bation conditions were described previously:[43] 4.5 mM *n*-octylamine, 1 mM EDTA, 0.5 mM $NADP^+$, 2 mM glucose 6-phosphate, and 1 IU of glucose-6-phosphate dehydrogenase was dissolved in 50 mM potassium buffer (pH 7.8) in a total of 0.5 mL, the mixture was cooled to 4 °C, and flavin-containing monooxygenase (100 μg of purified enzyme or 2.5 mg of hog liver microsomal protein) was added. Reactions were initiated by the addition of 2 μCi [*Me*-^{3}H]-MPTP and were carried out in triplicate at 33 °C under air with constant shaking. After 20 min of incubation, another 50 μg of purified flavin-containing monooxygenase or 1.25 mg of hog liver microsomal protein was added to insure that maximal conversion to [*Me*-^{3}H]-MPTP *N*-oxide was achieved. After an additional incubation of 15 min, two 1-mL portions of ice-cold dichloromethane was added and mixed, and the layers were separated by centrifugation. The dichloromethane layer was reduced in volume and applied to alumina preparative TLC plates and developed in chloroform/methanol (9:1) as described previously.[29] The bands corresponding to the *N*-oxide and MPTP were scraped and filtered through a small column of Celite (100 mg, 0.4 × 1.0 cm), eluted with ethyl acetate/dichloromethane/methanol (60:30:10), and evaporated in vacuo to afford purified [*Me*-^{3}H]-MPTP *N*-oxide and recovered [*Me*-^{3}H]-MPTP. While the results described herein concerning microsomal N-oxygenation were obtained with hog liver microsomes and purified hog liver flavin-containing monooxygenase, very similar results were obtained with rat and mouse liver microsomes.[30] In principle, hog, rat, or mouse liver microsomes can be utilized to very efficiently biotransform MPTP to MPTP *N*-oxide, by using the procedure described above.

Chemical Oxidation of MPTP with H_2O_2. Two microcuries of [*Me*-^{3}H]-MPTP (6.5 ng, 0.024 nmol) was combined with 475 μL of ethanol. A 25-μL aliquot of diluted 30% aqueous H_2O_2 was added to the reaction in order to achieve the concentrations of H_2O_2 listed in Table I. The reaction proceeded with shaking under an atmosphere of air at room temperature. At the appropriate time, as described in Table I, a 50-μL aliquot was withdrawn from the reaction and combined with 450 μL of dimethyl sulfoxide/acetonitrile (20:80). A 50-μL aliquot of the quenched reaction mixture was analyzed directly by high-performance liquid chromatography (HPLC) by monitoring the amount of radioactivity with scintillation counting of material coeluting with authentic synthetic MPTP and MPTP oxidation products, as described previously.[29]

Transformation of [*Me*-^{3}H]-MPTP *N*-Oxide to [*Me*-^{3}H]-MPDP$^+$. Typically, two μCi (7 ng, 0.024 nmol) of purified [*Me*-^{3}H]-MPTP *N*-oxide from the enzymatic incubates was dried by azeotroping with toluene. [*Me*-^{3}H]-MPTP *N*-oxide was combined with 2 mL of dichloromethane and cooled to −20 °C and 50 μL of trifluoroacetic anhydride (74 μg, 0.35 μmol) was added. The reaction mixture was allowed to warm to room temperature and after 10 min was evaporated to dryness and was taken up in 500 μL of acetonitrile. The acetonitrile fraction was analyzed directly by HPLC.

Analytical Procedures. The composition of chemical and enzymatic N-oxygenation reaction products were determined by TLC and HPLC analysis. HPLC analysis was performed as previously described,[29] except that 50 mM *N,N*-dimethyloctylamine was added to the elution buffer to improve the chromatographic separations. Analysis was performed on an IBM Model 9300 Ternary Gradient HPLC system with a 5-μm Altex ultrasphere-ODS reverse-phase analytical HPLC column with UV detection at 242 nm for MPTP *N*-oxide and 342 nm for MPDP$^+$. The structures of radiolabeled reaction products were confirmed by pooling the materials from preparative HPLC runs and determining their UV–vis spectra with a Perkin-Elmer Model 595 UV–vis spectrophotometer. Radioactivity was quantitated by scintillation counting with a Searle Mark III scintillation counter. During the handling and use of MPTP, special precautions as outlined previously[44] were employed.

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Registry No. [Me-^{3}H]MPTP, 114130-43-7; [Me-^{3}H]MPTP *N*-oxide, 114096-17-2; [Me-^{3}H]MPDP$^+$, 114096-18-3; H_2O_2, 7722-84-1; flavin-contg. monooxygenase, 62213-32-5.

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C-Nor-9,11-secoestranes as Modified Estrogens and Fertility Regulation†

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The synthesis of *C*-nor-9,11-secoestradiol (4) has been achieved from 17β-acetoxy-11-chloro-3-methoxy-*C*-nor-9,11-secoestra-1,3,5(10)-trien-9-one (1) through a sequence of reactions without affecting the stereochemistry of estradiol-17β. Removal of the 9-keto function of 1 by hydrogenolysis and its subsequent treatment with Na/NH_3 gives *C*-nor-9,11-secoestradiol 3-(methyl ether) (3), which has been demethylated under alkaline conditions to furnish *C*-nor-9,11-secoestradiol (4). Pyridinium chlorochromate oxidation of 3 gives the corresponding 17-ketone 6. Jones' oxidation of 4 to the ketone 5 and reaction of 5 and 6 with lithium acetylide gives corresponding 17α-ethynyl derivatives 7 and 8. Relative binding affinity to estradiol-17β receptors and uterotropic, antiuterotrophic, and antiimplantation activities of compounds 3–8 have been studied. The effect of conformational flexibility on ligand–receptor interaction of these compounds is discussed.

The action of hormones is mediated[1] through their interaction with specific receptors and presumably is a measure of a complimentarity existing between the receptor and the interacting molecule. Therefore, a study of structure–activity relationships (SAR) of secoestradiols was undertaken as an approach to estrogen receptor mapping and toward the development of modified estrogens for fertility regulation.

In the estradiol (E_2-17β) molecule, oxygen functions at C-3 and C-17 and its specific stereochemistry are consid-

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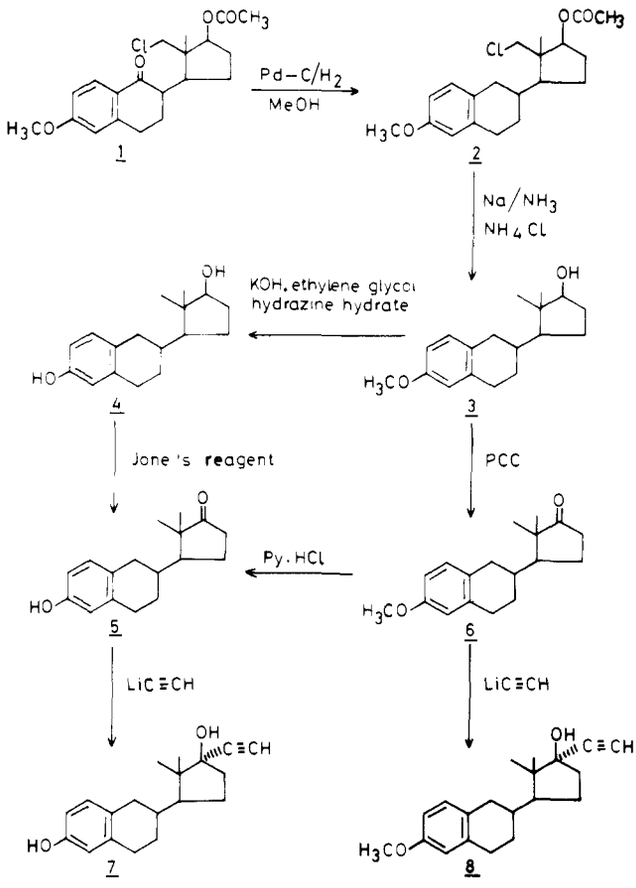
0022-2623/88/1831-1261$01.50/0

Scheme I



ered to be crucial for the estrogenic response. However, the high order of estrogenic activity possessed by some of the secoestradiol molecules[2] such as (−)-α-bisdehydrodoisynolic acid and substituted allenolic acids indicates a more limited molecular requirement at the receptor site.

Further, it was considered that a properly designed flexible molecule, such as *C*-nor-9,11-secoestradiol in which the receptor binding sites at C-3 and C-17 are retained, could initially undergo specific receptor binding with high affinity. It may, however, fail to initiate an estrogenic response, possibly as a result of premature release from the receptor surface, and thus act as an antiestrogen; such a modified estrogen might be of potential value in fertility regulation.

Chemistry

The ketone 1,[3] prepared from estradiol (as shown in Scheme I) through its oxidative cleavage[4] and chlorodecarboxylation,[3] on hydrogenolysis with Pd–C/H_2 gave 17β-acetoxy-11-chloro-3-methoxy-*C*-nor-9,11-secoestra-1,3,5(10)-triene (**2**). A likely retention of configuration at C-8 during hydrogenolysis has been reported.[5] Reaction of **2** with Na/NH_3 furnished *C*-nor-9,11-secoestradiol 3-methyl ether (**3**), which on demethylation with KOH and diethylene glycol in the presence of hydrazine hydrate led to *C*-nor-9,11-secoestradiol (**4**). Jone's oxidation of compound **4** afforded the corresponding 17-ketone **5**. Pyridinium chlorochromate oxidation of **3** gave *C*-nor-9,11-secoestrone 3-(methyl ether) (**6**). Demethylation of **6** with pyridine hydrochloride also afforded compound **5** in good yield. Treatment of **5** and **6** with lithium acetylide gave corresponding 17α-ethynyl derivatives **7** and **8** respectively.

Homogeneity of the compounds **7** and **8** on thin-layer chromatography (TLC) and a pair of sharp singlets for the C-13 methyl substituents in ^1H NMR suggest the formation of a single isomer during ethynylation. On the basis of the reports of almost exclusive formation of 17α-ethynyl isomers from estrone[6] and *trans*-1-methyl-2-(6-methoxy-2-naphthyl)-5-oxocyclopentaneacetic acid,[7] a 17α-ethynyl stereochemistry has been tentatively assigned to the compounds **7** and **8**. The methyl group at C-13 of **3** appearing upfield at δ 0.75 has been assigned β-stereochemistry (cf. angular methyl groups of estradiol and 9,11-secoestradiol appearing at δ 0.78 and 0.76, respectively). However, this assignment is subject to further confirmation.

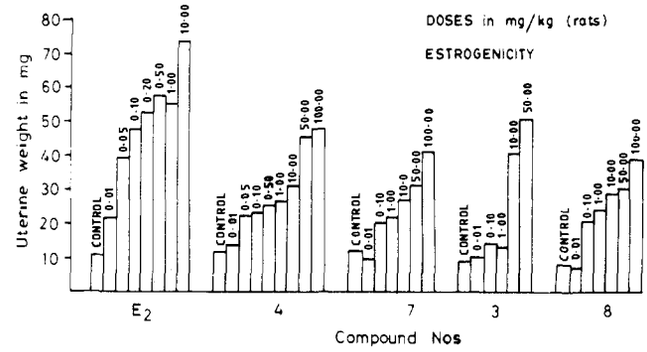


Figure 1.

Table I. RBA and Uterotrophic and Antiimplantation Activity Data of Compounds

compd no.	RBA (%) of E_2: mean ± SEM (*n*)	uterotrophic activity, %	antiimplantation activity: MED[a] 100 (rats), mg/kg
control (vehicle)	*f*	*f*	*f*
estradiol	100	100 (6)[c]	0.015 sc[e] (6)
3	0.087 ± 0.014 (3)	0.37 (6)	1.5 sc (6)
			10.5 po (5)
4	78.95 ± 1.80 (3)	10 (6)	0.01 sc (7)
			10.0 po (5)
5	0.96 ± 0.04 (3)	*f*	*f*
6	not detectable	*f*	*f*
7	30.51 ± 7.37 (6)	0.47 (6)	0.025 sc (7)
			0.75 po (6)
8	0.057 ± 0.004	12.5 (6)	0.025 sc (6)
			1.0 po (6)
17α-ethynyl E_2	191[d]	*f*	0.15 po[b] (6)

[a] Minimum effective dose for percent animals. [b] Number of determinations indicated in parentheses. [c] Number of animals indicated in parentheses. [d] See ref 9. [e] See ref 18. [f] Not determined.

Results

Uterotrophic activity of compounds measured as gain in uterine weight at various doses are shown in the Figure 1. Relative binding affinity (RBA) and uterotrophic and antiimplantation activity data of the compounds studied are given in the Table I. Compound **4** showed the highest RBA (78%) and a significant uterotrophic activity and was the most potent antiimplantation agent when administered subcutaneously. However, the corresponding 17α-ethynyl compound **7** was found to be most active on oral administration. In a limited study 38% and 13% inhibition in uterotrophic response of E_2-17β at a 0.1-mg dose were

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observed when administered along with 1 mg of compounds 4 and 7, respectively. At a 10-mg dose, these inhibitions were 31% and 12%, respectively.

Discussion

The high RBA (78%) observed with C-nor-9,11-secoestradiol (4) would apparently suggest that the intact estradiol framework is not essential for the receptor binding. However, a study of the Dreiding model shows that such a flexible system gives rise to rotamers having unfavorable orientations of the hydroxyl groups. This loss of only ~20% in the binding affinity would therefore indicate that hydrophobic interaction provided by alkyl substituents[8] at C-13 may cause an enrichment of the preferred rotameric population. However, a twofold drop in RBA of compound 7 on introduction of a 17α-ethynyl substituent, instead of an increase as observed for 17α-ethynylestradiol,[9] could be due to a likely perturbation in their molecular geometry. This deleterious effect of substitution in these flexible molecules[10] may also account for their impeded estrogenic character and, coupled with high RBA, could be responsible for the observed antiuterotrophic activity of compounds 4 and 7.

As a result of weaker interaction with the receptor, compound 7 shows weaker uterotrophic as well as antiuterotrophic activities as compared to compound 4. However, compound 4 is 10 times less active than compound 7 as an antiimplantation agent on oral administration. By analogy with estradiol, this could be due to poor oral absorption[11] because on sc administration the compound is 1000 times more potent as an antiimplantation agent. In this respect D-secoestranecarboxylic acids differ, being equipotent when administered orally or subcutaneously.[12] Similar to C,D-secoestranes[13] a sharp drop in RBA and correspondingly uterotrophic activity is observed on homologating the alkyl substituent at C-13, i.e., in going from C-nor-9,11-secoestradiol to 9,11-secoestradiol.[14]

Methylation of the phenolic groups as in compounds 3, 6, and 8 reduces the receptor binding ability considerably. A significant drop in RBA value is also observed when the 17-hydroxy function is converted into a 17-ketone (compound 5; RBA, 0.96%). This effect is much less pronounced in estrone (RBA, 66%).[9] This shows the importance in these molecules of hydroxyl functions at C-3 and C-17 in receptor binding as has been reported for estradiol. Apart from the presence of these hydroxy groups, a precise conformation of these molecules plays an important role in deciding the biological activity. A high conformational flexibility, such as in 4-(1,2,3,4-tetrahydro-6-hydroxy-2-naphthyl)butan-2-ol,[15] leads to a biologically inert molecule presumably because it is incapable of binding to the receptor. On the other hand, active isomers of D-secoestrane series such as (-)-α-bisdehydrodoisynolic acid, have a fairly rigid geometry, allowing them to bind to the receptor with high affinity and to elicit full estrogenic response. There is yet another possibility; an ideal competitive antiestrogen would bind to the estrogen receptor with high affinity, producing a very short lived[16] or inert receptor–ligand complex incapable of initiating estrogenic response. C-Nor-9,11-secoestradiol (4) could be considered as an example in this last category, and in this paper we have described its high affinity for the estrogen receptor, its relatively low estrogenicity, and its partial antiestrogenic behavior.

Experimental Section

The melting points were determined in sulfuric acid bath and are uncorrected. The ^{1}H NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) and EM-360 (60 MHz) spectrometers with Me_4Si as internal standard. Mass spectra were recorded on JEOL JMS-D300 instrument. Optical rotations were taken on JASCO DIP-180 polarimeter.

17β-Acetoxy-12-chloro-3-methoxy-C-nor-9,11-secoestradiol (2). A solution of 1 (1.0 g, 0.002 mol) in methanol (20 mL) was hydrogenated over Pd–C (10%, 0.25 g) for 5 h in a Parr hydrogenator under 50 psi of pressure. The catalyst was removed by filtration through a pad of Hyflo Super-Cel, and the solvent was distilled off to give a residue, which was crystallized from methanol to give 2: yield 0.9 g (93.5%), mp 101 °C; IR (KBr) 1720 (17-O-$COCH_3$), 1600, 1580 (aromatic) cm^{-1}; ^{1}H NMR (CCl_4) δ 0.91 (s, 3 H, 18-CH_3), 1.92 (s, 3 H, 17-OCOCH_3), 2.65 (m, 4 H, C-6 and C-9 protons), 3.48 (s, 2 H, CH_2Cl), 3.64 (s, 3 H, 3-OCH_3), 4.9 (m, 1 H, 17-C*H*), 6.31–6.89 (m, 3 H, Ar *H*); mass spectrum (M^+) *m/e* 350; $[\alpha]^{28}_D$ +50°. Anal. C, H.

***C*-Nor-9,11-secoestradiol 3-(Methyl ether) (3).** Sodium (0.5 g, 21.73 × 10^{-3} g-atom) was added portionwise with stirring to a solution of 2 (2.0 g, 0.005 mol), liquid ammonia (50 mL), aniline (0.5 mL, 0.005 mol), and THF (20 mL) at −40 °C. Stirring was continued for 2 h at −40 °C. Solid NH_4Cl was added carefully to discharge the blue color. Water (50 mL) was added, and the reaction mixture was extracted with ethyl acetate (4 × 15 mL). The organic layer was washed with dilute HCl to remove the aniline and then with water to neutrality and dried (Na_2SO_4), and the solvent was distilled off to give 3, which was crystallized from *n*-heptane, yield 1.5 g (83%); mp 87–88 °C; IR (KBr) 3500 (17-OH), 1600, 1580, 1500 (aromatic) cm^{-1}; ^{1}H NMR (CCl_4) δ 0.76 (s, 3 H, 18-CH_3), 1.07 (s, 3 H, 12-CH_3), 2.60 (m, 2 H, C-9 protons), 2.77 (m, 2 H, C-6 protons), 3.42 (m, 1 H, 17-C*H*), 3.67 (s, 3 H, 3-OCH_3), 6.33–6.90 (m, 3 H, Ar *H*); mass spectrum (M^+), *m/e* 274; $[\alpha]^{28}_D$ +66°. Anal. C, H.

***C*-Nor-9,11-secoestradiol (4).** A mixture of 3 (0.5 g, 0.002 mol), KOH (3.6 g), hydrazine hydrate (1.0 mL), and diethylene glycol (20 mL) was refluxed under nitrogen atmosphere at 200–220 °C for 1.5 h. The reaction mixture was cooled, water was added, and the resultant mixture was extracted with ethyl acetate, washed with water, and dried over Na_2SO_4 (anhydrous). The organic extract was distilled off, and the residue obtained was purified by silica gel column chromatography with use of increasing amounts of benzene in hexane as eluant to give 4: 0.20 g (42%); mp 136–137 °C; IR (KBr) 3400 (17-OH), 3200 (3-OH, intermolecular hydrogen bonded), 1600, 1580, 1500 (aromatic) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 0.67 (s, 3 H, 18-CH_3), 1.0 (s, 3 H, 12-CH_3), 2.45 (m, 2 H, C-9 protons), 3.47 (m, 1 H, 17-C*H*), 6.32–6.68 (m, 3 H, Ar *H*); mass spectrum (M^+), *m/e* 260; $[\alpha]^{28}_D$ +87°. Anal. C, H.

***C*-Nor-9,11-secoestrone (5). Method i.** To a stirred solution of 4 (0.5 g, 0.0019 mol) in acetone (80 mL, distilled over $KMnO_4$) at 0–15 °C under nitrogen atmosphere was added Jone's reagent (0.5 mL), and the mixture was further stirred for 10 min. The reaction mixture was diluted with water (500 mL), extracted with ether, washed with water, dried (Na_2SO_4), and concentrated. The residue was taken in benzene and filtered through a silica gel column to give 5: 0.4 g (80.6%); mp 196–198 °C; IR (KBr) 3200 (3-OH), 1745 (17-C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 0.8 (s, 3 H, 18-CH_3), 1.15 (s, 3 H, 12-CH_3), 1.3–2.8 (m, 12 H, 5 CH_2 and 2 C*H*), 6.4–6.9 (m, 3 H, Ar *H*); mass spectrum (M^+), *m/e* 258; $[\alpha]^{28}_D$ +43°. Anal. C, H.

Method ii. A mixture of 6 (0.5 g, 0.002 mol) and pyridine hydrochloride (2.0 g, 0.017 mol) was heated at 220 °C for 1 h,

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decomposed with water (50 mL), extracted with ether (3×25 mL) washed with water, dried (Na_2SO_4), and concentrated to give an oil, which on crystallization with benzene–hexane gave a compound identical in all respects with **5** (0.3 g, 54.8%).

***C*-Nor-9,11-secoestrone 3-(Methyl ether) (6).** A solution of **3** (0.30 g, 0.001 mol) in anhydrous dichloromethane (5 mL) was added in one portion to a stirred solution of pyridinium chlorochromate (0.50 g, 0.002 mol) in dry CH_2Cl_2 (5 mL). Stirring was continued at room temperature for 1 h. The dark reaction mixture was diluted with anhydrous ether (20 mL). The supernatant was decanted off from the dark gum. The insoluble residue was washed thoroughly with anhydrous ether (3 × 10 mL), when it became a granular solid. The combined organic solution was passed through a short column of Florisil, and the solvent was removed to give **6**, which was crystallized from hexane, yield 0.275 g (92.3%): mp 64–65 °C; IR (KBr) 1720 (17-C=O), 1600, 1580 (aromatic) cm^{-1}; ^1H NMR (CCl_4) δ 0.87 (s, 3 H, 18-CH_3), 1.10 (s, 3 H, 12-CH_3), 2.45 (m, 2 H, C-9 protons), 2.68 (m, 2 H, C-6 protons), 3.67 (s, 3 H, 3-OCH_3), 6.32–6.88 (m, 3 H, Ar *H*); mass spectrum (M^+), *m/e* 272; $[\alpha]^{28}_D$ +151°. Anal. C, H.

17α-Ethynyl-*C*-nor-9,11-secoestradiol (7). To a stirred solution of lithium acetylide–ethylenediamine complex prepared from lithium (0.27 g, 0.038 g-atom) and dry ethylenediamine (75 mL) was added a solution of **5** (0.3 g, 0.0011 mol) in dry THF (25 mL), and the mixture was further stirred for 2 h. Dry acetylene was passed into the mixture throughout the reaction. NH_4Cl was added to decompose excess of lithium, and the mixture was diluted with water and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4, concentrated to give an oil, and filtered through short silica gel column with use of increasing amounts of benzene in hexane as eluant to give **7**: 0.2 g (58%); mp 93–95 °C; IR (KBr) 3400 (3- and 17-OH), 1600, 1580 (aromatic) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (s, 3 H, CH_3), 1.3 (s, 3 H, 12-CH_3), 2.5 (s, 1 H, CH≡C*H*), 6.45–7.0 (m, 3 H, Ar *H*); mass spectrum, *m/e* (M^+) 284; $[\alpha]^{28}_D$ +14°. Anal. C, H.

17α-Ethynyl-*C*-nor-9,11-secoestradiol 3-(Methyl ether) (8). To a stirred solution of lithium acetylide–ethylenediamine complex prepared from lithium (0.25 g, 0.37 g-atom) and dry ethylenediamine (75 mL) was a solution of **6** (0.5 g, 0.0018 mol) in dry THF (30 mL), and the mixture was further stirred for 2 h. Dry acetylene was passed into the reaction mixture throughout the reaction time. The excess of lithium was decomposed with solid NH_4Cl, and the mixture was diluted with water and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4, and concentrated to give an oil, which was crystallized with benzene–hexane to give **8**: 0.35 g (60.3%); mp 103 °C; IR (KBr) 3400 (OH), 1600, 1580 (aromatic) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 3 H, 18-CH_3), 1.23 (s, 3 H, 12-CH_3), 2.58 (s, 1 H, C≡C*H*), 3.76 (s, 3 H, OCH_3), 6.6–6.7 (m, 2 H, 2-C*H* and 4-C*H*), 6.92–7.02 (d, 1 H, 1-C*H*, J = 8 Hz); mass spectrum, *m/e* (M^+) 298; $[\alpha]^{28}_D$ +5.5°. Anal. C, H.

Biochemical and Biological Methods. Receptor Affinity. The relative binding affinity (RBA) of the compounds for uterine cytosol estrogen receptors, obtained from immature Sprague–Dawley rats, 21–25 days old, were determined by a competitive inhibition assay, employing dextran-coated charcoal (DCC) for separation of unbound steroids as reported earlier.[17]

Uterotrophic Activity. The uterotrophic activity of the compounds was evaluated in ovariectomized immature rats (25–30 g) as assayed by uterine weight gain. The compounds were administered subcutaneously once daily, over a 3-day period, in 0.5 mL of saline–propylene glycol (1:1, v/v). Autopsy was performed 24 h after the last administration. The uteri were carefully dissected, blotted to release intraluminal fluid, and then weighed. Control animals received the vehicle only for similar period. The dose–response curves were constructed and relative uterotrophic activity (estradiol as 100%) at double uterine weight were computed.

Antiuterotrophic Activity. The antiuterotrophic activity of the compounds were assayed in immature rats (25–30 g). The compounds were administered subcutaneously in 0.5 mL of propylene glycol–saline (1:1, v/v) along with 0.1 mg of E_2-17β (in 0.2 mL of olive oil) at two different sites for 3 consecutive days. Inhibition is expressed as percent inhibition from the formula of Hartman et al.[18]

Antiimplantation Activity. This was studied in sperm-positive female albino rats mated to coeval males of proven fertility. The compounds were given subcutaneously (sc) in 0.5 mL of propylene glycol–saline (1:1, v/v) or were administered orally (po) as a suspension in gum acacia to colony-bred adult female rats (150–170 g) on days 1–7 postcoitum, with five to seven animals in each group. The animals were examined by laparotomy on day 10 of pregnancy for the number of implants. The minimum dose of compounds in which implants were totally absent in both the uterine horns were recored.[16]

Registry No. **1**, 84371-12-0; **2**, 113507-89-4; **3**, 113507-90-7; **4**, 113507-91-8; **5**, 113507-92-9; **6**, 113507-93-0; **7**, 113507-94-1; **8**, 113507-95-2.

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Book Reviews

Drugs and the Body. Robert M. Julien. W. H. Freeman, New York. 1988. xvi + 297 pp. 15 × 23 cm. ISBN 0-7167-1842-1. $12.95.

This book presents a minipharmacology and miniphysiology text for graduate students or premedical college seniors who want to acquire an overview of materia medica and its biological and clinical applications. It is written in a clear and understandable manner but is much too technical for a liberal-arts-oriented person. Nevertheless, it will fill a gap between professional texts and popular home-medicine compendia.

All types of diseases, their symptoms and treatment, and hundreds of drugs with their advantages, disadvantages, and dosage regimes and general reading references are listed. Notably absent are chapters on pain and, even more so, on psychopharmacological agents; imipramine is presented as a drug to prevent bed wetting, not as an antidepressant. There are five appendices: cough and cold mixtures; antibiotics (antibiotics are poorly defined on pp 189–190) and their specific uses; anticancer drugs (here one misses retro-pathways and any mention of AIDS); and a long list of poison control centers all over the country.

There are many grievous errors in structural formulas: malathion (p 27); scopolamine (p 29); furosemide (p 102); allopurinol (p 108); aldosterone (p 134); ascorbic acid (p 176). These should be corrected immediately. Cardiac glycosides are called alkaloids (p 61), uracil is called pyrimidine nucleus (p 219), and there are spelling mistakes (p 104, l. 5; p 17, l. 2–3), etc. These errors occur so frequently that they annoy an attentive reader.

The book is printed nicely and inexpensively. It will be useful (after a correcting revision) for non-medical students, health professionals, and even general practitioners.

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