Table II. Antihypertensive Activity of Compounds in Unanesthetized Renal Hypertensive Dogs (RHD)

compd	dose, mg/kg po		max Δ in BP[a] day 1	day 2	day 3	day 4
22	100	MBP:	−32 ± 10.8	−14 ± 16.2	−13 ± 16.1	−6 ± 13.6
		HR:	+74 ± 12.5*	+61 ± 13.2	+52 ± 13.6	+48 ± 28.6
34	100	MBP:	−30 ± 8.5	−46 ± 18.4	−56 ± 5.0*	−51 ± 5.2*
		HR:	+35 ± 12.7	+78 ± 17.2	+51 ± 13.5	+44 ± 10.1*
54	100	MBP:	−15 ± 6.8	−9 ± 1.7*	−4 ± 1.8	
		HR:	+16 ± 10.6	+11 ± 12.7	+11 ± 12.7	
55	100	MBP:	−21 ± 16.0	−25 ± 7.5		
		HR:	+1 ± 8.1	+39 ± 2.3		
65	100	MBP:	−69 ± 13.7*	−41 ± 0.3*	−49 ± 2.9*	−48 ± 9.0*
		HR:	+37 ± 10.7	+60 ± 13.1*	+52 ± 18.6	+41 ± 37.0
71	100	MBP:	+11 ± 6.1	−67 ± 5.2*	−40 ± 15.5	
		HR:	+20 ± 8.0	+112 ± 22.0*	+107 ± 8.1*	
fusaric acid	60	MBP:	−50 ± 7	−45 ± 12	−30 ± 7	
		HR:	+32 ± 18	+35 ± 17	+33 ± 5	

[a] Values are mean ± SE; an asterisk indicates $p < 0.05$. MBP = mean blood pressure (mm Hg); HR = heart rate (beats/min).

sensor was attached to a pneumatic pulse transducer (Narco Bio Systems), and a solenoid-controlled manifold connected to a blood pressure cuff pump (Narco Bio Systems) was calibrated to deliver a maximum air pressure of 250 mmHg. Upon completion of all connections, the chamber door was closed and a warm-air delivery system turned on. The system was electrically modified to heat upon demand of a thermistor probe within the chamber to maintain a temperature of 32.5 ± 0.5 °C. Air volume was such as to exchange three chamber volumes per minute. Animals were allowed to acclimate for 1 h to ensure adequate circulation in the tail. During this time, pressure calibration was checked and set on each of the electrophygmographs (Narco Bio Systems).

After 1 h of acclimation at least three systolic blood pressure readings were taken on each group of animals. Pressure in the occlusion cuff was raised to 250 mmHg, so that arterial pulse displacements were no longer apparent, and then gradually lowered. The systolic pressure was identified by th location of the point that the pulse reemerged. Heart rates were determined by counting the pressure pulses.

All drugs were administered at a standard dose of 50 mg/kg (in some cases also at 100 and 25 mg/kg) by gavage in a mixture containing 3% cornstarch, 5% PEG-400, and 1 drop of Tween 80 per milliliter.

Animals were dosed daily for either 2 or 4 consecutive days with four to six rats used for each drug studied. Blood pressures were recorded at 1, 2, 3 and 24 h after each drug administration. Reported antihypertensive activity represented peak falls in pressure.

Antihypertensive Assay in Renal Hypertensive Dogs. Male mongrel dogs were made hypertensive by unilateral nephrectomy and either renal artery constriction[12] or kidney encapsulation[13] on the contralateral side.

Four to six weeks were allowed to elapse after experimental surgery for convalescence and the establishment of elevated blood pressure. Animals were trained to lie quietly in a supine position while their blood pressure was measured by direct femoral artery puncture with a 22-gauge, 1-in. hypodermic needle connected by polyethylene tubing to a Statham 23AA pressure transducer and displayed on a Sanborn recorder. Heart rate was counted manually. Drugs were given orally once daily in solid form by gelatin capsule. Blood pressures were determined at 1.5, 3, 6, and 24 h after each drug administration with reported activity represented by maximum changes in blood pressure and heart rate over a daily monitored session.

Acknowledgment. We acknowledge the support and encouragement of Dr. Max Wilhelm and helpful discussions with Professor Peter Yates. We thank G. Robertson for microanalyses, Ms. R. Behnke for NMR spectra, and Ms. N. Cahoon for IR and UV spectra.

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Synthesis and Antifertility Activity of 3,9-Dihydroxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a*,*g*]biphenylene, a Structural Relative of Diethylstilbestrol

P. H. Ruehle, C. E. Browne,[1a] E. H. Vickery,[1b] N. R. Beller, E. J. Eisenbraun,*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078

R. A. Loghry, and Dick van der Helm

Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019. *Received February 8, 1980*

The title diphenol, **1a**, was synthesized from *p,p'*-dihydroxy-α-truxillic acid and shown to be active as an oral postcoital antifertility agent in rats: ED_{100} = 100 (μg/kg)/day. The oral uterotropic potency was estimated to be 16% of that of diethylstilbestrol (95% confidence limits of potency 8–35%). The structure of the diphenol, **1a**, was confirmed by single-crystal X-ray analysis of the dimethyl ether.

Despite the widespread use of antifertility drugs, some of the currently available ones exhibit undesired estrogenic side effects.[2] The apparent structural relationship of 3,9-dihydroxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodi-

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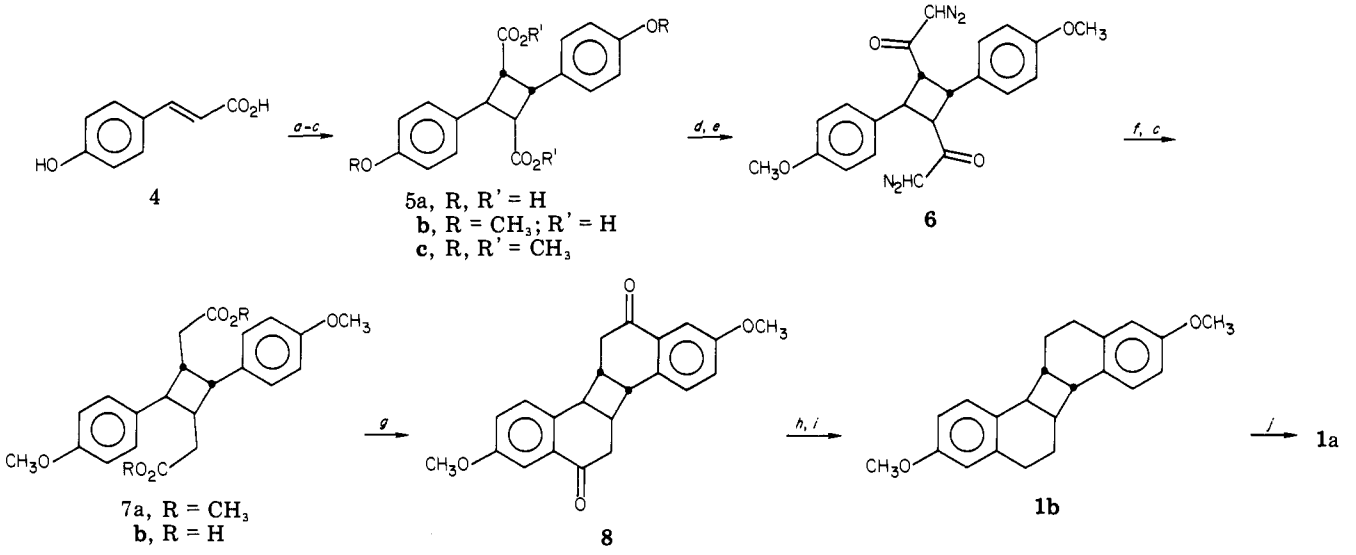
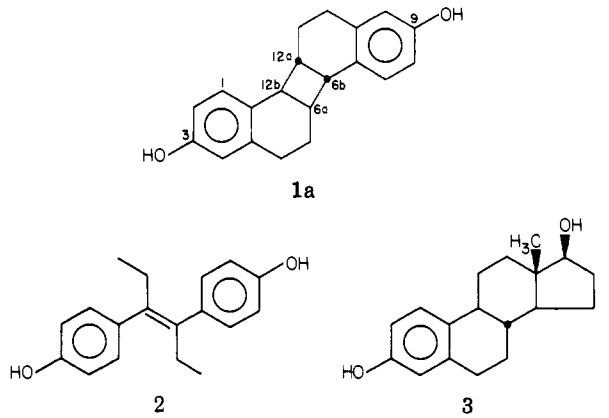
Scheme I



[a] hν, H_2O. [b] Dimethyl sulfate, OH^-. [c] OH^-, H^+. [d] $SOCl_2$, Py. [e] CH_2N_2. [f] $C_6H_5CO_2Ag$, $(C_2H_5)_3N$, CH_3OH. [g] PPA, Δ. [h] Raney Ni, EtOAc. [i] H_2, Pd/C, HOAc, Δ. [j] BBr_3, CH_2Cl_2.

Chart I. Structural Relationship between Diphenol 1a, DES (2), and Estradiol (3)



benzo[a,g]biphenylene (**1a**) to diethylstilbestrol (**2**, DES) and estradiol (**3**) (Chart I) encouraged us to develop a stereospecific synthesis of **1a** to determine if structures of this type would provide significant postcoital antifertility activity with reduced estrogenic activity. Although estrogenicity generally parallels antifertility activity, some success has been achieved in separating these effects.[3]

Chemistry. The synthesis of diphenol **1a** is shown in Scheme I. The photodimerization of 4-hydroxycinnamic acid (**4**) fixes the stereochemistry of the cyclobutane ring.[4] It should be noted that all of the reaction products shown in Scheme I possess a center of symmetry and that any disturbance of this stereochemistry would result in diastereomeric products. Subsequent single-crystal X-ray analysis[5] of **1b** verified its structure and the stereochemical assignments in Scheme I.

Large-scale preparation (Scheme I) of **5a** was accomplished by exposure of a well-stirred and finely divided slurry of **4** in water to Pyrex-filtered UV light.[4,6] Methylation of **5a** directly provided the dimethoxy diester **5c**[4] and its hydrolysis gave the diacid **5b**. Bishomologation of **5b** was accomplished through the Arndt–Eistert reaction[7] involving steps d, e, and f. The intermediate bis(diazo ketone) **6** was sufficiently stable at room temperature to allow collection of spectral data. It was rearranged to the dimethyl ester **7a** using a silver benzoate–triethylamine catalyst in anhydrous methanol,[8] which proved superior to silver nitrate, sodium thiosulfate, and water[9] in effecting the Wolff rearrangement of **6**. The diester **7a** was purified by chromatography on activated acidic alumina[10] and hydrolyzed to the diacid **7b** to give a 53% overall yield for the steps **5b** → **6** → **7a** → **7b**.

Cyclization of **7b** to **8**, which gave the desired carbon skeleton, was accomplished in 82% yield with PPA.[11] The reaction conditions are critical and variation of time or temperature resulted in decreased yields. Aluminum chloride-catalyzed cyclization via the acid chloride of **7b** in benzene solution gave a lower yield (55%) of **8**.

Hydrogenolysis of **8** with Pd/C in acetic acid[12] afforded **1b**. Initial hydrogenolysis attempts were unsuccessful with **8** being recovered. This was overcome by prior treatment of **8** with freshly prepared Raney Ni catalyst[13] in refluxing ethyl acetate, which provides samples of **8** that readily hydrogenolyzed to **1b**.[14,15] The catalyst-deactivating contaminant probably resulted from earlier use of thionyl

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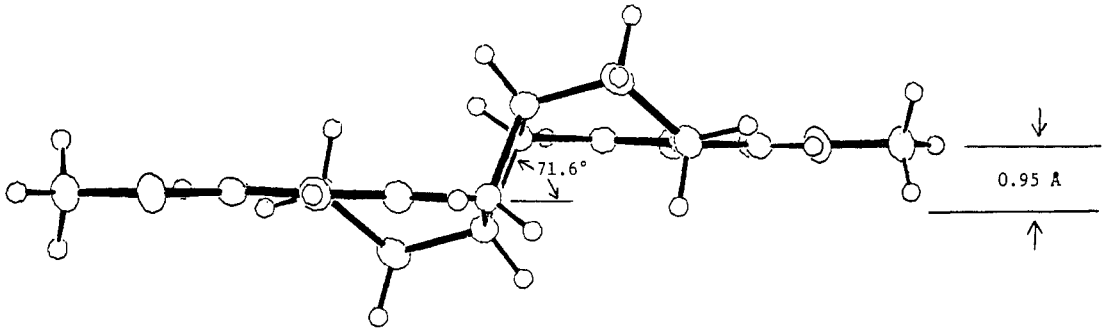

Figure 1. Computer-generated side view of dimethyl ether 1b.

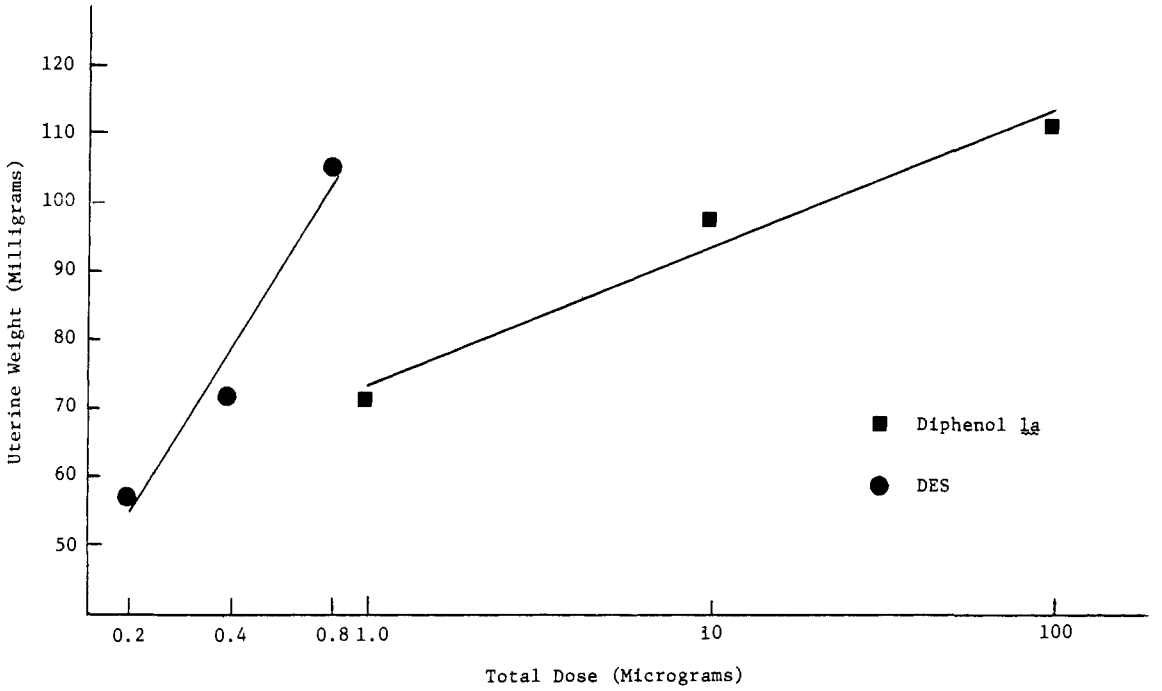

Figure 2. Oral uterotropic response.

chloride during the Arndt–Eistert procedure.

The stereochemistry and structure of **1b** and, hence, that of **1a** and other products were verified through single-crystal X-ray analysis[5] of 1b, which provided the detailed structural information shown in Figure 1. An important feature is the planar cyclobutane ring. In contrast, most four-membered rings are puckered.[16] An appreciation of the general shape and the stair-step geometry of 1b can be gained from the side view presented in Figure 1. Again, the nearly vertical and planar cyclobutane ring is a dominant feature. It follows that the two phenolic rings are rigidly held in parallel planes with a 0.95 Å separation. In addition, the precise oxygen–oxygen distance (12.9 Å) for **1a** became available, which permits comparison with the corresponding dimensions of diethylstilbestrol (2) and estradiol (3), 12.1 and 10.9 Å, respectively.[17a] Although compound 1b is pentacyclic, the cyclobutane ring does not contribute appreciably to the overall oxygen–oxygen distance in the molecule due to the nearly vertical orientation (71.6°) of the planar cyclobutane ring.

Duax et al. have provided a detailed study of structure and estrogenic activity of numerous natural and synthetic estrogenic agents.[17b] They have concluded that the oxygen–oxygen distance is not as important as was previously believed. The current criteria included having one phenolic ring for binding at the estrogen receptor and a second moiety (D ring or second phenolic ring) available for interaction during subsequent events. Structural alteration and binding capability of the latter can determine estrogen–antiestrogen effects. These effects can also be influenced by conformational changes.

Biological Activity. The estrogenic activity of diphenol **1a** was estimated using an uterotropic assay.[18] The potency of **1a** administered orally to rats was estimated to be 16% of that of DES (95% confidence limits of potency 8–38%). The graph (Figure 2) of the average uterine weight (mg) vs. log of the total dose (μg of **1a** in sesame oil for 5 days) exhibits a fairly linear response in the doses 1, 10, and 100 μg. Responses to the dose of 1000 μg were not used for potency estimation. Data for the DES standard were obtained from doses of 0.2, 0.4, and 0.8 μg.[19a]

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The oral postcoital antifertility activity of **1a**, expressed as the minimum effective dose for completely preventing implantation, was 100 (μg/kg)/day (administered for 5 consecutive days). A dose of 50 (μg/kg)/day allowed two pregnancies out of ten (three normal fetuses). In comparison, under the same conditions, DES shows an oral ED_{100} of 36 (μg/kg)/day.[19a] Based on these results, the displacement of the A and B rings from the plane of the C and D rings, while reducing the uterotropic activity, does not abolish the postcoital antifertility activity. These activities suggested[19b] that **1a** might be active as an antitumor agent. Studies comparing parenterally administered **1a** and DES in the 11095 transplantable carcinoma of the Fischer rat prostate[19b,c] indicate that **1a** shows antitumor activity (about one-tenth of DES) but that this activity does not exceed that expected from the estrogenic activity of **1a** compared with that of DES.

Experimental Section

Chemical Synthesis. ^1H NMR spectra were obtained on a XL-100-15 Varian instrument using $CDCl_3$ (unless otherwise specified) as a solvent and Me_4Si as an internal standard. Chemical shifts are expressed in δ units. IR spectra were obtained on a Beckman IR-5A spectrophotometer. Ultraviolet spectra were obtained in 95% ethanol using a Cary 14 spectrophotometer. Mass spectra were obtained on a Consolidated Electrodynamics Corp. Model 21-110B mass spectrometer. Our report of mass spectral data is restricted to hemicleavage which is a characteristic and dominant feature in this series. Elemental analyses were carried out by Galbraith Laboratories. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not corrected.

2α,4β-Bis(4-hydroxyphenyl)cyclobutane-1α,3β-dicarboxylic Acid (5a). (*E*)-4-Hydroxycinnamic acid (**4**;[4] 300 g, 1.83 mol) and 5.5 L of H_2O were mixed portionwise in a 1-gal. Waring Blendor. The resulting finely divided suspension was added to a cylinder housing a quartz water-jacketed immersion well containing a 450-W Hanovia lamp and Pyrex filter. The stirred slurry was irradiated for 7 days (the side of the well was cleaned intermittently and H_2O added to maintain the level of the slurry as needed). The resulting product was collected by filtration, dried, and extracted with ether in a Soxhlet apparatus to remove unreacted **4**, leaving a residue of 270 g (90%) of diacid **5a**, mp 335 °C dec. A small sample recrystallized from 95% ethanol had mp 350 °C dec (lit.[4] mp 340 °C).

2α,4β-Bis(4-methoxyphenyl)cyclobutane-1α,3β-dicarboxylic Acid (5b). To a stirred solution of 1000 g (3.1 mol) of diacid **5a** in 6.25 L of 2 M NaOH under a N_2 atmosphere was added 1530 g (12 mol) of dimethyl sulfate over a period of 1 h, during which time the temperature rose to 50 °C. During 0.5 h of additional stirring of the solution, the pH dropped to 6. A solution of 200 mL of 7.5 M NaOH was added, followed by the dropwise addition of 190 g (1.5 mol) of dimethyl sulfate. After 0.5 h of stirring, the mixture again became acidic. The addition of base and dimethyl sulfate was repeated three times. The reaction mixture was then made strongly basic by the addition of 1.5 L of 12 M NaOH and then slowly heated to 80 °C. This temperature was maintained for 4 h, and then the homogenous solution was filtered through Dicalite and acidified. The product was collected by filtration and dried to give 1003 g (95%) of **5b**, mp 255–260 °C. Recrystallization of a small sample from acetic acid gave **5b**, mp 260–261 °C (lit.[4] 260.5–262.5 °C).

1α,3β-Bis(diazoacetyl)-2α,4β-bis(4-methoxyphenyl)cyclobutane (6). To a stirred slurry of 190 g (0.53 mol) of diacid **5b** in 1.5 L of benzene containing 3 mL of pyridine was added 175 mL (2.4 mol) of $SOCl_2$. The mixture was cautiously warmed until gas evolution started and then refluxed for 1 h. The warm solution was filtered through Dicalite, and the solvent and excess $SOCl_2$ were then removed under reduced pressure. The residue was dissolved in warm benzene, passed through a small column of acidic alumina,[10] and concentrated under reduced pressure, leaving 192 g (92%) of the acid chloride, mp 145–147 °C.

A solution of 60 g (0.15 mol) of the acid chloride of diacid **5b** in 600 mL of benzene was added dropwise with stirring to a chilled (0 °C) solution of 32 g (0.76 mol) of CH_2N_2 in 2 L of ether.[7] This mixture was stirred overnight and then evaporated to a small volume. The solid was collected by filtration and washed with ether to give 54 g (87%) of bis(diazo ketone) **6**. An analytical sample was prepared by recrystallization from $CHCl_3$–isohexane:[20] mp 143 °C dec; IR ($CHCl_3$) 2090, 1620 ($COCHN_2$) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (m, 4, Ar H), 6.82 (m, 4, Ar H), 4.88 (s, 2, CHN_2), 4.50 (m, 2, Ar CH), 3.80 (m, 2, *CH*$COCHN_2$), 3.76 (s, 6, Ar OCH_3); MS (70 eV) *m/e* $M^+/2$ (hemicleavage), 174 (100).

1α,3β-Bis(carbomethoxymethyl)-2α,4β-bis(4-methoxyphenyl)cyclobutane (7a) and Diacid (7b). To a magnetically stirred slurry of 145 g (0.36 mol) of bis(diazo ketone) **6** in 1.5 L of anhydrous CH_3OH was added dropwise a solution of 6.0 g of silver benzoate in 48 mL of $(C_2H_5)_3N$ at a rate sufficient to maintain a slow steady evolution of N_2.[8] After 24 h, N_2 evolution ceased and the mixture was heated to reflux for 0.5 h and then filtered while hot through Dicalite. The filtrate was evaporated and dried under reduced pressure. The residue was dissolved in benzene and chromatographed over acidic alumina. The eluate was concentrated, the residue was triturated with ether, and the solid was collected by filtration to give, after drying, 102 g (69%) of diester **7a**, mp 110–115 °C. An analytical sample was prepared by recrystallization from methanol: mp 120–121 °C; IR (KBr) 1720 (CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (m, 4, Ar H), 6.86 (m, 4, Ar H), 3.78 (s, 6, Ar OCH_3), 3.48–3.30 (m, 4, *CHCH*), 3.40 (s, 6, CO_2CH_3), 2.40–2.10 (m, 4, $CH_2CO_2CH_3$); MS (70 eV), *m/e* $M^+/2$ (hemicleavage), 206 (100). Anal. ($C_{24}H_{28}O_6$) C, H.

Hydrolysis of diester **7a** (101 g, 2.45 mol) with methanolic NaOH gave, after workup, 90.1 g (96%) of the diacid **7b**, mp 240–243 °C. Recrystallization from 2-propanol gave **7b**: mp 248–250 °C; IR (KBr) 3000 (Br, OH), 1700 (CO) cm^{-1}; MS (70 eV), *m/e* $M^+/2$ (hemicleavage), 192 (77). Anal. ($C_{22}H_{24}O_6$) C, H.

3,9-Dimethoxy-6aα,6bβ,12aβ,12bα-tetrahydrodibenzo[a,g]biphenylene-5,11(6*H*,12*H*)-dione (8). To 250 mL of polyphosphoric acid (11.5% P_2O_5),[11] prewarmed to 65 °C, was added over 5 min 30 g (0.078 mol) of finely powdered diacid **7b**. The mixture was stirred for 35 min and warmed to 70 °C. The contents of the flask were then poured into a slurry of ice and H_2O in a Waring Blendor and stirred until hydrolysis was complete. The solid was collected by filtration, rinsed with H_2O, and then slurried in a Waring Blendor for 5 min with 10% $NaHCO_3$. The solid was collected by filtration and dried. Recrystallization from ethyl acetate gave 16.5 g of diketone **8**. The mother liquor gave an additional 6.0 g (82% total yield), mp 160–162 °C. An analytical sample of **8** was prepared by recrystallization and sublimation (170 °C, 0.15 mm): mp 170–171 °C; IR (KBr) 1675 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (m, 2, Ar H), 7.14 (m, 4, Ar H), 3.84 (s, 6, Ar OCH_3), 3.46–3.38 (m, 2, Ar CH), 3.06–2.92 (m, 6, Ar CH*CH*CH_2); MS (70 eV), *m/e* $M^+/2$ (hemicleavage), 174 (100). Anal. ($C_{22}H_{20}O_4$) C, H.

3,9-Dimethoxy-5,6,6aα,6bβ,11,12,12β,12bα-octahydrodibenzo[a,g]biphenylene (1b). A solution of 43 g (0.124 mol) of dione **8** in 1 L of ethyl acetate and 15 g of Raney Ni[13] was refluxed for 15 min. The suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in 800 mL of acetic acid, 8 g of 5% Pd/C was added, and the mixture was hydrogenated at 70 °C and 50 psig. After H_2 uptake ceased (4 h), the cooled mixture was filtered through Dicalite and then concentrated under reduced pressure. The residue and the Dicalite containing the used catalyst were placed above a column of basic alumina in a modified Soxhlet apparatus[21] and extracted with an isohexane–benzene mixture (9:1). The eluate was cooled and allowed to crystallize, and the solid was collected by filtration to give 33.0 g (83%) of diether **1b**: mp 146–147 °C; IR (KBr) 1250, 1030 (Ar OCH_3), 850, 815, 795 (1,2,4 substituted aromatic) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00–6.64 (m, 6, Ar H), 3.75 (s, 6, OCH_3), 3.24–2.08 (m, 2, Ar CH), 3.04–2.68 (m, 4, Ar CH_2), 2.66–2.34 (m, 2, Ar CH*CH*), 2.04–1.52 (m, 4, Ar CH_2CH_2); MS (70 eV) *m/e* $M^+/2$ (hemicleavage), 160 (100); UV

(20) Phillips Chemical Co., isohexanes, bp 61 °C.
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(95% EtOH) λ_{max} 232.2 nm (log ϵ 4.31), 280.0 (3.54). Anal. ($C_{22}H_{24}O_2$) C, H.

3,9-Dihydroxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[a,g]biphenylene (1a). To a stirred solution of 1.0 g (3.1 mmol) of diether **1b** in 50 mL of CH_2Cl_2 was added dropwise a solution of 1.0 g (4.0 mmol) of BBr_3 in 5 mL of CH_2Cl_2.[22] The mixture was stirred for 12 h and then the solvent was removed under reduced pressure. The residue was treated with 50 mL of ether and 10 mL of H_2O and then extracted with 5% KOH. The aqueous phase was separated and acidified, and the precipitate was collected by filtration. Recrystallization from ether gave 0.60 g (55%) of diphenol 1a, mp 235-237 °C. An analytical sample was prepared by sublimation at 225 °C (0.2 mm): IR (KBr) 3300 (Ar OH) cm^{-1}; ^1H NMR (acetone-d_6) δ 7.84 (s, 2, Ar OH), 6.94-6.56 (m, 6, Ar H), 3.26-3.06 (m, 2, Ar CH), 3.04-2.66 (m, 4, Ar CH_2), 2.60-2.30 (m, 2, Ar CHCH), 2.04-1.56 (m, 4, Ar CH_2CH_2); MS (70 eV) m/e $M^+/2$ (hemicleavage), 146 (100); UV (95% EtOH) λ_{max} 280 nm (log ϵ 3.64), with added base, 300 (3.78). Anal. ($C_{20}H_{20}O_2$) C, H.

Biological Testing. Oral Uterotropic (Estrogenic) Activity. Twenty-one-day old female rats, weighing 45-55 g, were treated for 3 consecutive days with a suspension of the diphenol 1a in 0.1 mL of sesame oil. Total doses of 1, 10, 100, and 1000 μg were administered to groups of 10 rats. A vehicle control group of 10 rats treated with sesame oil alone was also run. Autopsy was performed on the 4th day, and the uteri were excised, cleaned, and weighed to the nearest 0.2 mg. The average uterine weights for the four doses were 71.2 ± 3.6, 97.6 ± 5.3, 111.1 ± 5.3, and 117.7 ± 5.1 mg, respectively. The weight of the uteri of the control group was 38.2 ± 2.0 mg. The standard (DES) was tested for doses of 0.2, 0.4, and 0.8 μg and gave uterine weights of 57.7 ± 3.3, 72.5 ± 4.0, and 105.8 ± 5.3 mg, respectively. The potency is expressed as percent activity relative to DES.[19a]

Oral Postcoital Activity. Adult female rats were caged overnight with proven males and checked the next morning for the presence of sperm in vaginal washings (day of sperm = day 0). The diphenol 1a was suspended in 0.1 mL of sesame oil and administered orally to groups of 10 rats for 5 consecutive days starting on day 0. On day 10, autopsy was performed and the number of normal and resorbing fetuses was determined. ED_{100} is defined as the minimum dose [(μg/kg)/day] necessary to completely prevent implantation.[19a]

Antitumor Activity. Diphenol 1a, dissolved in cotton seed oil, was administered parenterally to three young adult Fisher male rats in the dose range of 10 μg, 100 μg, and 1 mg for 10 injections. These rats had previously received a transplanted squamous cell prostate carcinoma (11095). Autopsy on the 11th day showed tumor weight change/gram to be +15, +8, and 0, respectively. A second series using five young adult Fisher males with a dose range of 31.6 μg, 100 μg, 316 μg, 1 mg, and 3.16 mg showed a weight change/gram of +11, +7, +3, +1, and -3, respectively. The weight change/gram of controls for the two studies were +12 and +20, respectively.

A simultaneous comparison study using five adult Fisher males having received a dose range of 1 μg, 10 μg, 100 μg, 1 mg, and 10 mg/kg of DES showed a weight change/gram of +24.6, +13.3, -7, -10, and -18, respectively.[19b]

Acknowledgment. We thank the Contraceptive Development Branch, Center for Population Research, National Institutes of Child Health and Human Development, NIH, for support of this work through contract (NO1-HD-3-2846) and for permission to cite biological data. Support for the purchase of the Varian XL-100-15 is acknowledged (NSF Grant 17641 and HE 76-05571. We are grateful to Dr. A. Segaloff and his associates of the Alton Ochsner Medical Foundation for data from antitumor studies. We also thank Drs. H. K. Kim and M. Karten for helpful suggestions during the course of the work. The investigation at the University of Oklahoma was supported by Grant CA-17562, awarded by the National Cancer Institute, DHEW.

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2-(Aminomethyl)phenols, a New Class of Saluretic Agents. 1. Effects of Nuclear Substitution[1]

G. E. Stokker,* A. A. Deana, S. J. deSolms, E. M. Schultz, R. L. Smith, E. J. Cragoe, Jr.,

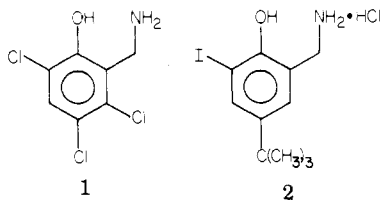
Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

J. E. Baer, C. T. Ludden, H. F. Russo, A. Scriabine, C. S. Sweet, and L. S. Watson[2]

Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486. *Received April 21, 1980*

A series of 2-(aminomethyl)phenols was synthesized and tested in rats and dogs for saluretic and diuretic activity. A number of these compounds exhibit a high order of activity on iv or po administration. The most active compounds belong to a subseries of 4-alkyl-6-halo derivatives of which **2**, 2-(aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenol, is the most active. Compound **2** also possesses significant antihypertensive activity, an adjunctive pharmacological parameter which distinguishes **2** from the other compounds prepared in this series. In addition, **2** displays both topical saluretic and antiinflammatory activities.

A continuing search for new renal agents in our laboratories by screening carefully selected compounds for diuretic and saluretic activity in rats and dogs led to the discovery of 2-(aminomethyl)-3,4,6-trichlorophenol (**1**). The unusual structural features, attractive electrolyte excretion profile and saluretic potency of **1**, relative to those of hydrochlorothiazide and furosemide provided impetus for an extensive synthetic program. The resulting data facilitated the delineation of the structure-activity relationships (SAR's) for a variety of 2-(aminomethyl)-phenols (**5**) and culminated in the development of 2-(aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenol hydro-



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(1) Portions of this work were presented in August, 1977, at the 174th National Meeting of the American Chemical Society. See "Abstracts of Papers", 174th National Meeting of the American Chemical Society, Chicago, Ill., 1977; American Chemical Society: Washington, D.C., 1977, and *ACS Symp. Ser.* 1978, *83*, 93-124.

(2) Deceased, May 31, 1977.

0022-2623/80/1823-1414$01.00/0