Experimental Section

Melting points were determined with an electrically heated metal block, using calibrated Anschütz thermometers. Microanalyses were performed by Dr. A. Bernhardt, Mülheim, West Germany. Ir spectra were determined on a Perkin-Elmer spectrophotometer Model 337 in KBr.

2-Methylbenzhydrol,[8] 2-chlorobenzhydrol,[9] 4-chlorobenzhydrol,[9] and 2,2′-dimethylbenzhydrol[10] were prepared as described in the literature.

Preparation of quinuclidinyl ethers was accomplished as illustrated for **3-quinuclidinyl benzhydryl ether (1).** Benzhydrol (7.4 g, 0.04 mole) and 3-quinuclidinol (5.6 g, 0.044 mole) were thoroughly mixed and heated to 70° to form a homogenous melt. *p*-Toluenesulfonic acid (8.75 g, 0.046 mole) was added and the flask was evacuated. This caused H_2O to evaporate from the mixture, and the melt solidified. The temperature was then raised to 140° when the solid melted, and the evacuated flask was kept at this temperature for 3 hr. After cooling, the solid material was dissolved in 5 *N* NaOH and extracted with Et_2O. The extract was washed with H_2O and dried (Na_2SO_4) and the hydrochloride precipitated with dry HCl. Recrystallization from EtOH–Et_2O afforded 8.3 g (69%) of **1**, mp 194–195.5°.

The MeI derivative (**6**) was obtained when a solution of the base **1** and 1 equiv of MeI in dry Me_2CO was allowed to stand at room temperature for 24 hr. The quaternary salt precipitated in an analytically pure state, mp 193–194°. Recrystallization from EtOH–Et_2O did not raise the melting point.

Acknowledgments.—The authors are indebted to Astra Pharmaceutical Products, Worcester, Mass., and AB Astra, Södertälje, Sweden, for carrying out the pharmacological tests.

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Alkylsulfonamido Estrogens

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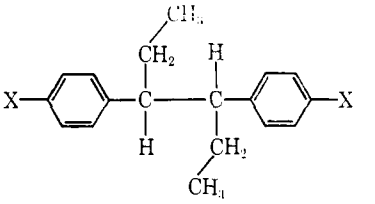
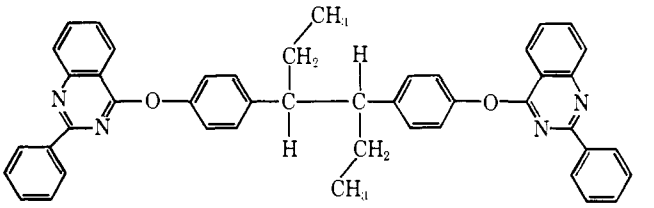
Received March 17, 1969

Recent papers from these laboratories have described the novel bioisosteric relationship between the methanesulfonamido group and the phenolic hydroxyl group in a phenethanolamine series.[1] As a logical extension of this work, we have attempted to determine whether this bioisosteric relationship could be projected to other compounds of biological interest possessing a phenolic hydroxyl group. The application of this bioisosteric relationship to steroidal and nonsteroidal estrogens was of special interest because of the potential usefulness of these compounds as antiuterotropic and/or antifertility agents.[2]

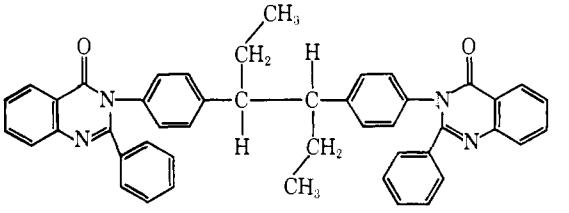
The amines and diamines used as starting materials were prepared according to the general method of Scherrer for conversion of phenols to anilines.[3] Application of the Scherrer method to the synthesis of *meso*-3,4-bis(4-aminophenyl)hexane (II) from *meso*-hexestrol (I) required forcing conditions in order to ensure bisarylation of (I). The *meso*-hexestrol (I) was condensed with 2 moles of 4-chloro-2-phenylquinazoline[4] in DMSO using KO-*t*-Bu as the condensing agent. The 3,4-bis[4-(2-phenyl-4-quinazolinyloxyphenyl)]hexane (V) thus formed, was heated at 330° to yield 3,4-bis[3-(4-oxo-2-phenyl-3(4H)-quinazolinylphenyl)]hexane (VI). This material was hydrolyzed in ethanolic NaOH to give II.[5] Amines II and VII gave the respective methane and butanesulfonamides III, IV, VIII, and IX. $NaBH_4$ reduction of 3-methanesulfonamidoestra-1,3,5-(10)-trien-17-one (VIII) gave the estradiol analog, 3-methanesulfonamidoestra-1,3,5(10)-trien-17β-ol (X).



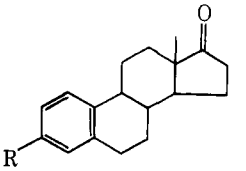
I, X = OH
II, X = NH_2
III, X = CH_3SO_2NH
IV, X = n-$C_4H_9SO_2NH$



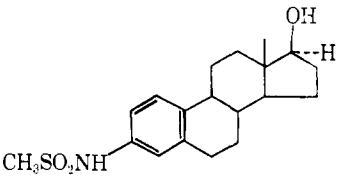
V



VI



VII, R = NH_2
VIII, R = CH_3SO_2NH
IX, R = $C_4H_9SO_2NH$



X

These alkylsulfonamido analogs were tested in our laboratories for one or more of the following three types of biological activity, uterotropic,[6] antiuterotropic,[7] and

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antifertility. For these tests all compounds were administered subcutaneously as solutions in corn oil.

The antifertility activity of the compounds was evaluated by dosing mated female rats on each of the first 6 days of pregnancy, with the day sperm are first found in a vaginal smear defined as day 1 of pregnancy. On the twelfth day of pregnancy, the uteri were examined for the presence, number, and appearance of implantation sites.

The uterotropic actions of III, VIII, and IX were examined using maximum doses of 10, 100, and 500 μg/animal per day, respectively. None of the compounds exhibited any activity at these dose levels. The estradiol analog X caused a statistically significant increase in uterine weight at a daily dose of 3.3 μg/animal, or $^1/_{300}$th the activity of the chemically related estrogen, estradiol. The antiuterotropic potential of III, IX, and X was investigated at dose levels of 100, 2000, and 100 μg/day, respectively. None of the compounds displayed any antiuterotropic activity.

The postmating antifertility effects of III, IV, VIII, IX, and X were examined at dose levels of 4.0, 2.5, 15.5, 2.0, and 2.0 mg/kg, respectively. None of the compounds had any statistically significant effect on fertility.

Experimental Section[8]

2-Phenyl-4-quinazolone[4] has generally been prepared by the method of Endicott, *et al.*,[4] but the following procedure was considered to be more convenient. To a stirred solution of 68.2 g (0.5 mol) of anthranilamide in 250 ml of DMF was added dropwise 70.3 g (0.5 mol) of BzCl. The mixture was stirred for 1 hr and poured into 2 l. of ice water. The collected N-benzoylanthranilamide was heated for 30 min in 1 l. of 5% NaOH according to the procedure of Stephen.[9] The solution was poured into 1 l. of 6 *N* HCl, filtered, and neutralized with concentrated NH_4OH. The solid was collected by filtration and dried giving 66 g (60%) of 2-phenyl-4-quinazolone, mp 232–234° dec (lit.[4] mp 235–236°).

4-Chloro-2-phenylquinazoline.—Although 4-chloro-2-phenylquinazoline has previously been prepared by the method of Endicott, *et al.*,[4] the method of Scarborough, *et al.*,[10] was found to give more satisfactory results.

3,4-Bis[4-(2-phenyl-4-quinazolinyloxyphenyl)]hexane (V).—To a solution of 5.4 g (0.02 mol) of *meso*-hexestrol[11] in 150 ml of dry DMSO was added 5 g (0.044 mol) of KO-*t*-Bu and the mixture was stirred under a N_2 atmosphere for 1 hr. To this solution was added 9.7 g (0.04 mol) of 4-chloro-2-phenylquinazoline and the reaction mixture was heated to 150° for 5 hr. The suspension was cooled and the product was isolated by filtration. Recrystallization from DMSO gave 11.5 g (85%) of white solid, mp 323–326.5°. Absorption bands of spectra (ir, nmr) were as expected. *Anal.* ($C_{46}H_{38}N_4O_2$) C, H, N.

3,4-Bis[3-(4-oxo-2-phenyl-3(4H)-quinazolinylphenyl)]hexane (VI).—A solution of 6.8 g (0.01 mol) of V in 70 ml of heavy mineral oil was heated at 330° under a N_2 atmosphere for 5.5 hr. The solution was cooled and poured into 600 ml of 30–40° petroleum ether. The solid was collected by filtration giving 6 g (88%) of white solid, mp 355–360°. The analytical sample was recrystallized from DMSO, mp >360°. Absorption bands (or peaks) of spectra (uv, ir, nmr) were as expected. *Anal.* ($C_{46}H_{38}N_4O_2$) C, H, N.

***meso*-3,4-Bis(4-aminophenyl)hexane (II).**—Although II has been previously reported by Baker,[5a] the following method of synthesis was judged more convenient. To a solution of 13.6 g (0.02 mol) of 3,4-bis[3-(4-oxo-2-phenyl-3(4H)-quinazolinylphenyl)]hexane (VI) in 750 ml of absolute EtOH was added 150 ml of 40% NaOH. The reaction mixture was refluxed for 20 hr, cooled, and acidified with 380 ml of 12 *N* HCl. The suspension was then refluxed for 1 hr, cooled, and filtered. The filtrate was evaporated to dryness, and the residue was dissolved in 200 ml of H_2O, filtered, and made basic with concentrated NH_4OH. The solid was extracted with Et_2O, dried, and concentrated giving 3.46 g (64%) of crude (II). Crystallization from *i*-PrOH gave 2.5 g of II, mp 137–140° (lit.[5b] mp 136–137°). Absorption bands (or peaks) of spectra (nmr) were as expected.

***meso*-3,4-Bis(4-methanesulfonamidophenyl)hexane (III).**—To a solution containing 270 mg (1 mmol) of II and 0.3 ml of Et_3N in 10 ml of C_6H_6 was added 0.23 g (2 mmol) of MSCl. The mixture was stirred for 4 hr. The solid was collected by filtration, washed with H_2O, and recrystallized from Me_2CO–H_2O giving 200 mg (47%) of III, mp 250.5–252.5°. Absorption bands (or peaks) of spectra (ir, nmr) were as expected. *Anal.* ($C_{20}H_{28}N_2O_4S_2$) C, H, N, S.

***meso*-3,4-Bis(4-butanesulfonamidophenyl)hexane (IV).**—A solution of 800 mg (3 mmol) of 3,4-bis(4-aminophenyl)hexane and 670 mg (6.6 mmol) of Et_3N in 15 ml of C_6H_6 was treated with 1.04 g (6.6 mmol) of butanesulfonyl chloride in the same manner as the procedure for III. The suspension was filtered to remove triethylamine hydrochloride and the C_6H_6 solution was washed with H_2O, dried, and evaporated to dryness. The residue was crystallized from Me_2CO giving 300 mg (20%) of product, mp 187.5–190°. Absorption bands (or peaks) of spectra (ir, nmr) were as expected. *Anal.* ($C_{28}H_{44}N_2O_4S_2$) N, S.

3-Aminoestra-1,3,5(10)-trien-17-one (VII).[12]—Compound VII was prepared by the method of Morrow and Hofer.[12b]

3-Methanesulfonamidoestra-1,3,5(10)-trien-17-one (VIII).—To a solution of 1 g (3.72 mmol) of VII[12b] in 10 ml of C_5H_5N cooled in an ice bath, was added slowly 0.46 g (4 mmol) of MSCl. After the reaction mixture had stirred for 0.5 hr with cooling, the ice bath was removed and stirring was continued for 1.5 hr. The bright red solution was poured into 100 ml of H_2O and acidified with 2 *N* HCl. The red gum was extracted into C_6H_6, washed with H_2O, and extracted with 0.1 *N* NaOH. The basic extracts were acidified with 2 *N* HCl and the product was isolated by filtration. Recrystallization from 12 ml of 95% EtOH gave 750 mg (58%) of the product, mp 196.5 and 209.5° (polymorphic),[13] $[\alpha]^{25}D$ + 126.2° (*c* 1, $CHCl_3$). Absorption bands (or peaks) of spectra (ir, nmr) were as expected. *Anal.* ($C_{19}H_{25}NO_3S$) C, H, N, S.

3-Methanesulfonamidoestra-1,3,5(10)-trien-17β-ol (X).—A solution of 348 mg (1.0 mmol) of VIII in 5 ml of MeOH was treated with 1 ml of 10% NaOH and 10 mg of $NaBH_4$. The solution was stirred for 1 hr and poured into 50 ml of H_2O. The solution was made acidic to pH 1 with 3 *N* HCl and the product was extracted with Et_2O. The extract was washed with H_2O and saturated NaCl solution, dried, and concentrated to dryness. The residue was recrystallized from 95% EtOH–H_2O to yield 250 mg (72%) of X, mp 208–209°, $[\alpha]^{26}D$ +42.2° (*c* 0.5, $CHCl_3$). Absorption bands (or peaks) of spectra (uv, ir, nmr) were as expected. *Anal.* ($C_{19}H_{27}NO_3S$) C, H, N, S.

3-Butanesulfonamidoestra-1,3,5(10)-trien-17-one (IX).—To a solution of 540 mg (2 mmol) of VII in 5 ml of C_5H_5N cooled in an ice bath was added 340 mg (2.2 mmol) of butanesulfonyl chloride. When addition was complete, the reaction mixture was stirred for 3 hr at room temperature and worked up in the same manner as VII. The product was sublimed at 150° (0.1 mm) giving 650 mg (83%) of IX, mp 75–78°. Absorption bands (or peaks) of spectra (ir, nmr) were as expected. *Anal.* ($C_{22}H_{33}NO_3S$) C, H, N, S.

Acknowledgment.—The authors are grateful to Mr. C. I. Kennedy for the analytical data and to Messrs. J. G. Schmidt and C. M. Combs for the spectral data.

(8) All melting points are corrected and were determined in open capillaries on a Thomas–Hoover Unimelt melting point apparatus. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical value.

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(13) Polymorphic transitions were determined on a DuPont Model 900 differential thermal analyzer.