washed twice with 200 ml of deionized water, dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator (25°) to give 3.067 g of a dark red residue. Column chromatography on 50 g of silica gel (Woelm 0.05–0.20 mm) and elution with 0.5% C_2H_5OH in $CHCl_3$ gave 2.1 g of a green crystalline solid: ir (film) 2240 (C≡N, strong), 1640 cm^{-1} (C=O amide, strong); TLC (10% MeOH–$CHCl_3$ on silica gel) showed one spot, R_f 0.7. The solid was recrystallized from approximately 5 ml of 1:1 *i*-Pr_2O–CH_2Cl_2 to yield 0.921 g (29% yield) of bronze-colored crystals: mp 81–85° dec; mass spectrum (70 eV) *m/e* 390 (M^+), 347, 333, 307. Anal. ($C_{24}H_{30}N_4O$) C, H, N.

***d*-6-Cyano-6-norlysergic Acid Methyl Ester (1a).**[8] The method described above was used except that after work-up the crude product was crystallized directly (*i*-Pr_2O–CH_2Cl_2, 37% yield) and no column chromatography was carried out: mp 138–140° (lit.[8] 146°).

1-(*d*-6-Cyano-6-norlysergoyl)piperidine (1b). This compound was prepared as 1c in 15% yield. It was crystallized from *i*-Pr_2O–$CHCl_3$: mp 114–117°; mass spectrum (70 eV) *m/e* 346 (M^+), 262, 234, 233, 207. Anal. ($C_{21}H_{22}N_4O$) C, H, N.

1-(*d*-6-Cyano-6-norlysergoyl)pyrrolidine (1d).[10] Compound **2d**[11] was treated with BrCN as in **1c**. After work-up the crude material was purified by two preparative TLC separations on 2-mm thick silica gel plates (Merck, 10% CH_3OH–$CHCl_3$) and crystallized from a mixture of $CHCl_3$–Et_2O: mp 220–223° (40% yield); mass spectrum (70 eV) *m/e* 332 (M^+), 262, 234, 207, 193, 192.

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Studies in Antifertility Agents. 11. Secosteroids. 5. Synthesis of 9,11-Secoestradiol[1]

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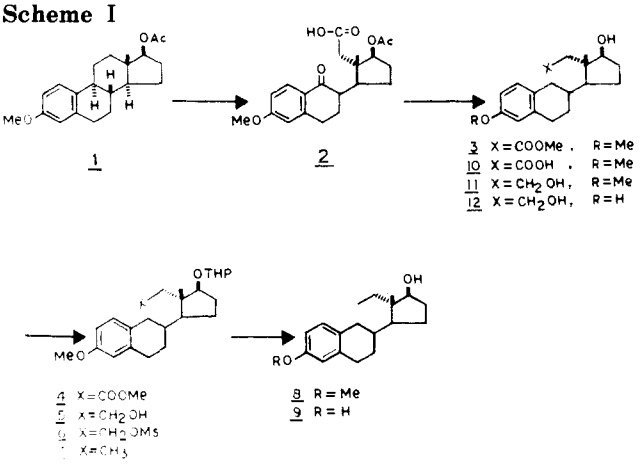
9,11-Secoestradiol (**9**) and 11-hydroxy-9,11-secoestradiol (**12**) have been synthesized starting from 17-acetoxyestradiol 3-methyl ether (**1**) and found to possess significant antifertility activity in rats. 3-Methoxy-9,11-seco-9-oxo-17β-acetoxyestra-1,3,5(10)-trien-11-oic acid (**2**), prepared by CrO_3 oxidation of 1, on hydrogenolysis gave methyl 17β-hydroxy-3-methoxy-9,11-secoestra-1,3,5(10)-triene-11-carboxylate (**3**). The 17-O-THP derivative of **3** was treated with $LiAlH_4$ to give 17β-(*O*-tetrahydropyranyl)-3-methoxy-11-hydroxy-9,11-secoestra-1,3,5(10)-triene (**5**). The 11-*O*-mesylate of **5** on $LiAlH_4$ reduction followed by mild acid treatment and demethylation under alkaline conditions gave **9**. $LiAlH_4$ reduction of **3** gave 9,11-seco-11-hydroxyestradiol 3-methyl ether (**11**) which on demethylation gave 9,11-seco-11-hydroxyestradiol (**12**).

In a search for atypical estrogens (substances with dissociated activity of estrone) possessing specific antifertility, hypocholesteramic, or antiinflammatory activity and as probes for study of "estrogenic" receptors, secoestrones have been under investigation in this laboratory for sometime.[2] A recent communication by Chinn et al.[3] describing the synthesis of secoequilenin prompted us to describe our work on 9,11-secoestradiol and some related compounds. In order to ensure estradiol stereochemistry in the compounds it was considered practical to start with estradiol and carry out chemical operations on it which are not likely to affect the stereochemistry of the nucleus.

3-Methoxy-17β-acetoxyestra-1,3,5(10)-triene (**1**) on CrO_3 oxidation gave 3-methoxy-9,11-seco-9-oxo-17β-acetoxyestra-1,3,5(10)-trien-11-oic acid (**2**),[4] which on hydrogenolysis gave methyl 17β-hydroxy-3-methoxy-9,11-secoestra-1,3,5(10)-triene-11-carboxylate (**3**). The 17-tetrahydropyranyl derivative of **3** on lithium aluminum hydride reduction gave 17β-(*O*-tetrahydropyranyl)-3-methoxy-11-hydroxy-9,11-secoestra-1,3,5(10)-triene (**5**). The 11-*O*-mesylate **6**, prepared from **5**, on lithium aluminum hydride reduction followed by acid treatment to remove the tetrahydropyranyl group and demethylation[5] with potassium hydroxide and hydrazine hydrate in diethylene glycol gave the desired 9,11-secoestradiol (**9**). Alkaline hydrolysis of **3** gave 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-11-oic acid (**10**). 11-Hydroxyestradiol (**12**) was obtained from **3** by lithium aluminum hydride reduction to **11** followed by demethylation under alkaline conditions.

Biological Activity. Compounds **9–12** were tested for their antifertility activity in pregnant female albino rats of proven fertility. The day on which the vaginal smears showed the presence of spermatozoa was considered day 1 of pregnancy. In the primary screening the compounds were fed for 5 days from day 1 to day 5 of pregnancy using five animals in each group. The compounds were macerated with gum acacia and administered orally to animals. The results were scored as positive only if implantations were totally absent in both uterine horns, examined on day 10 of pregnancy; control animals had an average of seven

Scheme I



implantations. Compounds **11** and **12** at 10 mg/kg and **9** at 20 mg/kg have been found 100% effective in preventing implantation. These compounds are under further biological evaluation.

Experimental Section

Melting points were determined in a sulfuric acid bath and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Infracord 137. NMR spectra of all the compounds were taken in $CDCl_3$ solution with a Varian A-60D spectrometer and mass spectra were run on a Hitachi RMU-6E mass spectrometer. The ir, NMR, and mass spectra and elemental analysis of the compounds were consistent with the assigned structure.

Methyl 17β-Hydroxy-3-methoxy-9,11-secoestra-1,3,5(10)-triene-11-carboxylate (3). A solution of **2** [1 g, 2.67 mmol; $[\alpha]^{25}D$ −9.93° (dioxane, *c* 1.91)] in methanol was hydrogenated at room temperature using 10% Pd/C at 50 psi in the presence of traces of concentrated HCl. The reaction was over in 20 hr. The mixture on work-up by the usual method gave **3**: yield 0.55 g (62%); mp 87°; $[\alpha]^{25}D$ +52.4° (dioxane, *c* 1.59); M^+ 332. Anal. ($C_{20}H_{28}O_4$) C, H.

Methyl 17β-*O*-Tetrahydropyranyl-3-methoxy-9,11-secoestra-1,3,5(10)-triene-11-carboxylate (4). Dihydropyran (2 ml, 22 mmol) was added dropwise during 5 min under stirring to a solution of **3** (1 g, 3 mmol) and dry *p*-toluenesulfonic acid (0.25 g) in dry dioxane (7 ml) and kept at 18–20°. Stirring was continued for 45 min, methanolic ammonia (0.5 ml) added, the solvent distilled off, and the residue extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), passed through a short column of basic alumina, and concentrated to give **4** as a syrup: yield 1.2 g (96%); M^+ − THP, 331. Anal. ($C_{25}H_{36}O_5$) C, H.

17β-(*O*-Tetrahydropyranyl)-3-methoxy-9,11-secoestra-1,3,5(10)-triene (7). A solution of **4** (1 g, 2.4 mmol) in dry ether was added gradually to a stirred suspension of $LiAlH_4$ (0.8 g, 21 mmol) in dry ether (20 ml). Stirring was continued for an additional 1 hr; the complex was decomposed by careful addition of water and the reaction mixture was extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and concentrated to give 0.9 g (96%) of 17β-(*O*-tetrahydropyranyl)-3-methoxy-11-hydroxy-9,11-secoestra-1,3,5(10)-triene (**5**), as a syrup, which was taken to the next step without further purification. Methylsulfonyl chloride (1 ml, 12.8 mmol) was added to a stirred solution of **5** (1.2 g, 3.09 mmol) in dry pyridine (3 ml) at 0°; the reaction mixture was kept at 20° for 16 hr; pyridine was distilled off under high vacuum and the residue was extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and concentrated when **6** was obtained as a syrup, yield 1.33 g (92%), which was carried to the next step without further purification.

A solution of **6** (1.33 g, 2.85 mmol) in dry ether (20 ml) was added gradually to a stirred suspension of $LiAlH_4$ (0.7 g, 18.4 mmol) in dry ether at room temperature. Stirring was continued for a further 1 hr; the reaction mixture was decomposed by careful addition of water and worked up as mentioned for **5**, when **7** was obtained as a syrup which was purified by chromatography on a basic alumina column using increasing amounts of benzene in hexane as eluent: yield 1.04 g (98%): M^+ − THP, 287. Anal. ($C_{24}H_{36}O_3$) C, H.

9,11-Secoestradiol (9). A solution of **7** (0.9 g, 2.42 mmol) in 20 ml of ethanol containing 0.001 *N* HCl was heated under reflux for 1 hr; solvent was distilled off; the residue was extracted with ether. The ether extract was washed with water until neutral, dried (Na_2SO_4), and concentrated when 9,11-secoestradiol-3-methyl ether (**8**) was obtained: yield 0.68 g (97.6%).

A mixture of **8** (0.3 g, 1.04 mmol), potassium hydroxide (2.5 g), 100% hydrazine hydrate (0.2 ml), and diethylene glycol (15 ml) was heated at 220–230° for 2 hr under nitrogen. The reaction mixture was poured onto 500 ml of water containing sodium dithionite (0.3 g) and the pH was made acidic by addition of glacial acetic acid. The reaction mixture was then extracted with ethyl acetate; the organic layer was washed with water, dried (Na_2SO_4), and concentrated. The oily residue was chromatographed on silica gel using benzene containing increasing amounts of ethyl acetate as eluent when **9** was obtained as colorless crystalline solid which was recrystallized from benzene: yield 150 mg (52%): mp 144–145°; $[\alpha]^{25}D$ +46.34° (dioxane, *c* 0.41); M^+ 274. Anal. ($C_{18}H_{26}O_2$) C, H.

3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-11-oic Acid (10). Hydrolysis of **3** in 10% ethanolic NaOH gave **10** in 85% yield. The solid product was recrystallized from benzene–hexane: mp 133°; M^+ 318. Anal. ($C_{19}H_{26}O_4$) C, H.

9,11-Seco-11-hydroxyestradiol 3-Methyl Ether (11). $LiAlH_4$ reduction of **3** following the process mentioned for **5** gave **11** in 80% yield. The solid product was recrystallized from ethanol–benzene: mp 195°; M^+ 304. Anal. ($C_{19}H_{28}O_3$) C, H.

9,11-Seco-11-hydroxyestradiol (12). Demethylation of **11** under conditions mentioned for **9** followed by chromatography gave **12** as a solid in 50% yield which was recrystallized from ethanol–benzene: mp 146°; $[\alpha]^{25}D$ +47.5° (dioxane, *c* 0.40); M^+ 290. Anal. ($C_{18}H_{26}O_3$) C, H.

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