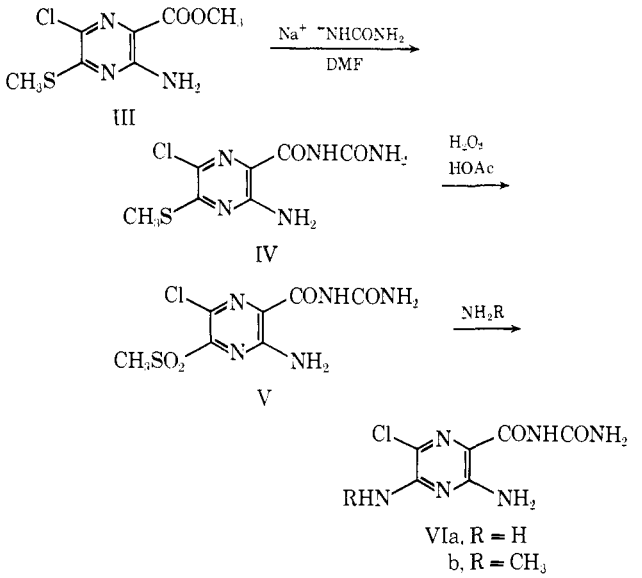
azinecarboxamide (IV). Oxidation of IV with H_2O_2 gave the 5-mesyl derivative V, which is then easily converted to VIa by treatment with NH_3. The 5-methylamino compound VIb was also prepared in this manner.



Pharmacology.—All of these compounds were tested for diuretic activity in both normal rats and hydrated dogs. The normal rats and hydrated dogs were given several doses according to the procedures of Cummings, *et al.*,[10] and Little and Cooper,[11] respectively. Compounds IIa–f and VIa,b were found to be active in the rat. They increased the total urine volume and enhanced the excretion of Na^+ and Cl^-. However, only one of the compounds, IIa, showed antikaliuretic activity. When coadministered with quinethazone, N-carbamoyl-3-aminopyrazinecarboxamide (IIa) showed a slight potentiation of the quinethazone-induced natriuresis. All of the compounds were tested in the dog and found to be inactive. IIa at low doses in combination with quinethazone again showed a natriuretic effect, but it was too small to be significant.

Experimental Section[12]

Methyl 3-aminopyrazinecarboxylate (Ia) was prepared from 3-aminopyrazine-2-carboxylic acid by the method of Ellingson, Henry, and McDonald.[13]

Substituted methyl 3-aminopyrazinecarboxylates (Ib–i, III) were prepared following the procedure of Cragoe, *et al.*[1]

General Procedure for the Substituted N-Carbamoylpyrazinecarboxamides (IIa–i).—To 15 ml of dry DMF was added 0.9 g (0.015 mole) of urea. To the stirred solution cooled to −15° was added 0.7 g (0.015 mole) of NaH (50% in oil). The mixture was left to stir for 1 hr. To the cooled mixture was then added 0.004 mole of the methyl substituted 3-aminopyrazinecarboxylate. This was left to stir for 2 hr. The reaction mixture was then poured onto 25 g of ice–H_2O made slightly acidic with AcOH. The mixture was stripped to dryness and H_2O was added to precipitate the crude product. The solid was then dissolved in hot 3 *N* HCl, filtered, and precipitated with dilute NaOH. An analytical sample was prepared by crystallizing the product from MeOH.

TABLE I

YIELDS, PHYSICAL, AND ANALYTICAL DATA

No.	Yield, %	Mp, °C	Recrystn solvent[a]	Formula	Analyses
IIa	32	288[b]	W	$C_6H_7N_5O_2$	C, H, N
IIb	16	240	M	$C_6H_6ClN_5O_2$	C, H, N, Cl
IIc	28	218	M	$C_8H_{11}ClN_6O_2$	C, H, N, Cl
IId	29	198	M	$C_{10}H_{15}ClN_6O_2$	C, H, N, Cl
IIe	27	165	M	$C_{12}H_{19}ClN_6O_2$	C, H, N, Cl
IIf	16	148	M	$C_{11}H_{17}ClN_6O_2$	C, H, N, Cl
IIg	24	191	M	$C_{10}H_{15}ClN_6O_2$	C, H, N, Cl
IIh	36	168	M	$C_{10}H_{13}ClN_6O_2$	C, H, N, Cl
IIi	54	176	M	$C_{11}H_{17}ClN_6O_2$	C, H, N, Cl
IV	27	225[b]	M	$C_7H_8ClN_5O_2S$	H, N, Cl, S; C[c]
V	41	215[b]	M	$C_7H_8ClN_5O_4S$	C, H, N, Cl, S
VIa	82	260[b]	M	$C_6H_7ClN_6O_2$	C, H, N, Cl
VIb	37	245[b]	M	$C_7H_9ClN_6O_2$	C, H, N, Cl

[a] W = H_2O, M = MeOH. [b] Compound melts with decomposition. [c] C: calcd, 32.1; found, 32.6.

N-Carbamoyl-3-amino-5-methylmercapto-6-chloropyrazinecarboxamide (IV).—To 15 ml of dry DMF was added 0.3 g (0.005 mole) of urea. To the stirred solution cooled to −15° was added 0.25 g (0.005 mole) of NaH (50% in oil). This was left to stir for 1 hr. To the cooled mixture was added 1.0 g (0.004 mole) of methyl 3-amino-5-methylmercapto-6-chloropyrazinecarboxylate and stirring continued an additional 2 hr. The reaction mixture was then poured onto 15 g of ice–H_2O made slightly acidic with AcOH. A yellow solid precipitated from solution was filtered and washed with H_2O to give 0.7 g of crude product. Crystallization from MeOH gave 0.3 g (27%) of product, mp 225° dec, λ_{max}^{KBr} 5.77 and 5.93 μ.

N-Carbamoyl-3-amino-5-mesyl-6-chloropyrazinecarboxamide (V).—A suspension of 1.0 g (0.004 mole) of N-carbamoyl-3-amino-5-methylmercapto-6-chloropyrazinecarboxamide (IV) in 40 ml of AcOH and 10 ml of 30% aqueous H_2O_2 was stirred at room temperature. After 110 hr an additional 3 ml of 30% H_2O_2 was added and stirring was continued for a total of 168 hr. The yellow solid which precipitated was removed by filtration and washed with EtOAc to give a total crude yield of 0.65 g. Recrystallization from MeOH yielded 0.45 g (41%) of product: mp 215° dec; λ_{max}^{KBr} 5.80, 5.88, and 5.97 μ.

N-Carbamoyl-3,5-diamino-6-chloropyrazinecarboxamide (VIa).—A suspension of 0.42 g (0.0014 mole) of N-carbamoyl-3-amino-5-mesyl-6-chloropyrazinecarboxamide (V) in 2 ml of *i*-PrOH was stirred while 0.14 g of NH_3 in 4 ml of *i*-PrOH was added and the mixture was refluxed for 1 hr. The solution was cooled in an ice bath and the yellow product that separated was removed by filtration. Crystallization from MeOH yielded 0.27 g (82%), mp 260° dec, λ_{max}^{KBr} 5.84 and 6.01 μ.

Acknowledgments.—We wish to thank Drs. J. R. Cummings and R. Z. Gussin and associates for the pharmacological data.

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(11) J. M. Little and C. Cooper, Jr., *Fed. Proc.*, **9**, 296 (1950).

(12) Yields, physical data, and analyses are listed in Table I. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(13) R. Ellingson, R. L. Henry, and F. G. McDonald, *J. Am. Chem. Soc.*, **67**, 1712 (1945).

Potential Antiparkinsonism Agents. Quinuclidinyl Benzhydryl Ethers

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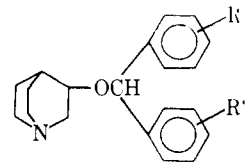
As part of our current study of quinuclidine derivatives of potential pharmacological value,[1] we have

(1) (a) J. L. G. Nilsson, J. Wågermark, R. Dahlbom, and W. M. Benson, *Acta Pharm. Suecica*, **5**, 9 (1968); (b) J. L. G. Nilsson, J. Wågermark, and R. Dahlbom, *ibid.*, **5**, 71 (1968); (c) R. Dahlbom and J. Dolby, *ibid.*, **6**, 277 (1969).

TABLE I
3-QUINUCLIDINYL BENZHYDRYL ETHERS



Compd	R	R'	Derivative	Yield, %	Mp, °C	Formula[a]
1	H	H	HCl	69	194–195	$C_{20}H_{23}NO \cdot HCl$
2	2-CH_3	H	HCl	64	184–185	$C_{21}H_{25}NO \cdot HCl$
3	2-Cl	H	HCl	55	165–166	$C_{20}H_{22}NO \cdot HCl$
4	4-Cl	H	HCl	49	195–196	$C_{20}H_{22}NO \cdot HCl$
5	2-CH_3	2-CH_3	HCl	65	185–186	$C_{22}H_{27}NO \cdot HCl$
6	H	H	CH_3I	83	193–194	$C_{21}H_{26}INO$

[a] The compounds were analyzed for C, H, and N. Analytical results were within ±0.4% of the theoretical value.

prepared a series of 3-quinuclidinyl benzhydryl ethers. These have been tested for specific centrally acting anticholinergic effect to evaluate them as antiparkinsonism agents.

Benzhydryl ethers of amino alcohols have a well-established position in therapy as antihistaminic (*e.g.*, diphenhydramine) or antiparkinsonism (*e.g.*, orfenadrine, diphenylpyraline, and benztropine) agents. We considered it worthwhile to prepare benzhydryl ethers of 3-quinuclidinol, since several esters of this amino alcohol have been shown to have pronounced peripheral and central anticholinergic activity.[2,3]

The effect of substitution in the aromatic rings of basic benzhydryl ethers have been studied extensively among others by Nauta, *et al.*[4,5] These investigators have demonstrated that it is possible to obtain compounds with either pronounced antihistaminic or pronounced anticholinergic activity by the introduction of substituents in the aromatic rings. The benzhydryl ethers presented here consequently include compounds with substituents in one or both of the aromatic rings (Table I). They were synthesized by a method previously employed in the preparation of a tropinyl benzhydryl ether.[3] 3-Quinuclidinol and the benzhydrol were heated with *p*-toluenesulfonic acid *in vacuo* without solvent, and the ethers were subsequently isolated in 50–70% yield as hydrochlorides.

Compounds **2**–**4** have two asymmetric carbon atoms and can exist in two pairs of enantiomers. Attempts were made to isolate a second racemate through crystallization and chromatography (tlc and glpc) but the compounds appeared to be homogeneous, indicating that one of the racemates had been formed in predominating amounts.

Pharmacology.—The compounds were tested *in vivo* in mice for mydriatic activity and antagonism to the motor effects of oxotremorine. The methods used have previously been described in detail.[6] The "mydriatic dose" is the dose required to double the pupil size relative to the control, and the "tremorolytic dose" is approximately equivalent to the dose giving twofold protection against oxotremorine. The results are summarized in Table II.

TABLE II
MYDRIATIC AND TREMOROLYTIC ACTIVITY IN MICE *in Vivo*

Compd	Mydriatic dose,[a] mg/kg	Tremorolytic dose,[a] mg/kg
1	0.8	0.6
2	1.0	0.5
3	1.1	0.7
4	4.6	Inactive
5	3.6	Inactive
Atropine sulfate	0.15	0.19

[a] See text.

The compounds were also tested for acetylcholine and histamine antagonism on isolated guinea pig ileum according to methods described by Wiedling,[7] and their effects were compared to those of atropine sulfate and diphenhydramine hydrochloride. The results are summarized in Table III.

TABLE III
SPASMOLYTIC EFFECT ON ISOLATED GUINEA PIG ILEUM

Compd	Rel effect against spasms produced by: Acetylcholine	Histamine
1	15	0.7
2	25	0.3
3	30	0.22
4	6	0.1
5	6	0.06
6	30	
Diphenhydramine hydrochloride	1	1
Atropine sulfate	30	

It is evident from Table II that **1**–**3** have pronounced central and peripheral anticholinergic activity. If the ratio between the mydriatic and tremorolytic doses is taken as a measure of the selectivity of the compounds for the CNS, it can be concluded that they are somewhat more selective than atropine in this respect. The drop in mydriatic potency and loss of tremorolytic effect of **4** and **5** is noteworthy, but the experimental evidence available is too scanty to permit any conclusions to be drawn as to the cause of this.

Compounds **1**–**3** also display strong anticholinergic activity when tested on the isolated guinea pig ileum.

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(6) (a) R. Dahlbom, B. Karlén, R. George, and D. J. Jenden, *ibid.*, **9**, 843 (1966); (b) R. Dahlbom, B. Karlén, A. Lindquist, R. George, and D. J. Jenden, *Acta Pharm. Suecica*, **3**, 187 (1966).
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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.

(8) J. H. Lamneck, Jr., and P. H. Wise, *Natl. Advisory Comm. Aeron., Tech. Note 2330*, 17 (1950); *Chem. Abstr.*, **45**, 6609*h* (1951).
(9) A. E. Chichibabin and A. A. Shesler, *J. Russ. Phys. Chem. Soc.*, **56**, 149 (1925); *Chem. Abstr.*, **19**, 3269 (1925).
(10) D. R. Boyd and H. H. Hatt, *J. Chem. Soc.*, 898 (1927).

Alkylsulfonamido Estrogens

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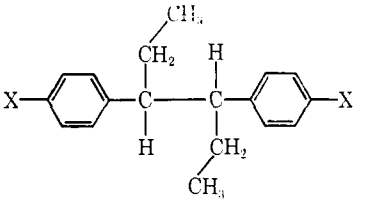
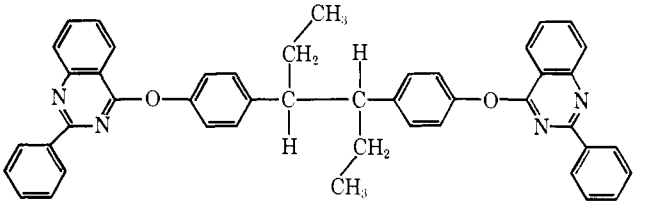
Recent papers from these laboratories have described the novel bioisosteric relationship between the methanesulfonamido group and the phenolic hydroxyl group in a phenethanolamine series.[1] As a logical extension of this work, we have attempted to determine whether this bioisosteric relationship could 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]

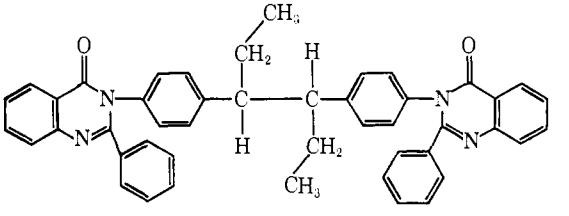
The amines and diamines used as starting materials were prepared according to the general method of Scherrer for conversion of phenols to anilines.[3] Application of the Scherrer method to the synthesis of *meso*-3,4-bis(4-aminophenyl)hexane (II) from *meso*-hexestrol (I) required forcing conditions 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).



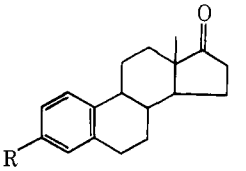
I, X = OH
II, X = NH_2
III, X = CH_3SO_2NH
IV, X = n-$C_4H_9SO_2NH$



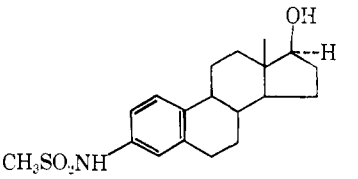
V



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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(5) B. R. Baker, *ibid.*, **68**, 1572 (1943); (b) G. Fodor and J. Wein, *J. Chem. Soc.*, 684 (1948), report mp 80° for the racemic diamine.
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