding alcohols were obtained quantitatively by alkaline hydrolysis or metal hydride reduction. The alcohol **7a** had the following: mp 167.5–169 °C (dichloromethane–ether); NMR ($CDCl_3$) δ 1.11 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3632 $cm^{-1}$ (free OH); mass spectrum, *m/e* 316 ($M^+$). The alcohol **8a** had the following: mp 92–94 °C (dichloromethane–ether); NMR ($CDCl_3$) δ 1.10 (s, 3 H, 13-Me); mass spectrum, *m/e* 316 ($M^+$).

(b) A stirred solution of 104 mg (0.33 mmol) of **8a** in 5 mL of anhydrous formic acid was heated at 100 °C for 2 h under nitrogen.

After the formic acid was evaporated, the residue was treated with 4 mL of aqueous 10% potassium hydroxide in 8 mL of methanol and 4 mL of tetrahydrofuran at room temperature for 1 h. The mixture was poured into ice–water and extracted with dichloromethane. After the usual workup, the crude product was purified by preparative TLC [benzene–ethyl acetate (9:1) with double development] which gave 41.1 mg (39.5%) of **7a** and 51.2 mg (49.2%) of recovered **8a**.

**3-Methoxy-16-thia-*D*-homoestra-1,3,5(10),8-tetraen-17aβ-ol Acetate (9b) and 3-Methoxy-17β-(acetoxymethyl)-16-thiaestra-1,3,5(10),8-tetraene (10b).** (a) A stirred solution of 600 mg (1.43 mmol) of **5b** in 35 mL of acetic acid containing 165 mg (1.72 mmol) of methanesulfonic acid was heated at 100 °C. After 3 h, the mixture was chilled, and the precipitated product was filtered to give 170 mg (33.1%) of **9b**, mp 177–178.5 °C. The filtrate was concentrated, and the residue was extracted with ether–dichloromethane (3:1). The extract was washed with aqueous sodium bicarbonate and worked up as usual. The crude product was purified through neutral alumina (activity II, 8 g) by eluting with benzene. The eluted material was triturated with ether–pentane, giving an additional 156 mg (30.4%) of **9b**, mp 175–177 °C. The oily residue was further subjected to high-performance LC [Lichrosorb SI-60 (10 μm, 10 mm × 250 mm), *n*-hexane–dichloromethane (7:3) plus 0.5% EtOAc] which isolated a third crop (31 mg, 6.0%) of **9b** (mp 177–179 °C) and 122 mg (2.4%) of **10b**, mp 99–102 °C. Recrystallization from dichloromethane–ether gave analytical specimens for both compounds. The major acetate **9b** had the following: mp 180–181.5 °C; NMR ($CDCl_3$) δ 0.91 (s, 3 H, 13-Me), 2.07 (s, 3 H, OAc), 3.78 (s, 3 H, OMe), 4.89 (br q, 1 H, $J$ = 6.5 and 10 Hz, 17a-H), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1740, 1724 $cm^{-1}$; UV (EtOH) 276 nm (ε 18500); mass spectrum, $m/e$ 358 ($M^+$). Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.11; H, 7.35; S, 9.15. The minor acetate **10b** had the following: mp 103–105 °C; NMR ($CDCl_3$) δ 0.88 (s, 3 H, 13-Me), 2.07 (s, 3 H, OAc), 3.79 (s, 3 H, OMe), 3.9–4.6 (m, 2 H, $CH_2O$), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1738 $cm^{-1}$; UV (EtOH) 276 nm (ε 14600); mass spectrum, $m/e$ 358 ($M^+$). Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.20; H, 7.29; S, 9.06. The corresponding alcohols were obtained on alkaline hydrolysis or metal hydride reduction. The alcohol **9a** had the following: mp 145.5–147 °C (dichloromethane–ether); NMR ($CDCl_3$) δ 0.84 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3632 $cm^{-1}$ (free OH). The alcohol **10a** had the following: mp 149–151 °C (dichloromethane–ether); NMR ($CDCl_3$) δ 0.87 (s, 3 H, 13-Me).

(b) A stirred solution of 154 mg (0.49 mmol) of **10a** in 5 mL of anhydrous formic acid was heated at 100 °C for 2 h under nitrogen. The mixture was cooled and then the formic acid was evaporated in vacuo. The residue was dissolved in 8 mL of methanol and 4 mL of tetrahydrofuran. To the resultant solution was added 6 mL of aqueous 10% potassium hydroxide. The mixture was stirred at room temperature for 1 h, poured into ice–water, and extracted with dichloromethane. The usual workup left a syrup which was purified by preparative TLC [benzene–ethyl acetate (9:1) with double development], affording 74.4 mg (48.3%) of **9a** along with 31.5 mg (20.5%) of recovered **10a**.

**3-Methoxy-16-thia-*D*-homo-14β-estra-1,3,5(10),8-tetraen-17a-one (11).** (a) Aluminum isoproxide (126 mg, 0.62 mmol) was added to a boiling solution of 126.4 mg (0.4 mmol) of **7a** in 15 mL of dry toluene and 5 mL of freshly distilled cyclohexanone. The stirred mixture was refluxed under slow distillation for 11 h, meanwhile 126 mg of aluminum isopropoxide in 15 mL of dry toluene containing 2.5 mL of cyclohexanone each was added after 3 h and 8.5 h. Saturated aqueous Rochelle salt solution was added dropwise. The mixture was diluted with ice–water and extracted with ether–dichloromethane (3:1) followed by usual workup. The residue was subjected to column chromatography over silica gel (20 g). Cyclohexylidenecyclohexanone was removed by continuous elution with petroleum ether. Successive elution with benzene gave, on trituration with pentane, 45.8 mg (36.5%) of **11**, mp 122–123 °C. The crude oily residue was purified by TLC [cyclohexane–ether (4:1)] which afforded 18.3 mg (14.6%) of **11** (mp 122–125 °C) together with 18.1 mg of recovered **7a**. The total yield of **11** was 59.6% based upon the recovered starting material. Recrystallization from ether–pentane furnished an analytical sample: mp 123–125 °C; NMR ($CDCl_3$) δ 1.17 (s, 3 H, 13-Me), 3.78 (s, 3 H, OMe), 6.6–7.3 (s, 3 H, Ar H); IR ($CHCl_3$) 1696 $cm^{-1}$; UV (EtOH) 279 nm (ε 17800); mass spectrum, $m/e$ 314 ($M^+$). Anal. Calcd for $C_{19}H_{22}O_2S$: C, 72.57; H, 7.05; S, 10.20. Found: C, 72.29; H, 7.07; S, 10.31.

(b) A stirred solution of 316.4 mg (1 mmol) of **7a** in 50 mL of dry toluene was refluxed with 11 g of silver carbonate–Celite reagent[4] (1 mmol/0.57 g) under nitrogen. After 4 h, the reaction was stopped. The solid was filtered off, and the colorless solution was evaporated. The crude product was triturated with ether, giving 51.7 mg (16.4%) of **11** as a crystalline solid, mp 120–124 °C. The oily residue was purified by preparative high-performance LC [Lobar (size B, Merck), benzene–ethyl acetate (40:1)] which afforded a further 128.6 mg (40.9%) of **11**, mp 119–125 °C.

**3-Methoxy-16-thia-*D*-homoestra-1,3,5(10),8-tetraen-17a-one (12).** A stirred solution of 167 mg (0.528 mmol) of **9a** in 27 mL of dry toluene was refluxed with 3 g of silver carbonate–Celite reagent[4] (1 mmol/0.57 g) under nitrogen. A further 3 g of the solid reagent was added after 24 h. After the reaction was continued for total 32 h, the solid was filtered off, and the filtrate was evaporated. The residue was chromatographed on silica gel (2 g). The fractions eluted with petroleum ether–benzene (1:2, and 1:4) gave 67.1 mg (40.4%) of **12**, mp 166–168 °C. Further elution with benzene and benzene–ethyl acetate (4:1) recovered 38.1 mg of **9a**. The overall yield of **12** was 52.4% based upon the recovered starting material. The analytical specimen was obtained by recrystallization from dichloromethane–ether: mp 168–170 °C; NMR ($CDCl_3$) δ 1.19 (s, 3 H, 13-Me), 3.77 (s, 3 H, OMe), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1703 $cm^{-1}$; UV (EtOH) 277 nm (ε 16900); mass spectrum, $m/e$ 314 ($M^+$). Anal. Calcd for $C_{19}H_{22}O_2S$: C, 72.57; H, 7.05; S, 10.20. Found: C, 72.30; H, 7.06; S, 10.33.

**3-Methoxy-16-thia-*D*-homo-14β-estra-1,3,5(10),8-tetraen-17aβ-ol (13a).** LAH (20 mg) was added in portions to a stirred solution of 176 mg (0.56 mmol) of **11** in 6 mL of dry tetrahydrofuran. After 20 min, the reaction was quenched by aqueous ammonium chloride. Extraction with ether–dichloromethane (3:1) followed by the usual workup left a foam which was purified by preparative TLC [benzene–ethyl acetate (9:1) with double development] to yield 64.8 mg (36.6%) of **13a** [mp 134-136 °C (ether–pentane)] and 61.4 mg (34.7%) of **7a**, mp 160–163 °C (ether–pentane). The product ratio was 1.1:1. The former material was recrystallized from dichloromethane–ether to provide an analytical sample: mp 143–144 °C; NMR ($CDCl_3$) δ 1.05 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3502 $cm^{-1}$ (bonded OH). The acetate **13b**, prepared in usual manner, had the following: mp 149–151 °C (dichloromethane–ether); NMR ($CDCl_3$) δ 1.01 (s, 3 H, 13-Me), 2.12 (s, 3 H, OAc), 3.79 (s, 3 H, OMe), 4.88 (br t, 1 H, $J$ = 5 Hz, 17a-H), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1738 (sh), 1726 $cm^{-1}$; UV (EtOH) 277 nm (ε 19300); mass spectrum, $m/e$ 358 ($M^+$). Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.16; H, 7.31; S, 9.14. Similar reduction by SMEAH (benzene–THF) indicated the product ratio of 1:2.

**3-Methoxy-16-thia-*D*-homoestra-1,3,5(10),8-tetraen-17aα-ol (14a).** Ketone **12** (200 mg, 0.64 mmol) was treated with 200 mg of LAH in 20 mL of dry tetrahydrofuran at room temperature for 1 h. The mixture was worked up as before to give an oily residue which was purified by preparative TLC [benzene–ethyl acetate (20:1) with double development] to afford 134 mg (66.6%) of **14a** [mp 142–144 °C (dichloromethane–ether)] together with 42 mg (20.9%) of **9a**, mp 140–143 °C (dichloromethane–ether). The product ratio was 3.2:1. The former material provided an analytical specimen by recrystallization from the same solvent: mp 146–147.5 °C; NMR ($CDCl_3$) δ 0.87 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3528 $cm^{-1}$ (bonded OH). The acetate **14b**, obtained by usual method, had the following: mp 159–161 °C (dichloromethane–ether); NMR ($CDCl_3$) δ 0.95 (s, 3 H, 13-Me), 2.14 (s, 3 H, OAc), 3.78 (s, 3 H, OMe), 4.78 (t, 1 H, $J$ = 3 Hz, 17a-H), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1726 $cm^{-1}$; UV (EtOH) 275 nm (ε 19100); mass spectrum, $m/e$ 358 ($M^+$). Anal. Calcd for $C_{21}H_{26}O_3S$: C, 70.35; H, 7.31; S, 8.94. Found: C, 70.24; H, 7.19; S, 9.08. Similar reduction with SMEAH (benzene–THF) indicated the product ratio of 1.3:1.

**3-Methoxy-16-thia-*D*-homo-14β-estra-1,3,5(10)-trien-17aα-ol (15a) and Its 8α Isomer 16a.** Lithium metal (172 mg, 25.4 mmol) was dissolved in 60 mL of liquid ammonia. To the resulting blue solution was added dropwise under stirring a solution of 316.5

mg (1 mmol) of **7a** in 17 mL of dry tetrahydrofuran containing 6 mL of freshly distilled aniline at −70 °C. After 15 min, the reaction was quenched with ammonium chloride, and the ammonia was evaporated. The residue was extracted with ether–dichloromethane (4:1). The usual workup afforded a viscous syrup which was purified by preparative high-performance LC [Lobar (size B, Merck), benzene–ethyl acetate (40:1)] which afforded 113 mg (35.5%) of **15a** [mp 156–158 °C (ether)] and 88 mg (27.6%) of **16a**, mp 134.5–136.5 °C (ether–pentane). Recrystallization from dichloromethane–ether provided analytical samples of both. The major isomer **15a** had the following: mp 158–160 °C; NMR ($CDCl_3$) $\delta$ 1.22 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3632 $cm^{-1}$ (free OH); mass spectrum, $m/e$ 318 ($M^+$). The acetate **15b**, obtained in the usual way, had the following: mp 199–200.5 °C (dichloromethane–ether); NMR ($CDCl_3$) $\delta$ 1.09 (s, 3 H, 13-Me), 2.05 (s, 3 H, OAc), 3.75 (s, 3 H, OMe), 4.91 (q, 1 H, $J$ = 4.5 and 10.5 Hz, 17a-H), 6.5–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1736 (sh), 1723 $cm^{-1}$. Anal. Calcd for $C_{21}H_{28}O_3S$: C, 69.96; H, 7.83; S, 8.89. Found: C, 69.83; H, 7.90; S, 8.91. The minor isomer **16a** had the following: mp 136–137 °C; NMR ($CDCl_3$) $\delta$ 1.15 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3632 (s, free OH), 3524 $cm^{-1}$ (w, bonded OH); mass spectrum, $m/e$ 318 ($M^+$). The acetate **16b** had the following: mp 150–151.5 °C (dichloromethane–ether); NMR ($CDCl_3$) $\delta$ 1.10 (s, 3 H, 13-Me), 2.05 (s, 3 H, OAc), 3.75 (s, 3 H, OMe), 4.86 (q, 1 H, $J$ = 5 and 9 Hz, 17a-H), 6.5–7.2 (m, 3 H, Ar H); IR ($CHCl_3$) 1737 (sh), 1725 $cm^{-1}$. Anal. Calcd for $C_{21}H_{28}O_3S$: C, 69.96; H, 7.83; S, 8.89. Found: C, 69.60; H, 7.85; S, 8.95.

**3-Methoxy-16-thia-*D*-homo-14$\beta$-estra-1,3,5(10)-trien-17a$\beta$-ol (17a) and Its 9$\beta$ and 8$\alpha$ Isomers 18a and 19a.** As described above, 70.4 mg (0.22 mmol) of **13a** was reduced by using 23.4 mg (3.4 mmol) of lithium metal and 4.5 mL of dry tetrahydrofuran in 17 mL of liquid ammonia containing 1.7 mL of aniline. The crude product was purified by preparative high-performance LC [Lobar (size B, Merck), *n*-hexane–ethyl acetate (7:3)], whereupon three major components were isolated. The first component (5 mg, 7.1%) was identified as **17a**: mp 152–153.5 °C (dichloromethane–ether); NMR ($CDCl_3$) $\delta$ 1.17 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3503 $cm^{-1}$ (bonded OH). The second one (8.1 mg, 11.4%) was **18a**, obtained as a crystalline solid on trituration with ether–pentane: mp 158–162 °C; NMR ($CDCl_3$) $\delta$ 1.07 (s, 3 H, 13-Me). The most abundant isomer, **19a** (19.3 mg, 27.3%), as the third component failed to crystallize: NMR ($CDCl_3$) $\delta$ 0.93 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3613 (sh), 3628 $cm^{-1}$ (free OH). The corresponding acetates prepared by the usual method showed the following data.

For **17b**: mp 188–189 °C (dichloromethane–ether); NMR ($CDCl_3$) $\delta$ 1.06 (s, 3 H, 13-Me), 2.14 (s, 3 H, OAc), 3.75 (s, 3 H, OMe), 4.61 (q, 1 H, $J$ = 2 and 4 Hz, 17a-H), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1724 $cm^{-1}$; mass spectrum, $m/e$ 360 ($M^+$). Anal. Calcd for $C_{21}H_{28}O_3S$: C, 69.96; H, 7.83; S, 8.89. Found: C, 69.62; H, 7.82; S, 9.03.

For **18b**: mp 175–176 °C (ether–pentane); NMR ($CDCl_3$) $\delta$ 1.11 (s, 3 H, 13-Me), 2.00 (s, 3 H, OAc), 3.77 (s, 3 H, OMe), 5.40 (q, 1 H, $J$ = 5 and 10 Hz, 17a-H), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1730 $cm^{-1}$; mass spectrum, $m/e$ 360 ($M^+$). Anal. Calcd for $C_{21}H_{28}O_3S$: C, 69.96; H, 7.83; S, 8.89. Found: C, 69.77; H, 7.80; S, 9.05.

For **19b**: foam; NMR ($CDCl_3$) $\delta$ 0.93 (s, 3 H, 13-Me), 2.04 (s, 3 H, OAc), 3.76 (s, 3 H, OMe), 5.63 (q, 1 H, $J$ = 5 and 10 Hz, 17a-H), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1733 $cm^{-1}$; mass spectrum, $m/e$ 360 ($M^+$).

**16-Thia-*D*-homoestradiol 3-Methyl Ether (20a).** Trifluoroacetic acid (0.4 mL) was added to a stirred solution of 71.7 mg (0.2 mmol) of **9b** and 0.4 mL of triethylsilane in 4 mL of dry dichloromethane. The solution was stirred at room temperature for 23 h and then poured into cold aqueous sodium bicarbonate. Extraction with dichloromethane followed by the usual workup gave an oily residue which was dissolved in 4 mL of dry tetrahydrofuran and treated with 20 mg of LAH. After being stirred for 1 h, the mixture was poured into ice–water and extracted with dichloromethane. The crude product, obtained after usual workup, was purified by preparative TLC [cyclohexane–ether (2:1) with double development], affording 34.0 mg (53.4%) of crystalline **20a** [mp 127–130 °C (dichloromethane–ether)] which furnished on acetylation its acetate **20b**, mp 166–168 °C (dichloromethane–ether). These materials were identical in all respects with their authentic samples, obtained in 72% yield by an already reported lithium–ammonia reduction of **9a**.[7]

**3-Methoxy-16-thia-*D*-homoestra-1,3,5(10)-trien-17a$\alpha$-ol (21a) and Its 9$\beta$ Isomer 22a.** (a) To a stirred solution of 35 mg (5 mmol) of lithium metal in 15 mL of liquid ammonia was added dropwise at −70 °C a solution of 63.3 mg (0.2 mmol) of **14a** in 2.5 mL of dry tetrahydrofuran. After 10 min, the reaction was quenched with ammonium chloride to discharge the blue color, and then the ammonia was allowed to evaporate. The residue was extracted with ether–dichloromethane (3:1) followed by the usual workup. The crude product was purified by preparative TLC [benzene–ethyl acetate (20:1) with double development] to afford 33.9 mg (53.2%) of crystalline **21a** (mp 152–154 °C) and 22.3 mg (35.0%) of **22a** as an oil. The analytical sample of **21a** was obtained by recrystallization from ether–dichloromethane: mp 159–161 °C; NMR ($CDCl_3$) $\delta$ 0.89 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3514 $cm^{-1}$ (bonded OH); mass spectrum, $m/e$ 318 ($M^+$). The acetate **21b**, prepared by usual method, had the following: mp 143–146 °C (ether–dichloromethane); NMR ($CDCl_3$) $\delta$ 0.98 (s, 3 H, 13-Me), 2.17 (s, 3 H, OAc), 3.77 (s, 3 H, OMe), 4.65 (q, 1 H, $J$ = 2 and 3.5 Hz, 17a-H), 6.5–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1725 $cm^{-1}$. Anal. Calcd for $C_{21}H_{28}O_3S$: C, 69.96; H, 7.83; S, 8.89. Found: C, 69.71; H, 7.90; S, 8.98. The pure material of **22a** as an oil showed NMR ($CDCl_3$) $\delta$ 0.98 (s, 3 H, 13-Me); IR (dilute $CCl_4$) 3520 $cm^{-1}$ (bonded OH); mass spectrum, $m/e$ 318 ($M^+$). The acetate **22b** was obtained as a crystalline solid: mp 136–140 °C (ether–pentane); NMR ($CDCl_3$) $\delta$ 1.07 (s, 3 H, 13-Me), 1.82 (s, 3 H, OAc), 3.76 (s, 3 H, OMe), 4.52 (t, 1 H, $J$ = 3 Hz, 17a-H), 6.6–7.3 (m, 3 H, Ar H); IR ($CHCl_3$) 1723, 1718 (sh) $cm^{-1}$. Anal. Calcd for $C_{21}H_{28}O_3S$: C, 69.96; H, 7.83; S, 8.89. Found: C, 69.82; H, 7.81; S, 8.87.

(b) Trifluoroacetic acid (0.5 mL) and 1 mL of triethylsilane were added to a solution of 95 mg (0.3 mmol) of **14a** in 10 mL of dry benzene. The solution was stirred at room temperature for 17 h and then poured into aqueous sodium bicarbonate. The aqueous layer was separated and further extracted with dichloromethane. The organic layers were combined and worked up as usual. The crude product was triturated with ether, giving 44.4 mg (46.5%) of **21a** as a crystalline solid, mp 156–159 °C (ether). The mother liquor residue was further purified by preparative TLC [benzene–ethyl acetate acetate (20:1) with double development] to afford an additional crop (14.4 mg, 15.1%) of **21a** (mp 153–157 °C) and 10.5 mg (11.0%) of **22a** as an oil.

**3-Methoxy-16-thia-*D*-homo-14$\beta$-estra-1,3,5(10)-trien-17a-one (23).** A stirred mixture of 88.0 mg (0.276 mmol) of **15a**, 3.15 g of silver carbonate–Celite[4] (1 mmol/0.57 g), and 14 mL of dry toluene was refluxed under nitrogen for 24 h. The solid was filtered off, and the solvent was evaporated. The residue was purified through a short column of silica gel (2 g) by elution with benzene to give 39.2 mg of **23** (mp 122–125 °C) and 30.4 mg of recovered **15a**. The total yield of **23** was 68.5% based upon the recovered starting material. The pure material of **23** was obtained from recrystallization from dichloromethane–ether as a crystalline solid: mp 124–126 °C; NMR ($CDCl_3$) $\delta$ 1.28 (s, 3 H, 13-Me), 3.76 (s, 3 H, OMe), 6.6–7.4 (m, 3 H, Ar H); IR ($CHCl_3$) 1699 $cm^{-1}$; mass spectrum, $m/e$ 316 ($M^+$). Anal. Calcd for $C_{19}H_{24}O_2S$: C, 72.11; H, 7.64; S, 10.13. Found: C, 71.88; H, 7.60; S, 10.15.

**3-Methoxy-16-thia-*D*-homo-8$\alpha$,14$\beta$-estra-1,3,5(10)-trien-17a-one (24).** Similarly, 40.5 mg (0.127 mmol) of **16** was oxidized with 1.45 g of silver carbonate–Celite[4] (1 mmol/0.57 g) in 9 mL of boiling dry toluene for 24 h under nitrogen. The mixture was worked up as above. The residue was purified through a short column of silica gel (1 g) by elution with petroleum ether–benzene (1:1) and benzene, giving 27.3 mg (67.8%) of **24** as a crystalline solid, mp 157–160 °C (ether–pentane). Recrystallization from dichloromethane–ether afforded an analytical specimen: mp 160–163 °C; NMR ($CDCl_3$) $\delta$ 1.15 (s, 3 H, 13-Me), 3.77 (s, 3 H, OMe), 6.6–7.4 (m, 3 H, Ar H); IR ($CHCl_3$) 1700 $cm^{-1}$; mass spectrum, $m/e$ 316 ($M^+$). Anal. Calcd for $C_{19}H_{24}O_2S$: C, 72.11; H, 7.64; S, 10.13. Found: C, 71.97; H, 7.63; S, 10.09.

**Hydride Reduction of 23 and 24.** (a) To a stirred solution of 50.6 mg (0.16 mmol) of **23** in 3 mL of dry tetrahydrofuran was added 12.2 mg (0.32 mmol) of LAH portionwise. The mixture

(7) Terasawa, T.; Okada, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 990.

was stirred at room temperature over 30 min and then poured into ice-water. Extraction with ether-dichloromethane (3:1) followed by the usual workup gave an oily residue which was purified by preparative TLC [benzene-ethyl acetate (20:1) with double development] to afford 19.8 mg (38.9%) of **17** and 14.2 mg (27.9%) of **15**. These materials were identical in all respects (TLC, IR, NMR) with their authentic samples.

(b) As above, 20 mg (0.063 mmol) of **24** was reduced with 5 mg of LAH in 1.2 mL of dry tetrahydrofuran and worked up. The crude product was shown to be a 1.5:1 (NMR) mixture of **16a** and **19a** which were, though incompletely separated, identified unambiguously with their authentic samples by NMR and IR data and their TLC behavior.

**16-Thia-*D*-homoestrone 3-Methyl Ether (25).** A stirred suspension of 50 mg (0.157 mmol) of **20a** and 3 g of silver carbonate-Celite[4] (1 mmol/0.57 g) in 8 mL of dry toluene was heated at gentle reflux under nitrogen for 24 h. The reagent was filtered off, and the toluene was evaporated. The residue was purified through a short column of silica gel (1 g). Elution with benzene gave 14.1 mg of **25** as a crystalline solid, mp 149-152 °C (ether-pentane). The successive fraction which eluted with benzene-ethyl acetate (1:1) yielded 29 mg of recovered **20a**. The total yield of **25** was 67.6% based upon the recovered starting material. Pure **25** was obtained by recrystallization from dichloromethane-ether as a crystalline solid: mp 151-153 °C; NMR $\delta$ ($CDCl_3$) 1.20 (s, 3 H, 13-Me), 3.76 (s, 3 H, OMe), 6.6-7.4 (m, 3 H, Ar H); IR ($CHCl_3$) 1705 $cm^{-1}$; mass spectrum, $m/e$, 316 ($M^+$). Anal. Calcd for $C_{19}H_{24}O_2S$: C, 72.11; H, 7.64; S, 10.13. Found: C, 71.91; H, 7.62; S, 10.16.

**Registry No.** 1, 64255-74-9; (±)-**2b**, 75878-69-2; (±)-**3b**, 75878-70-5; *meso*-**4a**, 74041-79-5; *meso*-**4b**, 75828-09-0; *meso*-**5a**, 74081-04-2; *meso*-**5b**, 75828-10-3; (±)-**6a**, 75828-11-4; (±)-**6b**, 75828-12-5; (±)-**7a**, 75828-13-6; (±)-**7b**, 75828-14-7; (±)-**8a**, 75828-15-8; (±)-**8b**, 75828-16-9; (±)-**9a**, 75828-17-0; (±)-**9b**, 75828-18-1; (±)-**10a**, 75828-19-2; (±)-**10b**, 75828-20-5; (±)-**11**, 75828-21-6; (±)-**12**, 75828-22-7; (±)-**13a**, 75828-23-8; (±)-**13b**, 75828-24-9; (±)-**14a**, 75828-25-0; (±)-**14b**, 75828-26-1; (±)-**15a**, 75828-27-2; (±)-**15b**, 75828-28-3; (±)-**16a**, 75828-29-4; (±)-**16b**, 75828-30-7; (±)-**17a**, 75828-31-8; (±)-**17b**, 75828-32-9; (±)-**18a**, 75828-33-0; (±)-**18b**, 75828-34-1; (±)-**19a**, 75828-35-2; (±)-**19b**, 75828-36-3; (±)-**20a**, 75828-37-4; (±)-**20b**, 75782-82-0; (±)-**21a**, 75828-38-5; (±)-**21b**, 75782-83-1; (±)-**22a**, 75828-39-6; (±)-**22b**, 75828-40-9; (±)-**23**, 75782-84-2; (±)-**24**, 75828-41-0; (±)-**25**, 75828-42-1; (±)-A, 75790-46-4; (±)-B, 75828-80-7; (±)-C, 75828-81-8; (±)-D, 75828-82-9.

# Addition of Dichlorocarbene to Oxyberberine and Berberine

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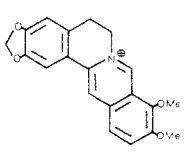
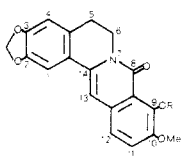
Dichlorocarbene adds to oxyberberine (**2**) to furnish the key adduct **5**. Hydrolysis of **5** in dilute hydrochloric acid yields oxyberberine-13-carboxaldehyde (**7**). Reduction of adduct **5** with zinc in acetic acid produces 13-methyloxyberberine (**11**). Alternatively, reduction of **5** with lithium aluminum hydride in hot THF leads to enlargement of ring C with formation of the vinylic chloride **14**. A complex transformation occurs when **5** is refluxed in aqueous pyridine, the product being keto lactam **15**. Dichlorocarbene in chloroform also adds to berberine (**1**) to form pentachloro derivative **22**. Acid hydrolysis of **22** gives rise to aldehyde **23** which loses hydrogen chloride in the presence of silver oxide to afford dichloro compound **25**. Sodium borohydride reduction of **23** produces alcohol **24**.

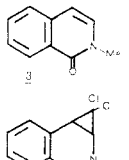
As part of a systematic study of the chemistry of berberine (**1**) and its close derivatives, we had occasion to investigate the reaction of oxyberberine (**2**) with dichlorocarbene. It had been previously demonstrated that the adduct **4** was formed in high yield when dichlorocarbene was generated by phase-transfer-catalyzed decomposition of chloroform in the presence of *N*-methylisoquinolone (**3**) and hydroxide ion.[1,2]



**1**



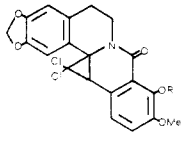
**2**, R = Me
**8**, R = H



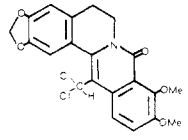
**3**

**4**

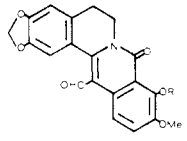
When this carbene reaction was extended to the yellow-colored oxyberberine (**2**)[3] using benzyldiethylmethylammonium iodide as catalyst, a colorless crystalline adduct **5** was obtained in 55% yield, $\nu_{max}$ ($CHCl_3$) 1648 $cm^{-1}$. Elemental combustion analysis clearly indicated addition of $CCl_2$. That the dichloro carbene had added to the C-13,14 double bond of **2** was suggested by the loss of the yellow color in the product, as well as by the fact that the oxyberberine H-13 NMR vinylic singlet at $\delta$ 7.18 had moved upfield to $\delta$ 3.52 in the adduct **5**.



**5**, R = Me
**9**, R = H



**6**



**7**, R = Me
**10**, R = H

With a reliable supply of adduct **5** on hand, it became logical to envision a series of transformations starting from this adduct which would lead to oxyberberine analogues substituted at C-13. In particular, we became interested in preparing oxyberberine-13-carboxaldehyde (**7**), especially since no 13-carboxaldehyde derivative of berberine or any of its congeners had previously been prepared. Indeed, it was found that when adduct **5** is refluxed in dilute hydrochloric acid in methanol, a 40% yield of the desired yellow aldehyde **7** is obtained, $\nu_{max}$ ($CHCl_3$) 1645 $cm^{-1}$ (br), with a characteristic NMR downfield singlet peak at $\delta$ 9.77 for the aldehydic proton. This transformation probably proceeds through the intermediacy of the allylic dichloro derivative **6** which can be readily hydrolyzed to the aldehyde **7**.

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(2) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).
(3) W. H. Perkin, Jr., *J. Chem. Soc.*, 722 (1918).

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