aqueous acetic acid–THF, gave the prostaglandin congeners **12** and **13**, respectively. The ^{13}C NMR spectra obtained for **12** and **13** clearly indicate that they are both mixtures of two C_{16} epimers, in approximately equal amounts.[8]

As indicated in Table I, **12** and **13** are potent inhibitors of histamine-induced gastric acid secretion in the dog gastric fistula preparation.[9] As illustrated in Figure 1, the activity and duration of **12** appear to be comparable to that of 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 methyl ester (SC-29333), a compound previously reported on by Collins et al.[2] Additional studies, to be reported subsequently, have demonstrated that the compounds are antisecretory in the rat, where they also protect against the formation of a variety of experimental ulcers. Intragastric doses of **12** as great as 100 times those required for antisecretory activity were well tolerated acutely and chronically in the dog. On the basis of this activity profile, the PGE_1 analogue **12** is now undergoing development as a therapeutic agent for the treatment of gastrointestinal ulcers and other hypersecretory states in man.

While the manner in which the hydroxymethylketo functional group modifies the metabolism of a prostaglandin still remains to be determined, we have demonstrated that this group is an effective replacement for the carboxylate group in this series of compounds. This observation might have utility outside the prostaglandin area.

Acknowledgment. We thank L. M. Brancone and his staff for microanalyses, W. Fulmor, G. O. Morton, and Dr. R. T. Hargreaves and staff for spectral data, W. Scruggs for his technical assistance in the gastric fistula secretion studies, and Dr. M. B. Floyd for helpful suggestions.

Allan Wissner,* Jay E. Birnbaum
Metabolic Disease Research Section
Medical Research Division
Lederle Laboratories
Pearl River, New York 10965

Donald E. Wilson
Department of Medicine, Section of Gastroenterology
University of Illinois
Abraham Lincoln School of Medicine
Chicago, Illinois 60612
Received December 26, 1979

(8) Satisfactory magnetic resonance, infrared, analytical or high-resolution mass spectral data were obtained for the prostaglandins reported herein.
(9) Three mongrel dogs (20–32 kg) were surgically prepared with stainless-steel cannulae. These were inserted into the most dependent portion of the ventral stomach and exteriorized through the abdomen for the collection of gastric secretions. The dogs were trained to stand quietly in a Pavlov support and were conscious during subsequent secretory studies.

Articles

Synthesis and Blood Pressure Lowering Activity of 3-(Substituted-amino)-1,2,4-benzothiadiazine 1-Oxide Derivatives

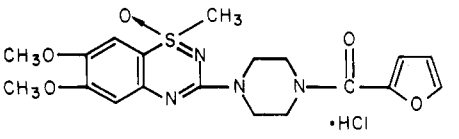
Robert D. Dillard,* Terence T. Yen, Paul Stark, and Donald E. Pavey

Chemical Research Division, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285.
Received October 22, 1979

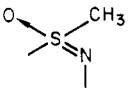
A series of (substituted amino)-1,2,4-benzothiadiazine 1-oxides has been synthesized and most members of the series have been shown to have blood pressure lowering effects in normotensive rabbits and in spontaneously hypertensive rats. The most active member of the series was 3-[4-(2-furoyl)-1-piperazinyl]-6,7-dimethoxy-1-methyl-1*H*-1,2,4-benzothiadiazine 1-oxide hydrochloride. This compound in animal tests was equipotent to the known antihypertensive Prazosin.

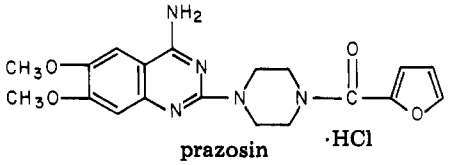
Our investigation of the synthesis of blood pressure lowering compounds has led to the development of a series of 3-amino-1,2,4-benzothiadiazine 1-oxides. These compounds have a unique structural relationship to a family of 4-aminoquinazolines with known blood pressure lowering properties.[1] One member of that series, "Prazosin"[1] is a clinically useful drug. In our series of compounds, the sulfoximine moiety replaced the amidine group in the quinazoline series.

The 1,2,4-benzothiadiazine 1-oxide ring structure has been described by Cohnen and Mahnke[2] in 1972 and by Williams and Cram[3] in 1973. Sulfoximine compounds were reviewed by Kennewell and Taylor in 1975.[4]

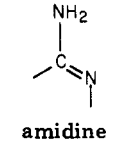


17f





prazosin



Generally, the sulfoximine function is a basic group forming stable salts with strong acids with pK_a values in

(1) A. Scriabine, J. W. Constantine, H.-J. Hess, and W. K. McShane, *Experimentia*, **24**, 1150 (1968); Chas. Pfizer and Co., Inc., U.S. Patent 3 511 836; J. W. Constantine, W. K. McShane, A. Scriabine, and H.-J. Hess, *Postgrad. Med.*, **56**, 18 (1975).
(2) E. Cohnen and J. Mahnke, *Chem. Ber.*, **105**, 757 (1972).
(3) T. R. Williams and D. J. Cram, *J. Org. Chem.*, **38**, 20 (1973).
(4) P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, **4**, 189 (1975).

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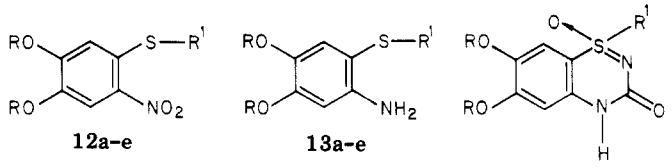
Table I. Sulfoximine Intermediates



12a-e 13a-e 14a-e

no.	R	R	R'	mp or bp (mmHg),[a] °C	recrystn[b] solvent	formula[c]
12a[d]	CH_3	CH_3	C_2H_5	145-147	A	$C_{10}H_{13}NO_4S$
12b	CH_3	CH_3	$CH(CH_3)_2$	107-109	B	$C_{11}H_{15}NO_4S$
12c	CH_3	CH_3	C_6H_5	110-112	C	$C_{14}H_{13}NO_4S$
12d	C_2H_5	C_2H_5	CH_3	105-108	B	$C_{11}H_{15}NO_4S$
12e	(CH_2)		CH_3	195-199	D	$C_8H_7NO_4S$
13a[e]	CH_3	CH_3	C_2H_5	104-113 (0.05)	E	$C_{10}H_{15}NO_2S$
13b	CH_3	CH_3	$CH(CH_3)_2$	106-115 (0.05)	E	$C_{11}H_{17}NO_2S$
13c	CH_3	CH_3	C_6H_5	70-74	F	$C_{14}H_{15}NO_2S$
13d	C_2H_5	C_2H_5	CH_3	112-115 (0.05)	E	$C_{11}H_{17}NO_2S$
13e	(CH_2)		CH_3	140-145 (3.0)	E	$C_8H_9NO_2S$
14a[f]	CH_3	CH_3	C_2H_5	284-286	G	$C_{11}H_{14}N_2O_4S$
14b	CH_3	CH_3	$CH(CH_3)_2$	253-255	G	$C_{11}H_{16}N_2O_4S$
14c	CH_3	CH_3	C_6H_5	245-247	H	$C_{15}H_{14}N_2O_4S$
14d	C_2H_5	C_2H_5	CH_3	282-285	G	$C_{12}H_{16}N_2O_4S$
14e	(CH_2)		CH_3	338-344	G	$C_9H_8N_2O_4S$

[a] Melting point or boiling range (pressure in mmHg). [b] A, EtOH-benzene; B, EtOH; C, benzene-Skellysolve B; D, methyl ethyl ketone; E, distillate, oil; F, benzene-hexane; G, product precipitated from reaction mixture; H, CH_2Cl_2. [c] All compounds analyzed for C, H, and N. [d] Method of synthesis, see Experimental Section for 3. [e] Method of synthesis, see Experimental Section for 4. [f] Method of synthesis, as described for 9, method B.

the range of 2–3. They are polar groups and as salts are water soluble. When the groups attached to sulfur are different, the tetrahedral configuration imparts chirality. Compounds of our series have not yet been resolved. Studies of cyclic conjugated sulfoximines have determined that this group does not impart aromaticity.[4]

Several 3-aminobenzothiadiazine 1-oxides have been reported in the literature,[5] but the 6,7-dialkoxy-substituted compounds have not been described. Compounds that have monoalkoxy substitution (6- or 7-MeO) or other than alkoxy have little or no blood pressure lowering effects (compounds not described in this paper). This article describes a large series of 6,7-dialkoxy-3-amino-1,2,4-benzothiadiazine 1-oxides and their blood pressure lowering effects.

Chemistry. The methods of preparation of these compounds are outlined in Scheme I. Detailed procedures under Experimental Section are given for the 10 steps in the formation of 11. On attempting to convert 7 to 8, it was found that strongly acidic conditions, such as hydrazoic acid in sulfuric acid, gave only tars. Similar results were always obtained when the aromatic group attached to sulfur was substituted with dialkoxy substitutents. However, *O*-(mesitylenesulfonyl)hydroxylamine (MSH),[6] which reacted under neutral and mild conditions, gave good yields of the corresponding sulfoximines. All compounds in this series were made in analogous sequence of reactions and are reported in the appropriate tables.

Caution should be taken when working with MSH. This compound can decompose with explosive violence when heated to approximately 60 °C. When working with large amounts, it should be handled in solution or in crystalline form (avoid neat liquid which may give off heat on solidification). It is best to generate the reagent as needed.

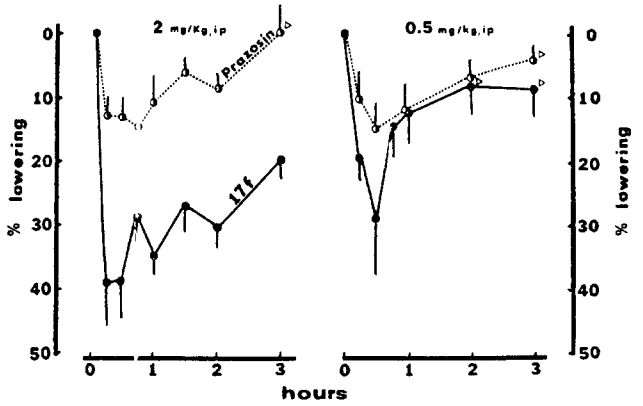


Figure 1. Effect of Prazosin (- - -) and **17f** (—) on systolic blood pressure of spontaneously hypertensive rats. Data are expressed as mean ± SE (vertical bar) with $n = 8$ for both doses of **17f**, $n = 7$ for Prazosin at 2 mg/kg, and $n = 5$ for Prazosin at 0.5 mg/kg. Blood pressure after either Prazosin or **17f** was lower ($p < 0.05$) than the control, except at time periods marked by a Δ.

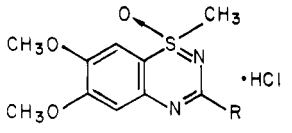
Pharmacology. The compounds listed in Tables II–V were tested for blood pressure lowering effects in normotensive rabbits and spontaneously hypertensive rats (SHR) (see Experimental Section), and the results are summarized in the Tables II–V.

Discussion

Our goal in the synthesis of this series of benzothiadiazine 1-oxides was to determine if the sulfoximine

(5) P. Stoss and G. Satzinger, *Chem. Ber.*, **109**, 2097 (1976); H. R. Squibb and Sons, Inc., U.S. Patent 3957769.
(6) Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.*, **38**, 1239 (1973).
(7) M. Friedman and S. C. Freed, *Proc. Soc. Exp. Biol. Med.*, **70**, 670 (1949); T. T. Yen, P. L. Yu, H. Roeder, and P. W. Willard, *Heredity*, **33**, 309 (1974); T. T. Yen, C. E. Powell, and D. V. Pearson, *Proc. Int. Symp. Spontaneously Hypertensive Rat, 2nd; DHEW Publ. (NIH) (U.S.)*, **NIH 77-1179**, 486 (1977); T. T. Yen, D. V. Pearson, C. E. Powell, and G. L. Kirschner, *Life Sci.*, **22**, 359 (1978); T. T. Yen, and D. V. Pearson, *Res. Commun. Chem. Pathol. Pharmacol.*, **23**, 11 (1979); T. T. Yen, N. B. Stamm, and J. A. Clemens, *Life Sci.*, **25**, 209 (1979).
(8) E. Stogryn, *J. Med. Chem.*, **13**, 1106 (1970).

Table II. 3-(Substituted amino)-1,2,4-benzothiadiazine 1-Oxides

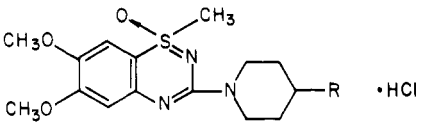


15a-f

compd	R	mp, °C	recrystn[a] solvent	formula[b]	normotensive[c] rabbits, min. effective, dose, iv in mg/kg	SHR[d] dose, mg/kg ip	SHR[d] % BP lowering (no. of animals)
Prazosin					0.025	0.5	14.7 ± 3.5 (5)
15a	$NHCH_3$	216-218	A	$C_{11}H_{15}N_3O_3S\cdot HCl$	0.16	50	11.3 ± 7.5 (5)[e]
15b	$NHCH(CH_3)_2$	226-228	B	$C_{13}H_{19}N_3O_3S\cdot HCl$	2.5	50	17.7 ± 3.8 (5)
15c	NHC_6H_5	245-247	A	$C_{16}H_{17}N_3O_3S\cdot HCl$	1.0	50	19.9 ± 3.1 (9)
15d	$NHCH_2C_6H_5$	205-207	B	$C_{17}H_{19}N_3O_3S\cdot HCl$	1.25	50	28.9 ± 4.7 (6)
15e	$N(CH_3)_2$	234-236	A	$C_{12}H_{17}N_3O_3S\cdot HCl$	0.125	50	24.8 ± 6.4 (6)
15f	$N(C_2H_5)_2$	210-212	B	$C_{14}H_{21}N_3O_3S\cdot HCl$	0.04	2	37.3 ± 5.7 (8)

[a] A, MeOH-isopropyl ether; B, EtOH-isopropyl ether; C, EtOH; D, MEK; E, MeOH. [b] All compounds were analyzed for C, H, and N. [c] See Experimental Section for methods. The minimum dose level to give significant blood pressure lowering, $p < 0.05$, is reported. In practice, a mean lowering over a 2-h period of 10 mmHg or greater of the mean BP was statistically significant. When Prazosin was given at 0.025 mg/kg iv, a mean BP lowering of 11.8 ± 2.1 mmHg ($n = 6$) was obtained. At 0.1 mg/kg iv, the BP lowering was 18.3 ± 2.4 ($n = 14$). [d] SHR = spontaneously hypertensive rats. The maximum blood pressure lowering within 3 h after the compound was given is expressed as the mean ± SE in percent lowering ($p < 0.05$). In most cases, the initial screening dose results are reported. [e] Not statistically significant.

Table III. 3-(4-Substituted piperidino)-1,2,4-benzothiadiazine 1-Oxides



16a-h

no.	R	mp, °C	recrystn[a] solvent	formula[b]	normotensive[c] rabbits, min. effective dose, iv in mg/kg	SHR[d] dose, mg/kg ip	SHR[d] % BP lowering (no. of animals)
16a	H	201-203	B	$C_{15}H_{21}N_3O_3S\cdot HCl$	1.25	50	17.1 ± 11.0 (6)[e]
16b	OH	209-210	C	$C_{15}H_{21}N_3O_4S\cdot HCl$	0.625	5	56.9 ± 2.8 (7)
16c	$OCOCH_3$	220-222	D	$C_{17}H_{23}N_3O_5S\cdot HCl$	0.25	20	43.0 ± 4.3 (6)
16d	COC_6H_5	220-222	B	$C_{22}H_{25}N_3O_4S\cdot HCl$	NT[f]	2	25.8 ± 5.8 (6)
16e	$CHOHC_6H_5$	232-234	B	$C_{22}H_{27}N_3O_4S\cdot HCl$	0.008	10	40.9 ± 7.6 (6)
16f	$C_7H_5N_2O$[g]	243-245	B	$C_{22}H_{25}N_5O_4S\cdot HCl$	2.5	50	22.5 ± 8.5 (5)
16g	OH, C_6H_5	222-224	B	$C_{21}H_{25}N_3O_4S\cdot HCl$	NT[f]	50	21.4 ± 7.5 (5)
16h	CN, C_6H_5	174-178	B	$C_{22}H_{24}N_4O_3S\cdot HCl$	NT[f]	50	1.6 ± 2.9 (5)[e]
11	C_6H_5	216-218	B	$C_{20}H_{25}N_3O_3S\cdot HCl$	0.16	50	30.2 ± 6.2 (4)

[a-e] See corresponding footnotes in Table II. [f] Not tested. [g] 1-(1,3-Dihydro-2*H*-benzimidazol-2-one).

moiety could be a bioisostere of the amidine moiety present in the antihypertensive 4-aminoquinazolines,[1] represented by Prazosin. The results in Tables II–V show that blood pressure (BP) lowering activity was retained throughout this new series. Generally, the results in the normotensive rabbit agree with the SHR results.

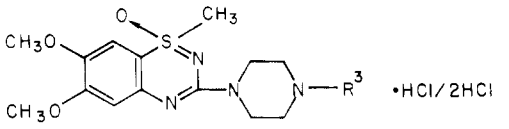
Compound **17f** (Table IV) has the closest structural similarity to Prazosin, the only difference being the replacement of the amidine function by *S*-methylsulfoximine. In the normotensive rabbit, **17f** was more potent than Prazosin, the blood pressure lowering being 11.9 ± 1.9 mmHg ($n = 9$) at 0.008 mg/kg iv for **17f** and 11.8 ± 2.1 mmHg ($n = 6$) at 0.025 mg/kg iv for Prazosin. In the SHR (Figure 1), Prazosin and **17f** had similar effects at 0.5 mg/kg ip, whereas **17f** gave a greater and more sustained hypotensive response at 2 mg/kg ip.

Changes in the 3 position either retained or decreased activity in comparison with **17f**. When the furanoyl group on the piperazine ring of **17f** was replaced with other substituents, blood-pressure activity was decreased but not lost (Table IV). Replacing the piperazinyl group of **17f** with a 4-substituted piperidine gave potent compounds (Table III). The α-hydroxybenzylpiperidinyl compound **16e** was similar to **17f** in lowering blood pressure in rabbits. Disubstitution at the 4 position, **16g** and **16h**, reduced activity. The 3-piperazinyl group of **17f** could be replaced by alkylamino with retention of activity (Table II). The most active of these, the *N,N*-diethylamino compound **15f**, had similar potency to **16e** and **17f**. Replacement of the 6,7-dimethoxy substituents by other di- and trialkoxy groups and increasing the size of the sulfur substituent (Table V) decreased blood pressure lowering effects.

In conclusion, these results indicate that the amidine moiety in the antihypertensive 4-aminoquinazolines could be replaced with the sulfoximine group to give benzothiadiazine 1-oxides with retention of blood pressure lowering activity in two animal systems.

Preliminary studies on isolated rat arterial strips[9] have

Table IV. 3-(4-Substituted piperazino)-1,2,4-benzothiadiazine 1-Oxides

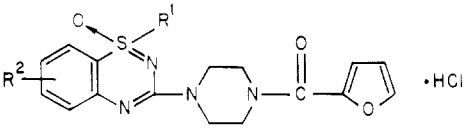


17a-g

no.	R	mp, °C	recrystn[a] solvent	formula[b]	normotensive[c] rabbits, min. effective dose, iv in mg/kg	SHR[d] dose, mg/kg ip	SHR[d] % BP lowering (no. of animals)
17a	H	239-241	E	$C_{14}H_{20}N_4O_3S \cdot 2HCl$	10.0	50	9.1 ± 4.4 (3)[e]
17b	CH_3	235-237	B	$C_{15}H_{22}N_4O_3S \cdot 2HCl$	5.0	50	19.7 ± 2.4 (5)
17c	C_6H_5	186-188	B	$C_{20}H_{24}N_4O_3S \cdot 2HCl$	0.625	25	30.8 ± 3.7 (6)
17d	$CH_2C_6H_5$	243-245	B	$C_{21}H_{26}N_4O_3S \cdot 2HCl$	2.5	50	32.9 ± 5.6 (5)
17e	COC_6H_5	208-210	B	$C_{21}H_{24}N_4O_4S \cdot HCl$	0.3125	50	25.5 ± 4.7 (6)
17f	$CO(C_4H_3O)$[f]	242-245	E	$C_{22}H_{22}N_4O_5S \cdot HCl$	0.008[h]	0.5	28.8 ± 3.4 (8)
17g	$CO(C_3H_3N_2OS)$[g]	230-232	A	$C_{18}H_{22}N_6O_5S_2 \cdot HCl$	0.2	1.0	14.0 ± 3.0 (5)

[a-e] See corresponding footnotes in Table II. [f] C_4H_3O = 2-furanyl. [g] $C_3H_3N_2OS$ = 5-(methylthio)-1,3,4-oxadiazol-2-yl. [h] At this dose, the mean BP lowering over 2 h was 11.9 ± 1.9 mmHg (n = 9). At 0.125 mg/kg iv, the lowering was 24.8 ± 1.9 mmHg (n = 4).

Table V. 3-[4-(2-Furoyl)-1-piperazinyl]-1,2,4-benzothiadiazine 1-Oxides



18a-e

no.	R^1	R^2	mp, °C	recrystn[a] solvent	formula[b]	normotensive[c] rabbits, min. effective dose, iv in mg/kg	SHR[d] dose, mg/kg ip	SHR[d] % BP lowering (no. of animals)
18a	C_2H_5	6,7-$(CH_3O)_2$	216-218	B	$C_{20}H_{24}N_4O_5S \cdot HCl$	2.5	50	18.2 ± 4.4 (6)
18b	$CH(CH_3)_2$	6,7-$(CH_3O)_2$	210-212	B	$C_{21}H_{26}N_4O_5S \cdot HCl$	NT[f]	50	34.3 ± 5.2 (5)
18c	C_6H_5	6,7-$(CH_3O)_2$	235-237	B	$C_{24}H_{24}N_4O_5S \cdot HCl$	1.25	50	26.1 ± 3.9 (6)
18d	CH_3	6,7-$(C_2H_5O)_2$	243-245	A	$C_{21}H_{26}N_4O_5S \cdot HCl$	2.5	50	16.4 ± 4.9 (5)
18e	CH_3	6,7-(-OCH_2O-)	242-245	A	$C_{18}H_{18}N_4O_5S \cdot HCl$	g	50	18.2 ± 5.9 (5)
19	h					1.25	20	-1.0 ± 5.0 (6)[e]
20	i					0.04	50	20.6 ± 3.4 (3)

[a-e] See corresponding footnotes in Table II. [f] Not tested. [g] Not active at 2.5 mg/kg iv. [h] Homopiperazinyl in place of piperazinyl; see Scheme I. [i] 6,7,8-Trimethoxy in place of 6,7-dimethoxy; see text.

indicated that **17f** is a postsynaptic α-adrenergic receptor blocker of equal potency to Prazosin (M. L. Cohen and R. D. Dillard, unpublished results).

Experimental Section

General. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Although the spectral data are not provided herein, all compounds exhibited IR and NMR spectra consistent with the reported structures. IR spectra were determined with a Beckman IR 4250 or a Perkin-Elmer 457A spectrometer. NMR were determined using a Varian Associates A-60A spectrometer with Me_4Si as an internal standard. All compounds were subjected to elemental analysis, and the results were within ±0.4% of theoretical values.

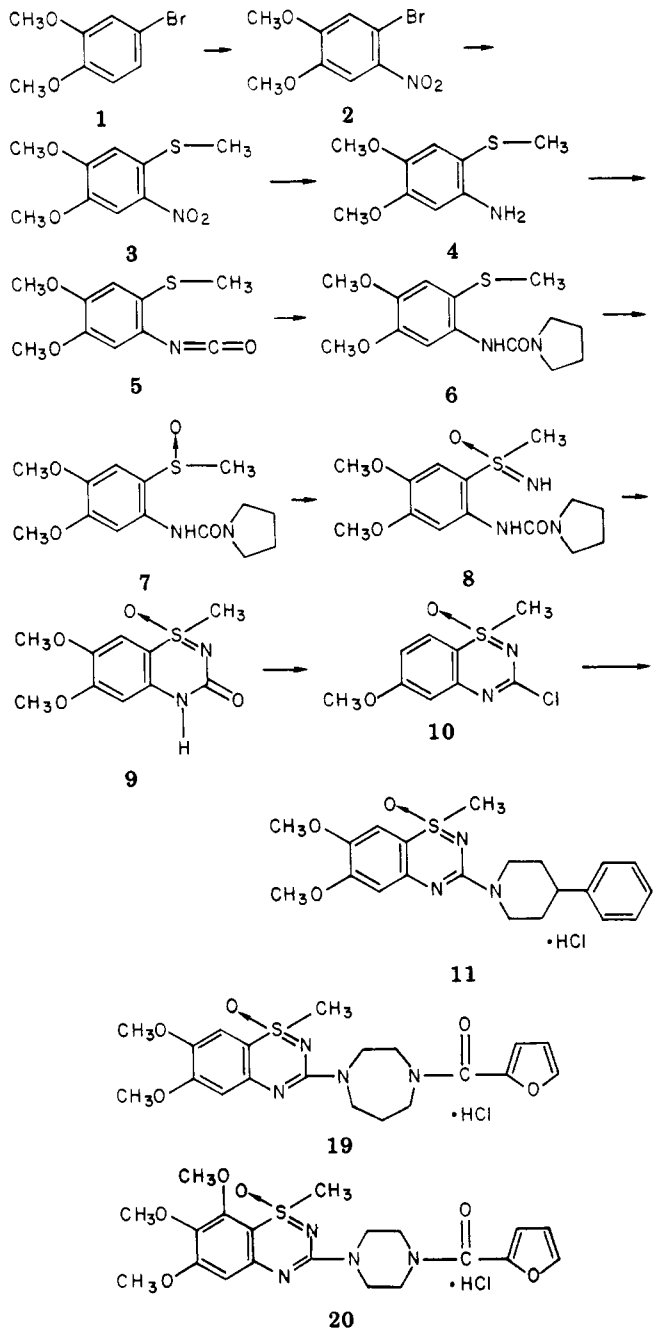
3-Bromo-4-nitroveratrole (2). With vigorous stirring, 100 g (0.46 mol) of 1 was added dropwise to 750 mL of HNO_3 (sp gr 1.42) over a 40-min period while maintaining a temperature of -8 to -4 °C with an ice–ethanol bath. After the addition was complete, stirring was maintained for 10 min and the reaction mixture was diluted with 3 L of cold water. The resulting precipitate was filtered, washed well with water, and recrystallized from 2.5 L of EtOH to give 83.4 g (69.3%), mp 120–122 °C. Anal. ($C_8H_8BrNO_4$) C, H, N.

3-(Methylthio)-4-nitroveratrole (3). Solid **2** (33.5 g, 0.127 mol) was added to a mixture of 21 g of K_2CO_3 and 25 g of methanethiol in 300 mL of EtOH cooled with an ice–water bath. Stirring was maintained for 1 h with cooling and for 24 h at room temperature. The reaction mixture was diluted with 3 L of water, and the precipitate was filtered and crystallized from benzene–EtOH to give 22.8 g (78.6%) of yellow crystals, mp 137–140 °C.[8] Anal. ($C_9H_{11}NO_4S$) C, H, N. Compounds **12a–e** in Table I were prepared in a similar manner.

2-(Methylthio)-4,5-dimethoxyaniline (4). Solid **3** (68.7 g, 0.3 mol) was added in small portions over a 20-min period to a mixture of Sn (200 mesh), 330 mL of HOAc, and 50 mL of concentrated HCl. When the addition was complete, the reaction temperature had risen to 105 °C and an additional 300 mL of concentrated HCl was added. The temperature was maintained at 100–105 °C for 1.5 h with a heating mantle. The mixture was cooled with an ice–water bath, made strongly basic with 50% NaOH solution, diluted with 2 L of water, and extracted 3 times with 2-L portions of ether. The combined ether extracts were dried ($MgSO_4$), the ether was removed at reduced pressure, and the residue was crystallized from benzene–petroleum ether (60–71 °C) to give 37 g (62%) of **4**, mp 72–74 °C.[8] Anal. ($C_9H_{13}NO_2S$) C, H, N. Compounds **13a–e** in Table I were prepared in a similar manner.

(9) For methods, see M. L. Cohen, K. S. Wiley, and I. H. Slater, *Blood Vessels*, **16**, 144 (1979).

Scheme I



***N*-(Pyrrolidinylcarbonyl)-2-(methylthio)-4,5-dimethoxyaniline (6).** A solution of 24 g (0.24 mol) of phosgene in 250 mL of toluene was added rapidly to a solution of 58.1 g (0.48 mol) of *N,N*-dimethylaniline in 500 mL of toluene that was cooled with an ice–water bath. After the solution stirred for 5 min, 39.8 g (0.2 mol) of **4** in 350 mL of toluene was added dropwise over a 30-min period, the cooling bath was removed, and the mixture was stirred for 4 h. The mixture was filtered, the filtrate was concentrated at reduced pressure to a thick oil (**5**), the oil was dissolved in 1 L of acetonitrile, 50 mL of pyrrolidine was added, and the mixture was stirred for 20 h. The mixture was concentrated, and the remaining oil was dissolved in 1 L of CH_2Cl_2, washed twice with 5% HCl, once with water, dried (Na_2SO_4), and concentrated to a solid. The solid was recrystallized from benzene–petroleum ether (bp 60–71 °C) to give 53.7 g (91%) of **6**, mp 141–143 °C. Anal. ($C_{14}H_{20}N_2O_3S$) C, H, N.

***N*-(Pyrrolidinylcarbonyl)-2-(methylsulfinyl)-4,5-dimethoxyaniline (7).** A solution of 52 g (0.176 mol) of **6** and 19.8 mL of 31% H_2O_2 in 1 L of HOAc was stirred for 20 h and concentrated at reduced pressure to a wax. The wax was dissolved in 1 L of CH_2Cl_2, washed with water, and dried (Na_2SO_4), and the CH_2Cl_2 was removed at reduced pressure. The residue was crystallized from benzene–petroleum ether (bp 60–71 °C) to give 44 g (80%) of **7**, mp 124–127 °C. Anal. ($C_{14}H_{20}N_2O_4S$) C, H, N.

***S*-Methyl-*S*-[2-[(pyrrolidinylcarbonyl)amino]-4,5-dimethoxyphenyl]sulfoximine (8).** A solution of 51.7 g (0.165 mol) of **7** and 0.48 mol of MSH[6] in 1 L of acetonitrile was stirred for 48 h and concentrated at reduced pressure. The residue was taken up in 2 L of CH_2Cl_2, shaken with 1.5 L of cold water containing 200 mL of concentrated NH_4OH, and with water. After the CH_2Cl_2 solution was dried (Na_2SO_4), the solvent was removed and the residue crystallized from $CHCl_3$–petroleum ether (bp 60–71 °C). A yield of 38 g (70%) of **8** was obtained, mp 312–314 °C. Anal. ($C_{14}H_{21}N_3O_4S$) C, H, N.

6,7-Dimethoxy-1-methyl-1*H*-1,2,4-benzothiadiazin-3-(4*H*)-one 1-Oxide (9). Method A. A mixture of 42.8 g (0.131 mol) of **8** and 1 L of bromobenzene was heated to boiling with a heating mantle. Heating was maintained for 3 h, with 20 mL of bromobenzene distilling off.

After cooling, the precipitate was filtered and heated with 700 mL of $CHCl_3$. After cooling, the $CHCl_3$ mixture was filtered to give 30.5 g (91%) of **9**, mp 326–328 °C. Anal. ($C_{10}H_{12}N_2O_4S$) C, H, N.

Method B. The sequence of reactions from **4** to **9** was carried out without purifying intermediates at each step, and diethylamine was used in place of pyrrolidine to form the corresponding ureas of **6–8**, to give **9** in an overall yield of 59%. This method was used to prepare **14a–e** in Table I.

6,7-Dimethoxy-1-methyl-3-(4-phenylpiperidino)-1*H*-1,2,4-benzothiadiazine 1-Oxide Hydrochloride (11). A mixture of 2.6 g (0.01 mol) of **9**, 25 mL of $POCl_3$, and 0.5 mL of water was heated to maintain reflux for 3 h, poured onto 200 g of ice, stirred for 10 min, and extracted with 1 L of $CHCl_3$. After drying (Na_2SO_4), the $CHCl_3$ extract was concentrated at reduced pressure to give a tan solid that consisted primarily of **10**. This solid was taken up in 100 mL of CH_3CN, and 5 g (0.03 mol) of 4-phenylpiperidine was added, heated to maintain reflux for 20 h, and concentrated at reduced pressure to a solid. This solid was taken up in 1 L of CH_2Cl_2, washed with a K_2CO_3 solution, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was crystallized from EtOH, the HCl salt was made on the precipitate, and the salt was crystallized from EtOH–isopropyl ether to give 2.4 g (55%) of **11**, mp 216–218 °C. Anal. ($C_{20}H_{25}N_3O_3S$·HCl) C, H, N. This procedure was used to prepare compounds in Tables II–V.

In a similar manner, **3-[4-(2-furanylcarbonyl)hexahydro-1*H*-1,4-diazepin-1-yl]-6,7-dimethoxy-1-methyl-1*H*-1,2,4-benzothiadiazine 1-oxide hydrochloride (19)** was prepared in 21.3% yield, melting at 216–218 °C. Anal. ($C_{20}H_{24}N_4O_5S$·HCl) C, H, N.

Also, **3-[4-(2-Furanylcarbonyl)-1-piperazinyl]-6,7,8-trimethoxy-1-methyl-1*H*-1,2,4-benzothiadiazine 1-oxide hydrochloride (20)** was prepared in 69.1% yield and melted at 130–132 °C. Anal. ($C_{20}H_{24}N_4O_6S$·HCl) C, H, N.

Pharmacological Methods. A. Blood Pressure of Rabbits. Male white rabbits weighing 2.5 to 3.5 kg were given permanent arterial cannulas. Under secobarbital (30 mg/kg iv) anesthesia, the abdomen was opened and a Tygon cannula was inserted into the aorta at its bifurcation and advanced to just distal to the renal artery. The distal end of the cannula was looped, anchored to the posterior abdominal wall, then passed through the muscle layers, run subcutaneously rostrally, and exited at the nape of the neck. Between recording sessions, the cannula was filled with heparin (100 units/mL) and plugged with a stylet. During recording, heparin (50 units/mL) in deionized water was infused through the transducer (Statham) and the cannula at the rate of 0.01 mL/min by a continuous-infusion pump (Harvard Apparatus Co.). Mean arterial blood pressure, obtained by electrical damping, and heart rate were recorded on a polygraph (Grass) and from thence into a computer. The rabbit was placed in a stock, and 30 min later a 30-min control period of recording was started. Drug was then administered into an ear vein, and recording was continued for 120 min. Mean arterial blood pressure and heart rate values at 10-min intervals were averaged over the 120-min period following drug. Dose levels of test compound were adjusted to the minimum level to give statistically significant blood pressure lowering ($p < 0.05$).

B. Blood Pressure of Spontaneously Hypertensive Rats. Male spontaneously hypertensive rats (SHR) of the Wistar/Kyoto strain were supplied by Laboratory Supply Co., Indianapolis, IN. They were kept four per cage and fed Purina Laboratory Chow and water ad libitum. Lights were on 12 h a day. At the time of experiments, rats were about 6 months of age and weighed between 300 and 400 g.

Two methods were employed in measuring the systolic blood pressure of SHR indirectly. In the beginning of this study, systolic blood pressure was measured by a modified method of Friedman and Freed.[7] Using this method, rats were warmed for 30 to 45 s with a microwave oven set at 32 °C. The details of that procedure have been published elsewhere.[7]

Most compounds in this study were, however, tested by the method using photoelectric sensors at 25 °C.[7] A detailed description of that procedure was published previously.[7]

All compounds reported here were synthesized at our Laboratories, except Prazosin which was a gift of Pfizer, Inc. Saline containing 2% Emulphor EL-620 (General Aniline and Film), a polyoxyethylated vegetable oil, was used as the vehicle to facilitate the suspension of all compounds.

Acknowledgment. The authors are indebted to Donovan V. Pearson for his technical assistance in testing compounds in SHR and to Tommy Smith for his technical assistance in testing compounds in rabbits.

Synthesis and Biochemical Screening of Phenylselenium-Substituted Steroid Hormones

Joseph P. Konopelski, Carl Djerassi,*

Department of Chemistry, Stanford University, Stanford, California 94305

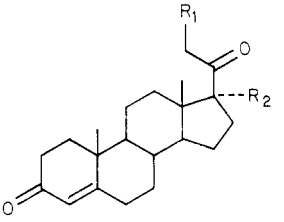
and J. P. Raynaud

Centre de Recherches, Roussel-Uclaf, 93230 Romainville, France. *Received November 26, 1979*

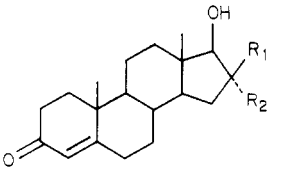
The syntheses of phenylselenium-substituted progesterone [21- (1) and 17α-(phenylseleno)progesterone (2)] and testosterone [16β- (3) and 16α-(phenylseleno)testosterone (4)] derivatives are described, along with data which help to establish the stereochemistry of the substituents in the testosterone molecules. Except for 21-(phenylseleno)-progesterone, the molecules exhibit greatly reduced receptor-binding capabilities.

Interest in the biological effects of organoselenium compounds stems from the dual nature of the element: selenium is both a toxic and essential substance for many living organisms, including humans.[1] Recent advances made in the introduction of organoselenium substituents into organic molecules[2] have also helped to stimulate research into the effects of selenium on natural systems. However, although steroids are among the most potent biological molecules, regulating many important biological functions, few organoselenium-substituted steroids have been prepared,[1e] and there is no report of organoselenium steroids bearing the Δ^4-3-ketone functionality common to many important steroid hormones. Recently, in connection with an unrelated problem, we had occasion to prepare a number of steroid hormones containing organoselenium substituents, and we report herein the synthesis of certain analogues of progesterone [21- and 17α-(phenylseleno)-progesterone (**1** and **2**, respectively)] and testosterone [16β- and 16α-(phenylseleno)testosterone (**3** and **4**, respectively)], together with the results of the biochemical screening of these molecules.

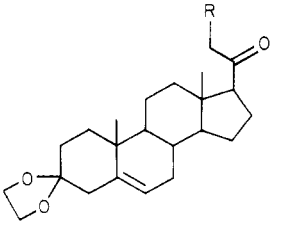
Chemistry. The syntheses of the desired phenylselenium-substituted steroids proved to be straightforward. 3,3-(Ethylenedioxy)pregn-5-en-20-one (**6**)[3] was treated with lithium diisopropylamide and PhSeCl[4] to give the keto-



1, R_1 = SePh; R_2 = H
2, R_1 = H; R_2 = SePh



3, R_1 = SePh; R_2 = H
4, R_1 = H; R_2 = SePh
5, R_1 = R_2 = H



6, R = H
7, R = SePh

selenide **7**, identified by the singlet signal in the NMR spectrum at δ 3.6 for the two protons on C-21. Hydrolysis of the ketal functionality gave the progesterone derivative **1**.

The synthesis of the related compound 17α-(phenylseleno)progesterone (**2**) started with pregnenolone (**8**),

(1) For reviews of this area, see (a) K. Schwarz and K. D. Pathak, *Chem. Scr.*, **8A**, 85 (1975); (b) D. V. Frost and D. Ingvoldstad, *ibid.*, **8A**, 96 (1975); (c) M. L. Scott, in "Organic Selenium Compounds: Their Chemistry and Biology", D. L. Klayman and W. H. H. Günther, Eds., Wiley, New York, 1973, p 629; (d) J. R. Shapiro, *ibid.*, p 693; (e) D. L. Klayman, *ibid.*, p 727.

(2) For a comprehensive review, see D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978).

(3) (a) W. S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954); (b) A. Bowers, L. Cuéllar Ibáñez, and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

(4) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).

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