1 aromatic proton), 7.79 (s, 1 aromatic proton); mass spectrum, m/z 329.18 ($M^+ - 0.3H_2O$, 0.8), 257 (retro-Diels–Alder ion, 100); exact mass calcd for $C_{18}H_{23}N_3O_3$, 329.17.

The crude amino alcohol obtained from bromohydrin **24** by the action of piperidine as above was taken up in an EtOAc–H_2O–HCl mixture. Separation of the layers and basification of the aqueous layer with Na_2CO_3 solution followed by extraction with EtOAc and preparation of the hydrochloride salt as above furnished compound **15** (see Table II).

Compound **16** (see Table II) was obtained directly from the bromohydrin **25** (1.55 g, 3.9 mmol) by the action of refluxing pyrrolidine (15 mL, 0.18 mol) during 30 min. Purification was achieved by acid–base extraction and salt formation as above: NMR (Me_2SO-d_6) δ 1.05 [s, 3 H, $C(Me)_2$], 1.42 [s, 3 H, $C(Me)_2$], 1.83–1.96 (m, 4 H, NCH_2CH_2), 2.93–2.99 (m, 2 H, NCH_2), 3.36–3.49 (m, 2 H, NCH_2) 3.97 (d, 10, H-3), 4.50 (d, 10, H-4), 6.21 (s, H-8), 8.26 (s, H-5).

Hydrolysis of 6-(Acetylamino) or 7-(Acetylamino) Amino Alcohols. The appropriate amino alcohol as the free base (1.2 mmol), 5 N HCl (4 mL), and EtOH (10 mL) were heated under reflux on a water bath for 3 h. Dilution with H_2O (200 mL) and basification with 10% aqueous NaOH and extraction via EtOAc furnished crude 6-amino or 7-amino compounds, which were purified as described in the previous experiment as their salts (**9**, **10**, **12**, **13**; see Table II).

***trans*-1,6,7,8-Tetrahydro-7-hydroxy-2,8,8-trimethyl-6-(1-pyrrolidinyl)-4*H*-pyrano[3,2-*g*]quinazolin-4-one Dihydrochloride (28).** The 7-(acetylamino)-6-cyano compound **14** (0.44 g, 1.3 mmol) was stirred vigorously with 5 N HCl (40 mL) in EtOAc (40 mL) for 10 min at room temperature. The mixture was basified with 10% aqueous NaOH, and the layers were separated. The EtOAc was washed with H_2O and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation gave a light brown foam (0.43 g), which was dissolved in EtOH and treated with Et_2O–HCl. The resulting precipitate was collected and recrystallized from aqueous EtOH to give the quinazolinone **28** (0.25 g, 47%): mp 258–260 °C; IR (KBr) 1715, 1660 cm^{-1}. Anal. ($C_{18}H_{23}N_3O_3 \cdot 2HCl$) C, H, N.

Pharmacological Testing. Hypertensive Rats. The results (see Table I) obtained in DOCA/saline hypertensive rats are quoted from ref 1, and the method for inducing this type of experimental hypertension is described therein.

In the present study (see Tables I and II) all of the test compounds and the standard drugs were evaluated for antihypertensive activity in conscious spontaneously hypertensive rats (14–24 weeks old), derived from the Japanese (Okamoto) strain. Animals with systolic blood pressure ≥ 180 mmHg (1 mmHg ≈ 133 Pa) were considered to be hypertensive.

Systolic blood pressure was recorded by the tail-cuff method using a W + W B.P. recorder, Model No. 8002. For all measurements of blood pressure, the rats were held in restraining cages in a heated environment (33.5 ± 0.5 °C), and each determination was the mean of at least six recordings. Blood pressure measurements were made prior to the oral administration of test compound and at intervals for up to 6 h postdose.

All compounds were administered (via on oral dosing needle placed in the esophagus) as a solution or suspension in 1% w/v methylcellulose solution. Doses are expressed as free base.

With use of the above procedure, vehicle alone typically has little or no effect on blood pressure apart from a slight reduction (by 5–10%) at 6 h postdose.

Registry No. 1, 86824-10-4; **2**, 86824-32-0; **3**, 65018-84-0; **4**, 86824-61-5; **5**, 86824-54-6; **6**, 86824-27-3; **7**, 78939-11-4; **7** (free base), 90867-39-3; **8**, 78939-08-9; **8** (free base), 78939-07-8; **9**, 78939-16-9; **9** (free base), 90867-40-6; **10**, 78939-13-6; **10** (free base), 78939-12-5; **11**, 79014-15-6; **11** (free base), 79014-14-5; **12**, 79014-20-3; **12** (free base), 79014-19-0; **13**, 79014-17-8; **13** (free base), 79014-16-7; **14**, 79014-28-1; **15**, 79014-30-5; **15** (free base), 79014-29-2; **16**, 79014-34-9; **16** (free base), 79014-33-8; **17**, 79014-11-2; **18**, 79014-12-3; **19**, 79014-24-7; **20**, 79014-25-8; **21**, 79014-26-9; **22**, 79014-31-6; **23**, 78939-05-6; **24**, 79014-27-0; **25**, 79014-32-7; **26**, 79014-13-4; **27**, 78939-06-7; **28**, 79714-18-4; 2,2-dimethyl-7-nitro-2*H*-1-benzopyran, 64169-76-2; 6-amino-2,2-dimethyl-7-nitro-2*H*-1-benzopyran, 64169-75-1; 6-iodo-2,2-dimethyl-7-nitro-2*H*-1-benzopyran, 79014-23-6.

Steroids. 2. Synthesis of C-18 Functionalized Steroids via the Smith–Hughes Route

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Received November 2, 1983

The total synthesis of a series of racemic C-18 functionalized steroids was carried out in a search for novel estrogen- and/or progestin-receptor agonists or antagonists. The target compound 3,18-dihydroxyestra-1,3,5(10)-triene (**2**), 13-(2-oxopropyl)gona-4-en-3-one (**3**), 13-(1-hydroxy-1-prop-2-ynyl)gona-4-en-3-one (**4a** and **4b**) and 13-(1-acetoxy-2-oxo-1-propyl)gona-4-en-3-one (**5**) are position isomers of the highly biologically active estradiol, progesterone, norethindrone, and 17-acetoxyprogesterone, respectively. Nevertheless the synthetic C-18 functionalized steroids **3–5** showed little activity in the Clauberg and anti-Clauberg assays. Compound **2** showed no antagonism in the postcoital assay despite the fact that it exhibited weak but measurable in vitro receptor-binding activity.

Although both naturally occurring and synthetic steroids functionalized at C-18 are known,[1] their number is rather small in comparison to those in other steroid classes. One of the main reasons for this is the somewhat greater synthetic difficulty of introducing substituents at this position as opposed to other locations in the molecule. As a consequence, the effect that changes in substitution at C-18 have on biological activity has not received extensive study.

We became interested in this particular class because of our search for steroid agonists and/or antagonists of both estradiol and progesterone. In particular the development of antagonists in the latter class would represent a new and perhaps more suitable means of regulating mammalian fertility at the level of estrus control.

The basic concept that led to the steroid syntheses described in this paper was the idea that if the C-17 functionality of a steroid were moved to C-18, then there was

(1) Besides the Apocynaceae alkaloids and aldosterone, examples of naturally occurring C-18 functionalized steroids are the holothurian sapogenins (Singh, H.; Pereira, V., Jr.; Parashar, V. V. *Indian J. Pharmacol.* **1965**, *27*, 150. Heftmann, E. *Lloydia* **1967**, *30*, 209), batrachotoxinin A, (Tokuyama, T.; Daly, J.; Witkop, B.) and 18-hydroxyesterone (Loke, K. H.; Marrian, G. F.; Johnson, W. S.; Meyer, W. L.; Camerru, D. D. *Biochim. Biophys. Acta* **1958**, *28*, 214. Karle, J. L.; Karle, J. *J. Am. Chem. Soc.* **1968**, *90*, 1917). For a series of synthetic 18-functionalized progesterone derivatives, see: Auel, R. A. M.; Freerksen, R. W.; Walt, D. S. *Steroids* **1978**, *31*, 2232.

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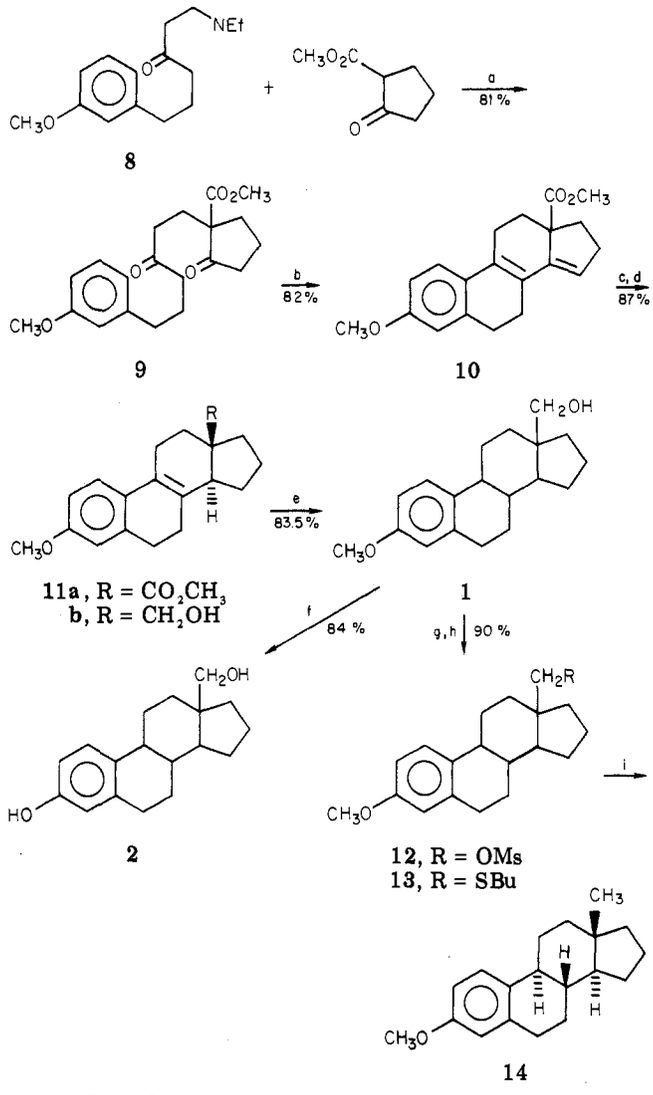
Scheme I[a]



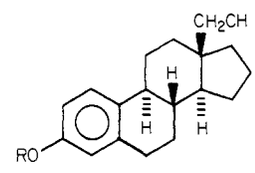
[a] (a) Et_3N, benzene, 80 °C, (b) CF_3COOH, 15 min, 25 °C, (c) $H_2/Pd/CaCO_3$, pyridine, 25 °C, (d) LAH, Et_2O, (e) Li, NH_3, THF, (f) $AlBr_3$, $(CH_2SH)_2$, 2 h 25 °C, (g) MsCl, pyridine, 25 °C, (h), K, *t*-BuOH, *t*-BuSH, 80 °C, (i) Ra-Ni, EtOH, 30 min, 90 °C.

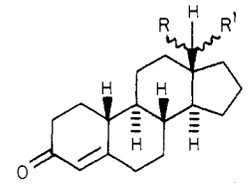
the possibility that the resulting compound would have agonist/antagonist action related to the parent isomer. This was based on the thought that one of the more stable C(13)–C(18) rotamers of such a group would partially occupy the same position that it would occupy when at C-17. However, unlike the C-17 analogues these compounds could be further substituted at C-18 to give a much wider range of compounds for biological testing.

In order to carry out the extensive program that we had in mind, it was necessary to have access to a substantial quantity of a C-18 functionalized steroid. This did not seem possible via a steroid alkaloid of the Apocynaceae class because of the lengthy degradation[2] needed first. Neither did partial synthesis, via one of the many photochemical approaches,[3] seem attractive because of the extensive chromatographic purifications usually needed. We therefore elected to prepare the desired compounds by total synthesis despite the fact that the final products would be racemic. This approach, however, has the advantage that there is little possibility that the final products could be contaminated by starting compounds that are biologically active. Such compounds are frequently used in partial synthesis.

Synthesis of Desired Steroids

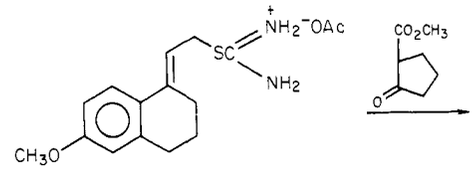
Our first synthetic objectives were compounds **2–5** on the basis of the supposition that these compounds might be related in biological activity to estradiol, progesterone, norethindrone, and 17-acetoxyprogesterone, respectively.

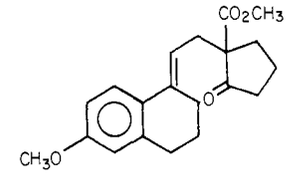




The primary goal, however, was an efficient synthesis of **1** because we envisaged that, besides **2**, the other three substances could be derived from it by using appropriate chemical transformations.

Two known totally synthetic approaches[4] give easy access to compounds of the estra-1,3,5(10)-triene series (and therefore by known methods to more highly reduced steroids of the 19-nor class), namely, those of Torgov[4a] and of Smith–Hughes.[4b] Because the former method appeared to be much the simpler of the two, we examined the coupling of the Torgov intermediate **6** with 2-(methoxycarbonyl)cyclopentanone. However, none of the better





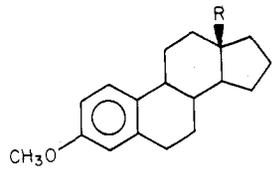
conditions described in the literature[5,6] gave yields of **7** higher than 15%, and although the latter could easily be cyclized to the desired tetracyclic compound **10**, we switched to the Smith–Hughes method, sacrificing shortness of synthesis for ease of purification of intermediates and better overall yields. The critical intermediate **8** was prepared as a pure substance in 51.5% yield from 3-

(2) Alazard, J. P.; Jusinchi, X. *Bull. Soc. Chim. Fr.* **1972**, 3267.
(3) For good examples of this approach, see: Barton, D. H. R.; Basu, W. K.; Day, M. J.; Hesse, R. J.; Pechet, M. M.; Staratt, A. N. *J. Chem. Soc., Perkin Trans 1* **1975**, 2243. Heusler, K.; Kalvoda, J.; Meystre, C.; Wieland, P.; Anner, A.; Wettstein, A.; Cainelli, C.; Arigoni, D.; Jeger, O. *Experientia* **1960**, *16*, 21.
(4) (a) For an excellent review of the Torgov approach, see: Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. "Total Synthesis of Steroids"; Academic Press: New York, 1974; p 86 ff. (b) For a review of the Smith–Hughes approach, see: p 161 ff of the same reference.
(5) Kuo, C. H.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1968**, *33*, 3126.
(6) Recently, after the work described in this paper was completed, a method was developed by us (Magriotis, P. A.; Murray, W. V.; Johnson, F. *Tetrahedron Lett.* **1982**, *23*, 1983) that gives good yields in the reaction of the Torgov intermediate with β-keto esters.

methoxybenzaldehyde by means of a modified version of the original method.[7] The latter we found adaptable easily to the preparation of **8** on a 0.4-mol scale.

The syntheses of the desired compounds **1** and **2** were then completed according to Scheme I. Significant improvements in this type of reaction sequence involve (a) the use of trifluoracetic acid at 25 °C in place of *p*-toluenesulfonic acid in boiling benzene for the cyclization of **9**, (b) the use of pyridine as the solvent during the reduction of the 14,15-double bond in **10**, which affords a very clean product **11a**, and (c) the demethylation of the 3-methoxy group of **1** by using the method of Fujita et al.[8] Because **1** was to be the precursor of all of the desired compounds, it was important at this point to establish its relationship to the normal 1,3,5(10)-estratriene series. This was done by mesylation of **1** to give **12** followed by conversion to the mixed sulfide **13** and then desulfurization to give 3-methoxy-1,3,5(10)-estratriene (**14**). This proved to be identical in all respects (except in optical activity) with an authentic sample of dextro-**14** prepared according to Huang-Minlon.[9]

A rapid approach to the synthesis of **3** and **5** via **15** and **16** was first attempted by the addition of (1-methoxyvinyl)lithium to **15**, itself easily obtained in 78% yield from **1** by oxidation with pyridinium chlorochromate in methylene chloride. Methods for the subsequent reductive



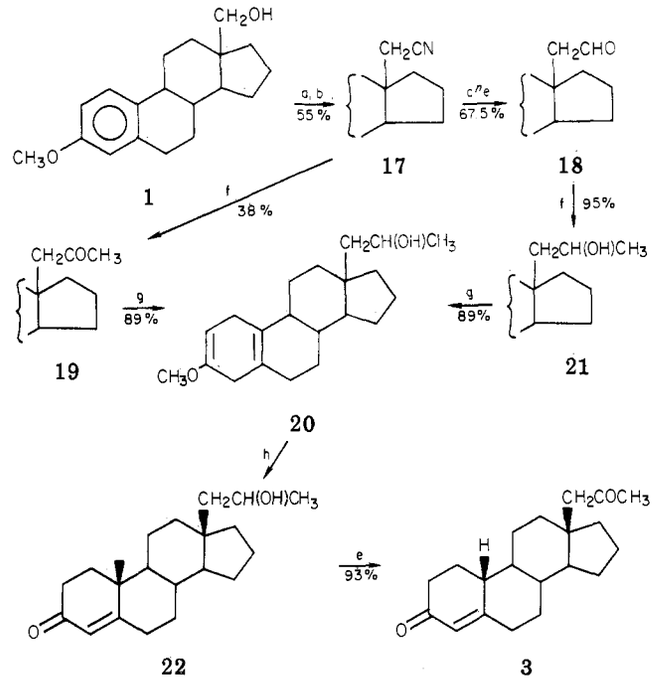
1, R = CH_2OH
15, R = CHO
16, R = $CH(OH)COCH_3$

removal of the C-18 hydroxyl group in the synthesis of **3** and the transformation of ring A were not expected to be troublesome. However, under all conditions used it did not prove possible to effect the transformation of **15** to **16** probably due to the sterically hindered nature of the aldehyde function. This was all the more disappointing because had it succeeded, **5** would also have been easily accessible from **16**.

Two longer methods (Scheme II) for the synthesis of **3** were then developed, both proceeding through the intermediate **20**. The first involves the conversion of **1** to **18** via the nitrile **17** by using conventional steps, the only difficulty being the hydrolysis of **17** to the intermediate acid. This required the use of potassium hydroxide in refluxing wet ethylene glycol for 3 days. The reaction of **18** with methylmagnesium bromide then smoothly gave a mixture of the two racemic diastereoisomeric alcohols **21**, which on reduction by lithium metal in liquid ammonia/*tert*-butyl alcohol then led to **20**. The latter when hydrolyzed led to **22**, again as a mixture of diastereoisomers. Oxidation of **22** then afforded the desired unsaturated diketone **3** as a single isomer.

The alternative route to **20** was developed in an attempt to obviate the lengthiness of the route via **18**. Treatment of **17** with methylmagnesium bromide led directly to **19** after acidic workup. However, the product required

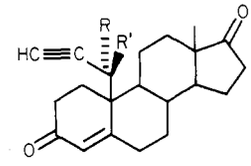
Scheme II[a]



[a] Reagents: (a) MsCl, pyr, (b) NaCN, HMPA, 110 °C, 40 h, (c) KOH, $(CH_2OH)_2$, 180 °C, 3 days, (d) $LiAlH_4$, Et_2O, (e) PCC, CH_2Cl_2, (f) CH_3MgI, Et_2O, (g) Li, NH_3, *t*-BuOH, (h) CH_3OH, H_2O, HCl.

chromatographic purification and the yield (38%) was unsatisfactory. Nevertheless, reduction of **19** gave **20** in excellent yield, again as a mixture of diastereoisomers.

The synthesis of the final two compounds **4** and **5** again utilized **1** as the starting material. In our initial approach to **4** (see Scheme III), ring A of **1** was reduced (85% yield) to **23** by conventional means and the product was hydrolyzed, under acidic conditions, to give **24** in 89% yield. Ketalization of **24** with ethylene glycol using fumaric acid as the catalyst led to **25**. This alcohol was oxidized to the very unstable aldehyde **26** and the latter, without purification, when allowed to react with acetylene magnesium bromide afforded a mixture of two racemates **27a** and **27b**. Hydrolysis of this crude material then yielded the desired product as a mixture of two racemic diastereoisomers **4a** and **4b** in a 3:2 ratio. The major isomer **4a** was easily purified in good yield by repeated crystallization (CH_2Cl_2) whereas **4b** was isolated by preparative TLC. The assignments of the *R* and *S* configurations to C-18, in the depicted forms **4a** and **4b**, respectively, were made by analogy with the assignments made to the corresponding isomers of **28** by Covey et al.[10] using Cram's rule. The

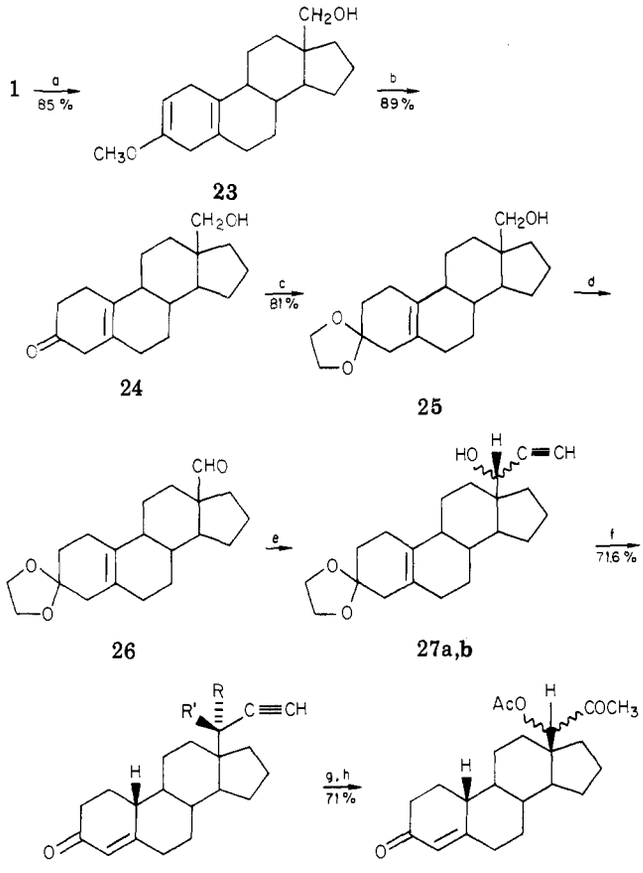


28a, R = OH; R′ = H; assigned as *S*
b, R = H; R′ = OH; assigned as *R*

relative positions in the NMR spectra of the carbinol protons of the major isomer **4a** (δ 4.76) and the minor isomer **4b** (δ 4.58) as the formula are written also are similar to those of **28a** (δ 4.83; assigned as *S*) and **28b** (δ 4.70;

(7) Douglas, G. H.; Graves, J. M. H.; Hartley, D.; Hughes, G. A.; McLaughlin, B. J.; Siddall, J.; Smith, H. *J. Chem. Soc.* **1963**, 5072.
(8) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275.
(9) Minton, H. *J. Am. Chem. Soc.* **1949**, *71*, 3301.
(10) Covey, D. F.; Parikh, V. D.; Chien, W. *Tetrahedron Lett.* **1979**, 2105.

Scheme III[a]



4a, R = OH; R' = H; assigned as *R*
b, R = H; R' = OH; assigned as *S*

[a] Reagents: (a) Li/NH_3, *t*-BuOH, (b) $(COOH)_2$, H_2O, (c) $(CH_2OH)_2$, fumaric acid, C_6H_6, (d) PCC, CH_2Cl_2, 25 °C, (e) HC≡CMgBr, THF, (f) HCl, H_2O, CH_3OH, (g) $Hg(OAc)_2$, EtOAc, (h) H_2S.

assigned as *R*). However, our assignments must be regarded as tentative.

Finally, isomer **4a** only was converted to a single diastereoisomer of **5**, of unknown geometry at C-18, by treatment[11] with mercuric acetate in ethyl acetate followed by decomposition of the intermediate complex with hydrogen sulfide.

Biological Activity

The biological activity of the C-18 substituted steroids was evaluated by in vitro receptor-binding assays and by in vivo testing. For the progestin derivatives receptor-binding activity was evaluated by the competitive binding assay as originally described by Smith et al.[12] This assay compares the ability of the test compound and progesterone to compete with radiolabeled progesterone for the oviduct progesterone receptor prepared from estrogen-primed chicks.[13] Relative binding activities and equilibrium dissociation constants were calculated by the method of Korenman.[14,15] As shown in Table I, progesterone has an equilibrium dissociation constant of 3.9×10^{-9} M when the binding of [^{3}H]progesterone is plotted by the method

Table I

compd	rel binding activity, %	K_D, M
progesterone	100	3.9×10^{-9}
norethindrone	350	6.3×10^{-10}
C-18 progesterone analogue **3**	2	2.2×10^{-7}
C-18 acetoxyprogesterone analogue **5**	0.1	5.1×10^{-6}
C-18 norethindrone analogues **4a** and **4b**	3.1	1.6×10^{-7}
C-18 norethindrone analogue **4a**	0.6	7.3×10^{-7}

of Scatchard.[16] In agreement with previous results,[12] the relative binding activity of norethindrone is seen to be greater than that of progesterone. The mixture of diastereoisomers (**4a** and **4b**) show approximately 0.1% of the binding activity of norethindrone, while the crystalline isomer **4a** shows a relative binding activity of only 0.02%. The C-18 progesterone analogue **3** shows 2% of the binding activity of progesterone itself, while the C-18 acetoxyprogesterone analogue **5** has even weaker activity (0.1%).

In vivo testing of the C-18 progestin analogues was carried out by the Contraceptive Development Branch of the Center for Population Research (National Institutes of Health). Progestational activity was measured with the Clauberg assay.[17] None of the C-18 functionalized compounds showed significant activity in this assay when administered at 50 times the dose necessary to produce a detectable response with progesterone. Similarly, none of these compounds showed significant activity in the anti-Clauberg assay when administered in 40–60-fold excess relative to progesterone. These data indicate that shifting the C-17 functionality to the C-18 position drastically reduces both the in vitro receptor binding and the in vivo activity of these progestin analogues.

Binding of compound **2** to the rat uterine estrogen receptor was determined as described in the literature.[18,19] Direct analysis of [^{3}H]estradiol binding gave an equilibrium dissociation constant of 6.2×10^{-10} M. Compound **2** yielded a relative binding activity of 0.25% and a calculated equilibrium dissociation constant of 3.1×10^{-7} M. The 3-*O*-methyl derivative **1** of compound **2** was devoid of detectable binding activity up to at least 2×10^{-6} M. In vivo agonist activity of **2** was tested with the rat uterotrophic assay[17] at the Contraceptive Development Branch. No agonist activity was detected with dose levels of this compound 10 000-fold greater than the minimum dose of ethynylestradiol (orally) or estradiol (subcutaneously) required to produce a significant response. We also tested whether or not **2** could induce the synthesis of apolipoprotein II or very low density lipoprotein when administered to roosters. A sensitive radioimmunoassay[20] capable of detecting even the low agonist activity of triphenylethylene antiestrogens was used for this purpose. No agonist activity of **5** was detected in this assay. The antagonist activity of compound **2** was tested at the Contraceptive Development Branch with the postcoital assay.[17] No antagonism was seen at a dose level of 2.5 mg/(kg day). The weak but significant in vitro receptor binding activity of **2** does not appear to be reflected in the in vivo agonist

(11) Kagan, H. B.; Marquet, S.; Jacques, J. J. *Bull. Soc. Chim. Fr.* **1960**, 1079.
(12) Smith, H. E.; Smith, R. G.; Toft, D. O., Neergaard, J. R.; Burrows, E. P.; O'Malley, B. W. *J. Biol. Chem.* **1974**, *249*, 5924.
(13) Sherman, M. R.; Corvol, P. L.; O'Malley, B. W. *J. Biol. Chem.* **1970**, *245*, 6085.
(14) Korenman, S. G. *Steroids* **1969**, *13*, 163.
(15) Korenman, S. G. *Endocrinology* **1970**, *87*, 1119.
(16) Scatchard, G. *Ann. N.Y. Acad. Sci.* **1949**, *51*, 660.
(17) Wani, M. C.; Rector, D. H.; White, D. H.; Pitt, G. G.; Kimmel, G. L. *J. Med. Chem.* **1977**, *20*, 547.
(18) Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Biochem. Biophys. Res. Commun.* **1973**, *50*, 1152.
(19) Katzenellenbogen, J. A.; Johnson, H. J., Jr.; Myers, H. N. *Biochemistry* **1973**, *12*, 4085.
(20) Blue, M. L.; Williams, D. L. *Biochem. Biophys. Res. Commun.* **1981**, *98*, 785.

or antagonist activity at the level of sensitivity afforded by these assay procedures.

Experimental Section[21]

2-(6-(3-Methoxyphenyl)-3-oxohexyl)-2-(methoxycarbonyl)cyclopentanone (9). A solution of 1-(diethylamino)-6-(3-methoxyphenyl)hexan-3-one (27.7 g, 100 mmol), anhydrous 2-(methoxycarbonyl)cyclopentanone (15.6 g, 110 mmol), dry triethylamine (2.5 g), and acetic acid (1.0 mL) in dry benzene (250 mL) was stirred at reflux under N_2 for 48 h. Ether and aqueous citric acid were added to the cooled reaction mixture, and stirring was continued for 15 min. The ether layer was separated, washed with 10% citric acid solution (3 × 50 mL) followed by water, and repeatedly washed with 3% NaOH solution to remove unreacted keto ester. It was washed again with water, dried, and concentrated. The residual oil, dissolved in $CHCl_3$, was then filtered through 200 g of silica gel and the column was eluted with the same solvent. The eluate on concentration gave pure **9** as a viscous oil (26.0 g, 81.4%); TLC 5% EtOAc/CH_2Cl_2 R_f 0.55, 30% acetone/hexane R_f 0.45; IR (neat) 1745, 1725 cm^{-1}; NMR ($CDCl_3$) δ 7.12–6.65 (m, 4 H, Ar H), 3.70 (s, 3 H, Ar OCH_3), 3.62 (s, 3 H, $COOCH_3$), 3.0–1.4 (m, 16 H); mass spectrum, m/z 346.1755 (M^+, calcd for $C_{20}H_{26}O_5$, 346.1780).

Methyl 6,7,11,12,16,17-Hexahydro-3-methoxy-13*H*-cyclopenta[*a*]phenanthrene-13-carboxylate (10). 2-(6-(3-Methoxyphenyl)-3-oxohexyl)-2-(methoxycarbonyl)cyclopentanone (34.6 g, 100 mmol) in trifluoroacetic acid (200 mL) was stirred at room temperature for 15 min. At this point methylene chloride (200 mL) was added and the mixture was slowly neutralized with saturated $NaHCO_3$ solution. The organic layer was separated, washed twice with aqueous $NaHCO_3$ and then water, dried ($MgSO_4$), filtered, and concentrated to afford a solid, which on crystallization, from ether, gave **10** as yellow needles (25.4 g, 82%): mp 124–125 °C (lit.[6] mp 125–126 °C); TLC CH_2Cl_2 R_f 0.65, 10% EtOAc/hexane R_f 0.50; IR ($CDCl_3$) 1715 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (m, 1 H, H-1), 6.7 (m, 2 H, H-2 and H-4), 5.85 (m, 1 H, H-15), 3.77 (s, 3 H, Ar OCH_3), 2.9–1.2 (m, 15 H); mass spectrum, m/z 310.1562 (M^+, calcd for $C_{20}H_{22}O_3$, 310.1568).

Methyl 6,7,11,12,14,15,16,17-Octahydro-3-methoxy-13*H*-cyclopenta[*a*]phenanthrene-13-carboxylate (11a). To a solution of **10** (31.0 g, 100 mmol) in anhydrous pyridine (300 mL) was added 10% $Pd/CaCO_3$ (2.0 g) and the mixture was vigorously stirred under H_2. Absorption ceased after 1 mol of gas had been absorbed. The solution was filtered through Celite and pyridine was removed in vacuo. The crude product was dissolved in ether and washed several times with water, dried ($MgSO_4$), and concentrated. The residual solid was recrystallized from ether–pentane to afford the desired ester as colorless needles (28.0 g, 89.7%): mp 151–152 °C; TLC CH_2Cl_2 R_f 0.68, 10% EtOAc/hexane R_f 0.55; IR ($CDCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 7.05 (m, 1 H, H-1), 6.68 (m, 2 H, H-2 and H-4), 3.77 (s, 3 H, Ar OCH_3), 3.56 (s, 3 H, $COOCH_3$), 2.8–1.5 (m, 15 H); mass spectrum, m/z 312.1743 (M^+, calcd for $C_{20}H_{24}O_3$, 312.1715).

18-Hydroxy-3-methoxyestra-1,3,5(10),8-tetraene (11b). The ester (12.48 g, 40 mmol) from the preceding experiment was dissolved in anhydrous THF (150 mL) and added to a suspension of lithium aluminum hydride (3.0 g, 75 mmol) in anhydrous ether (100 mL). The mixture was stirred for 4 h and decomposed slowly with 20% aqueous NaOH solution. The precipitate was removed by filtration and washed with ether (100 mL), and the combined organic filtrates were washed with water, dried ($MgSO_4$), and concentrated. The solid thus obtained was recrystallized from ether to afford **11b** as plates (11.2 g, 98.8%; overall yield from **10**, 87%): mp 145–147 °C; TLC 10% EtOAc/CH_2Cl_2 R_f 0.55, 30% acetone/hexane R_f 0.40; IR ($CDCl_3$) 3600 cm^{-1}; NMR ($CDCl_3$) δ 8.7–7.0 (m, 1 H, H-1), 6.65 (m, 2 H, H-2 and H-4), 3.78 (s, 3 H, Ar OCH_3), 3.58–3.26 (m, 2 H, CH_2OH), 2.76–1.12 (m, 16 H); mass spectrum, m/z 284.1769 (M^+, calcd for $C_{19}H_{24}O_2$, 284.1776).

18-Hydroxy-3-methoxyestra-1,3,5(10)-triene (1). To a solution of **11b** (8.4 g, 30 mmol) in anhydrous tetrahydrofuran (200 mL) containing liquid ammonia (250 mL) and aniline (30 mL) was added slowly lithium metal (2.25 g) over a period of 30 min. The mixture was stirred for 3 h more and then decomposed by aqueous ammonium chloride and extracted with ether (3 × 150 mL). The extract was washed with water and 10% aqueous HCl followed by water, dried ($MgSO_4$), and concentrated to give a solid, which was recrystallized from ether–pentane to afford **1** as needles (6.6 g, 83.5%): mp 137–139 °C; TLC 10% EtOAc/CH_2Cl_2 R_f 0.50, 30% acetone/hexane R_f 0.40; IR ($CDCl_3$) 3600 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (d, J = 7.9 Hz, 1 H, H-1), 6.75–6.62 (m, 2 H, H-2 and H-4), 3.76 (s, 3 H, Ar OCH_3), 3.72–3.20 (m, 2 H, CH_2OH), 2.36–1.30 (m, 16 H); mass spectrum, m/z 286.1930 (M^+, calcd for $C_{19}H_{26}O_2$, 286.1926).

3,18-Dihydroxyestra-1,3,5(10)-triene (2). A solution of aluminum bromide (1.87 g, 7 mmol) in ethanedithiol (10 mL) was cooled to 0 °C and the solid alcohol **1** (1.00 g, 3.49 mmol) was added. The solution was allowed to come to room temperature slowly and stirred for 2 h, and the complex and excess aluminum bromide was decomposed by methanol. The organic solvents were removed under reduced pressure, water was added, and the mixture was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed sequentially with water, 5% HCl, and water, then dried ($MgSO_4$), and concentrated. The resulting solid was recrystallized from methanol to afford **2** as a white powder (800 mg, 84.1%): mp 220–223 °C; TLC 5% CH_3OH/CH_2Cl_2 R_f 0.35, 60% EtOAc/hexane R_f 0.55; IR (Nujol) 3500, 3150 cm^{-1}; NMR (Me_2SO-d_6) δ 8.95 (s, 1 H, ArOH), 7.04 (d, J = 7.8 Hz, 1 H, H-1), 6.52 (m, 2 H, H-2 and H-4), 4.20 (t, 1 H, CH_2OH), 3.1–2.8 (m, 2 H, CH_2OH), 2.76–2.11 (m, 17 H); mass spectrum, m/z 272.1762 (M^+, calcd for $C_{18}H_{24}O_2$, 272.1770). Anal. ($C_{18}H_{24}O_2$) C, H.

3-Methoxyestra-1,3,5(10)-triene (14). Butanethiol (240 mg, 3 mmol) was added to a solution of potassium (117 mg) in *tert*-butyl alcohol (20 mL), followed by the mesylate **12** (120 mg, 0.33 mmol). The mixture was heated under reflux overnight, decomposed by the addition of water, extracted with ether (2 × 50 mL), washed with water, dried ($MgSO_4$), and concentrated. This solution (10 mL) was passed through a silica gel (20g) column, which was eluted with methylene chloride, and concentrated to give the sulfide **13** (106 mg): NMR ($CDCl_3$) δ 7.13 (d, J = 8 Hz, 1 H, H-1), 6.75–6.32 (m, 2 H, H-2 and H-4), 3.70 (s, 3 H, OCH_3), 2.85–1.06 (m, 25 H), 0.8 (t, 3 H, CH_3). This was dissolved in ethanol (10 mL) and boiled for 30 min with Raney nickel (200 mg). Filtration followed by concentration and recrystallization of the resulting solid afforded **14** as needles (70 mg): mp and mmp (with authentic **14** from *d*-estrone) 76–77 °C (lit.[9] mp 75–76 °C); TLC 20% CH_2Cl_2/hexane R_f 0.55, 10% acetone/hexane R_f 0.50; NMR ($CDCl_3$) δ 7.13 (d, J = 7.2 Hz, 1 H, H-1), 6.72–6.35 (m, 2 H, H-2 and H-4), 3.70 (s, 3 H, Ar OCH_3), 3.0–2.5 (m, 3 H, benzylic H), 2.4–0.8 (m, 14 H), 0.66 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 157.271, 138.009, 133.046, 126.287, 113.704, 111.342, 55.170, 53.523, 44.030, 41.070, 40.509, 39.167, 38.824, 29.981, 28.122, 26.775, 25.207, 20.580, 17.558. The IR and ^1H and ^{13}C NMR spectra were identical with those of an optically active sample prepared by the Wolff-Kishner reduction[9] of *d*-estrone.

18-Hydroxy-3-methoxyestra-2,5(10)-diene (23). To a solution of **1** (5.7 g, 20 mmol) in tetrahydrofuran (80 mL) containing *tert*-butyl alcohol (80 mL) and liquid ammonia (300 mL) was added 2.5 g of lithium ribbon over a period of 45 min. The reaction mixture was stirred for 2 h and left overnight, then decomposed with aqueous ammonium chloride, and extracted with methylene chloride. The extract was washed with water, dried ($MgSO_4$), and concentrated and the residue was crystallized from ether–pentane to afford **23** as white plates (4.9 g, 85.4%): mp 140–142 °C; TLC 10% EtOAc/CH_2Cl_2 R_f 0.60, 30% acetone/hexane R_f 0.50; IR ($CDCl_3$) 3600 cm^{-1}; NMR ($CDCl_3$) δ 4.64 (t, 1 H, H-2), 3.68 and 3.27 (dd, J = 10.8 Hz, 2 H, CH_2OH), 3.54 (s, 3 H, Ar OCH_3); mass spectrum, m/z 288.2090 (M^+, calcd for $C_{19}H_{28}O_2$, 288.2082).

3,3-(Ethylenedioxy)-18-hydroxyestr-5(10)-ene (25). To a solution of the preceding diene **23** (4.00 g, 1.38 mmol) in methanol (150 mL) was added a solution of oxalic acid (3.2 g) in water (25 mL) and the mixture was stirred at room temperature for 40 min. Methanol was removed in vacuo, water was added, and organic material was extracted with methylene chloride (3 × 75 mL). The

(21) NMR spectra were measured on a Varian CFT-20 instrument and IR spectra were taken on a Perkin-Elmer 257 instrument. Mass spectra were taken on a Hewlett-Packard HP5983 GC/MS spectrometer (low resolution) or a Kratos MS-30 spectrometer (high resolution). Solvent mixtures for TLC systems are given on volume/volume basis. The purified compounds described in this paper showed a single spot in each of the two TLC systems that were examined for each substance.

extract was washed with 10% $NaHCO_3$ solution and water, then dried ($MgSO_4$), and concentrated to afford the ketone **24** (3.0 g, 89.3%); IR ($CDCl_3$) 3600, 1710 cm^{-1}; NMR ($CDCl_3$) 3.69 and 3.28 (dd, J = 11.5 Hz, 2 H, CH_2OH), 2.0–0.8 (m, 23 H). To a solution of the latter in benzene (100 mL) were added ethylene glycol (10 mL) and fumaric acid (0.5 g), and the mixture was heated under reflux for 4 h, using a water separator. Saturated $NaHCO_3$ solution was added and the mixture was extracted with ether (3 × 50 mL). The extract was washed with water, dried ($MgSO_4$), and concentrated to afford **25**, which was crystallized from ether–pentane (2.85 g, 81.80%): mp 188–190 °C; TLC 20% EtOAc/CH_2Cl_2 R_f 0.40, 40% acetone/hexane R_f 0.38; IR ($CDCl_3$) 3600 cm^{-1}; NMR ($CDCl_3$) δ 3.97 (m, 4 H, OCH_2CH_2O), 3.68 and 3.22 (dd, J = 12 Hz, 2 H, CH_2OH), 2.0–0.8 (m, 23 H); mass spectrum, m/z 318.2196 (M^+, calcd for $C_{20}H_{30}O_3$, 318.2187).

13-(1-Hydroxy-1-prop-2-ynyl)gona-4-en-3-ones (4a and 4b). To a suspension of pyridinium chlorochromate (750 mg) in anhydrous methylene chloride (60 mL) under nitrogen was added a solution of **25** (750 mg, 2.35 mmol) in methylene chloride (30 mL) in one portion. The reaction mixture was stirred for 1 h and then poured through a column of Florisil (25 g) under nitrogen. Elution with methylene chloride led to a viscous oily product, which was used directly in the next step because it decomposed rapidly on standing. Acetylenemagnesium bromide was prepared by adding a THF solution of ethylmagnesium bromide (from Mg (350 mg) and ethyl bromide (2 mL) to a saturated solution of acetylene in tetrahydrofuran (50 mL) at 0 °C. A stream of acetylene gas was then passed through this solution while a solution of the aldehyde, obtained above, was added in the same solvent (25 mL). The reaction mixture was stirred for 1 h and then heated under reflux for 2 h. The solvent was removed under reduced pressure, methylene chloride and aqueous ammonium chloride were added to the residue, and the organic layer was then separated, washed with water, dried ($MgSO_4$), and concentrated to afford a yellow oil. Trituration with hexane then gave a mixture of the desired dioxolanes (**27a,b**; 580 mg) as a crude yellow solid. This was then dissolved in methanol (25 mL), 3 N HCl (25 mL) was added, and the solution was stirred for 4 h. The precipitated product was removed by filtration, dissolved in methylene chloride, washed with water, dried ($MgSO_4$), and concentrated to afford **4** as a 3:2 mixture of diastereomers (510 mg, 71.6%). On repeated crystallization from methylene chloride the major isomer **4a** was obtained as needles: mp 222–224 °C; TLC 10% EtOAc/CH_2Cl_2 R_f 0.55, 30% acetone/hexane R_f 0.45; IR ($CDCl_3$) 3600, 3300 cm^{-1}; NMR ($CDCl_3$) δ 5.84 (1 H, olefinic H), 4.76 (dd, J_1 = 1.8 Hz, J_2 = 6.3 Hz, 1 H, CHOH), 2.52 (d, J = 2.2 Hz, 1 H, C≡CH), 2.4–1.0 (m, 22 H); mass spectrum, m/z 298.1931 (M^+, calcd for $C_{20}H_{26}O_2$, 298.1926). Anal. ($C_{20}H_{26}O_2$) C, H. The second isomer **4b** was obtained by preparative TLC on silica gel, using 10% ethyl acetate in methylene chloride as the eluant: needles, mp 196–197 °C; TLC 10% EtOAc/CH_2Cl_2 R_f 0.50, 30% acetone/hexane R_f 0.45; IR ($CDCl_3$) 3600, 3300 cm^{-1}; NMR ($CDCl_3$) δ 5.83 (s, 1 H, olefinic H), 4.58 (dd, J_1 = 1.8 Hz, J_2 = 5.0 Hz, 1 H, CHOH), 2.48 (d, J = 2.2 Hz, 1 H, C≡CH), 2.5–1.0 (m, 22 H). Anal. ($C_{20}H_{26}O_2$) C, H.

13-(1-Acetoxy-2-oxo-1-propyl)gona-4-en-3-one (5). A solution of the acetylenic alcohol **4a** (56 mg) and mercuric acetate (120 mg) in ethyl acetate (200 mL) was stirred for 36 h under nitrogen. Hydrogen sulfide was passed through the solution for 30 min and the precipitate was removed by filtration through Celite. The filtrate was concentrated and the residue was crystallized from ether–pentane to furnish **5** as white needles (38 mg, 70.8%): mp 164–166 °C; TLC 10% EtOAc/CH_2Cl_2 R_f 0.60, 30% acetone/hexane R_f 0.48; IR ($CDCl_3$) 1750, 1725, 1660 cm^{-1}; NMR ($CDCl_3$) δ 5.84 (s, 1 H, olefinic H), 5.31 (s, 1 H, $CH_3COCHOCOCH_3$), 2.20 (s, 3 H, $OCOCH_3$), 2.13 (s, 3 H, $COCH_3$), 2.6–1.0 (m, 21 H); mass spectrum, m/z 358.2127 (M^+, calcd for $C_{22}H_{30}O_4$, 358.2136). Anal. ($C_{22}H_{30}O_4$) C, H.

18-Cyano-3-methoxyestra-1,3,5(10)-triene (17). To a solution of **1** (3.62 g, 1 mmol) in pyridine (25 mL) was added methanesulfonyl chloride (1.61 g, 1.5 mmol) and the mixture stirred overnight. Excess pyridine was removed in vacuo and then aqueous ammonium chloride was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The extract was washed with water, dried ($MgSO_4$), and concentrated to afford the mesylate **12** (3.6 g, 75.6%): mp 152–154 °C; NMR ($CDCl_3$) δ 7.2 (d, J = 7.9 Hz, 1 H, H-1), 6.75–6.62 (m, 2 H, H-2 and H-4), 4.23 and 3.80 (dd, J = 11.7 Hz, 2 H, $CH_2OSO_2CH_3$), 3.77 (s, 3 H, Ar OCH_3), 2.97 (s, 3 H, SO_2CH_3), 2.2–1.2 (m, 17 H). To a solution of this material (3.6 g) in HMPA (100 mL) containing water (1 mL) was added sodium cyanide (2.0 g) and the mixture was heated at 110 °C for 40 h under nitrogen. Water was added and the product was isolated in the usual way with use of ether (3 × 50 mL) as the extractant. The material crystallized from ether–pentane to afford **17** as needles (2.11 g, 70%; overall yield from **1**, 55%): mp 132–133 °C; TLC 50% CH_2Cl_2/hexane R_f 0.55, 10% acetone/hexane R_f 0.35; IR (Nujol) 2200 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 1 H, H-1), 6.72–6.61 (m, 2 H, H-2 and H-4), 3.70 (s, 3 H, Ar OCH_3), 2.8–1.0 (m, 19 H); mass spectrum, m/z 295.1918 (M^+, calcd for $C_{20}H_{25}NO$, 295.1929).

18-Formyl-3-methoxyestra-1,3,5(10)-triene (18). To a solution of KOH (1 g) in ethylene glycol (100 mL) containing water (2 mL) was added nitrile **17** (1.4 g, 4.74 mmol) and the mixture was boiled for 3 days under nitrogen. The clear solution was cooled and washed twice with ethyl acetate. The aqueous layer was acidified with dilute HCl and extracted with ethyl acetate, and the organic layer after separation was washed with water, dried ($MgSO_4$), and concentrated to afford the acid as a solid. This crystallized from ether–pentane as needles (1.24 g, 83.9%): mp 171–174 °C; IR ($CDCl_3$) 1700 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (d, J = 7.9 Hz, 1 H, H-1), 6.75–6.62 (m, 2 H, H-2 and H-4), 3.77 (s, 3 H, Ar OCH_3), 2.88 (brs, 2 H, CH_2COOH), 2.0–1.1 (m, 17 H). A solution of this acid (1.25 g, 3.9 mmol) in 50 mL of ether was added to a suspension of lithium aluminum hydride (400 mg) in anhydrous ether (50 mL). The mixture was stirred for 6 h and excess of reductant was decomposed with aqueous NaOH solution. The precipitate was removed by filtration and the ether layer was worked up in the usual way to afford the alcohol corresponding to aldehyde **18**, as a solid. This crystallized from ether–pentane to give needles (1.1 g, 92.1%): mp 100–101 °C; IR ($CDCl_3$) 3600 cm^{-1}; NMR ($CDCl_3$) δ 7.19 (d, J = 8.2 Hz, 1 H, H-1), 6.76–6.62 (m, 2 H, H-2 and H-4), 3.76 (s, 3 H, Ar OCH_3), 3.79–3.59 (m, 2 H, CH_2OH), 3.0–2.5 (m, 2 H, CH_2CH_2OH), 2.3–1.00 (m, 17 H). To a suspension of pyridinium chlorochromate (1.00 g) in anhydrous methylene chloride (50 mL) was added the above alcohol (1.1 g, 3.66 mmol) in the same solvent (10 mL) in one portion. The mixture stirred for 2 h, and the chromium salts were removed by percolation through a column of Florisil. The eluate was concentrated and the residue on trituration with pentane gave **18** as a colorless solid (1.03 g, 93%; overall yield from **17**, 67.5%): mp 90–91 °C; IR ($CDCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 9.85 (s, 1 H, CHO), 7.25 (d, J = 7.9 Hz, 1 H, H-1), 6.75–6.62 (m, 2 H, H-2 and H-4), 3.77 (s, 3 H, OCH_3), 2.5–0.8 (m, 19 H); mass spectrum, m/z 298.1935 (M^+, calcd for $C_{20}H_{26}O_2$, 298.1926).

13-(2-Oxopropyl)gona-4-en-3-one (3). To a solution of methylmagnesium iodide (made from Mg (200 mg) and methyl iodide (2.4 g)) was added dropwise the aldehyde **18** (1.00 g, 3.35 mmol) in ether (50 mL) and the mixture stirred for 5 h. The product was decomposed with aqueous ammonium chloride and worked up with ether (2 × 50 mL) in the usual way to afford the alcohol **21** (1.0 g, 95%). To a solution of this compound (628 mg, 2 mmol) in tetrahydrofuran (50 mL) containing *tert*-butyl alcohol (5 mL) and liquid ammonia (100 mL) was added very slowly lithium metal (70 mg, 10 mmol) and the reaction was left overnight. The mixture was then decomposed with aqueous ammonium chloride and extracted with methylene chloride (3 × 30 mL), and the extract washed with water, dried, and concentrated to afford the 1,4-dihydro derivative of **20** (575 mg). This was dissolved in methanol (30 mL), 3 N HCl (25 mL) was added, and the solution was kept at 60 °C for 45 min. Methanol was removed in vacuo, the residual liquid was extracted with methylene chloride (2 × 50 mL), and the product was isolated in the usual way to afford the unsaturated keto alcohol **22** as a white solid (522 mg). This was dissolved in methylene chloride (50 mL) and added in one portion to a suspension of pyridinium chlorochromate (600 mg) in the same solvent (25 mL) and the mixture was stirred for 1 h. The liquid phase was then decanted from solids and passed through a column of Florisil (25 g). The column was eluted with methylene chloride, and the combined eluates were concentrated to afford the desired product **3**, as a solid, which recrystallized from ether–pentane as white needles (400 mg, 93%; overall yield from **20**, 77.4%): mp 177–178 °C; TLC 10% EtOAc/CH_2Cl_2 R_f 0.60, 30% acetone/

hexane R_f 0.45; IR ($CDCl_3$) 1710, 1690 cm^{-1}; NMR ($CDCl_3$) δ 5.86 (s, 1 H, olefinic H), 2.17 (s, 3 H, $COCH_3$), 2.5–1.0 (m, 23 H); mass spectrum, m/z 300.2076 (M^+, calcd for $C_{20}H_{28}O_2$, 300.2082). Anal. ($C_{20}H_{28}O_2$) C, H.

13-(2-Oxopropyl)-3-methoxygona-1,3,5(10)-triene (19). To a solution of methylmagnesium iodide (made from Mg (48 mg, 2 mmol) and methyl iodide (580 mg, 2.2 mmol) in ether (25 mL) was added a solution of 17 (295 mg, 1 mmol) in anhydrous tetrahydrofuran (5 mL) and the mixture was stirred overnight. HCl (50%) was added and the mixture was stirred for 15 min. Isolation of the product by the standard procedure using ether extraction (2 × 50 mL) gave a viscous oil. This was purified by column chromatography on silica gel, using methylene chloride as the eluant, and led to a solid which on crystallization from ether–pentane afforded 19 as needles (118 mg, 37.8%): mp 122–123 °C; TLC CH_2Cl_2 R_f 0.45, 10% EtOAc/Hexane R_f 0.40; IR ($CDCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.12 (d, J = 7.9 Hz, 1 H, H-1), 6.70–6.60 (m, 2 H, H-2 and H-4), 3.70 (s, 3 H, Ar OCH_3), 2.15 (s, 3 H, $COCH_3$), 2.7–1.0 (m, 17 H); mass spectrum, m/z 312.2090 (M^+, calcd for $C_{21}H_{28}O_2$, 312.2082).

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Registry No. (±)-1, 90194-69-7; (±)-2, 90194-70-0; (±)-3, 90194-71-1; (±)-4a, 90194-72-2; (±)-4b, 90194-73-3; (±)-5, 90194-74-4; 6, 89321-99-3; (±)-7, 90194-75-5; 8, 3706-69-2; (±)-9, 90194-76-6; (±)-10, 90194-77-7; (±)-11a, 90194-78-8; (±)-11b, 90194-79-9; (±)-12, 90194-80-2; (±)-13, 90194-81-3; (±)-14, 64479-52-3; (±)-15, 90194-82-4; (±)-17, 90194-83-5; (±)-17 (acid), 90194-84-6; (±)-18, 90194-85-7; (±)-18-ol, 90194-86-8; (±)-19, 90194-87-9; (±)-20 (S alcohol), 90194-88-0; (±)-20 (R alcohol), 90194-96-0; (±)-21 (S alcohol), 90194-89-1; (±)-21 (R alcohol), 90194-97-1; (±)-22 (S alcohol), 90194-90-4; (±)-22 (R alcohol), 90194-98-2; (±)-23, 90194-91-5; (±)-24, 90194-92-6; (±)-25, 90194-93-7; (±)-18R-27a, 90194-94-8; (±)-18S-27b, 90194-95-9; 2-(methoxycarbonyl)cyclopentanone, 10472-24-9; butanethiol, 109-79-5; acetylenemagnesium bromide, 4301-14-8; methyl iodide, 74-88-4; ethylene glycol, 107-21-1.

Synthesis and Neuroleptic Activity of *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulfonamidobenzamides

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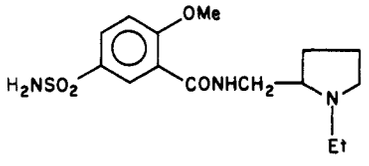
A series of some novel *N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamides involving replacement of the sulfamoyl group in sulpiride with a sulfonamido group was synthesized and tested for dopamine receptor blockade. In comparison with sulpiride, several compounds were considerably more potent than sulpiride as dopamine receptor blockers. The structure–activity relationships are discussed.

Sulpiride has been reported to be an effective antipsychotic agent and displays marked pharmacological differences from those of the "classical" neuroleptic drugs, e.g., haloperidol and chloropromazine.[1]

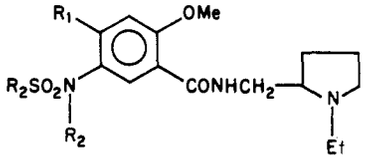
Sulpiride has a relatively low neuroleptic potency in both animals[1,2] and humans,[3] which could be due to a low degree of biological availability[4] including low penetration into the brain.[5] Thus, it should be of interest to synthesize and evaluate other types of neuroleptic benzamides[2,6] modified from sulpiride.

The present paper describes modifications involving replacement of the sulfamoyl residue in sulpiride with a sulfonamido residue, as shown in the general formula I.

Chemistry. A number of benzamides were synthesized by methods A–G from known 5-nitroanisic acids (**1a**,[7] **1b**,[8]



sulpiride



I

1c[9]) as depicted in Scheme I.

2-Methoxy-4-substituted-5-nitrobenzoic acids (**1a–c**) were esterified with methanol via the acid chlorides and gave the methyl esters that on treatment with tin/hydrochloric acid or catalytic hydrogenation on platinum catalyst were reduced to the 2-methoxy-4-substituted-5-aminobenzoic acid methyl esters. Treatment of the above products with methanesulfonyl chloride gave the 5-methanesulfonamidobenzoic acid methyl esters (**2a–c**). Compounds **2a–c** were methylated with dimethyl sulfate in the presence of potassium carbonate in acetone and

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