

matography (silica gel, 50% Et<sub>2</sub>O-petroleum ether) gave 23.1 g (73.5%) of 4-(benzyloxy)-3-nitro-*N,N*-di-*n*-propylphenethylamine, which was used without further purification. To a solution of the 23.1 g (0.065 mol) of the above nitro compound in 100 mL of MeOH was added 0.35 g of PtO<sub>2</sub> and sufficient dry HCl gas in Et<sub>2</sub>O to partially neutralize the amine. The mixture was hydrogenated at 60 psi with shaking. The catalyst was removed by filtration and the solvent by evaporation in vacuo. The residue was dissolved in *i*-PrOH and made acidic by the addition of ethereal HCl, Et<sub>2</sub>O was added slowly, and the salt was filtered; 24.8 g (96%, 71% overall).

**3-Formamido-4-hydroxy-*N,N*-di-*n*-propylphenethylamine Hydrochloride (46).** A solution of 5.0 g (0.015 mol) of the free base of 45 in 150 mL of ethyl formate was refluxed overnight. The ethyl formate was removed in vacuo and the residual oil dissolved in EtOAc/Et<sub>2</sub>O. A small amount of white solid was removed by filtration, and the solvents were again removed in vacuo. This crude product (5.2 g) was used without further purification. A solution of 1.75 g (0.0049 mol) of the above crude formyl derivative in 50 mL of MeOH containing a small amount of EtOAc was hydrogenated at 60 psi with shaking in the presence of 0.75 g of 10% Pd/C. After 1 h the catalyst was removed by filtration and the solvents were removed by evaporation in vacuo to give 1.3 g of an oily product. It was converted to the hydrochloride salt by the addition of ethereal HCl to a solution in MeOH, 0.925 g.

**3-Acetamido-4-hydroxy-*N,N*-di-*n*-propylphenethylamine Hydrochloride (47).** A solution of 2.1 g (0.0064 mol) of the free base of 45 in 75 mL of Ac<sub>2</sub>O was stirred overnight at room temperature. The Ac<sub>2</sub>O was removed in vacuo to give 2.4 g of a tan oil. This oil was dissolved in a mixture of 50 mL of MeOH and 10 mL of EtOAc and hydrogenated with shaking at 60 psi in the presence of 1.0 g of 10% Pd/C. The catalyst was filtered and the filtrate was concentrated to an oil in vacuo. This was converted to the hydrochloride in methanol with use of ethereal HCl, 1.75 g.

**Assay for Inhibition of Adrenergic Neurotransmission in the Isolated Perfused Rabbit Ear Artery (REA).** A 2-4-cm segment of central ear artery is mounted in a narrow cylindrical chamber where it is simultaneously perfused intraluminally and superfused extraluminally with oxygenated Krebs solution. Drugs can be administered by means of either the intraluminal or extraluminal flow. Changes in arterial diameter are reflected as changes in intraluminal perfusion pressure. At 4-min intervals, the vascular sympathetic nerves are excited by pulses from an electronic stimulator delivered through platinum electrodes

present in the chamber. The test drug is administered in increasing concentration. Each concentration is allowed to remain in contact with the tissue for 4 min. The drug concentration is increased immediately following the response to nerve stimulation. If the effect of dopaminergic blockade is to be determined (S)-sulpiride superfusion is begun after obtaining the initial concentration-effect curve for the test compound. Following a 30-min equilibration period, the curve is repeated in the presence of (S)-sulpiride.

**Acknowledgment.** We thank Calab Jervay and Robert Zeid for assistance with the biological assays and Arnold Krog for help in preparing synthetic intermediates. The assistance of the Analytical, Physical and Structural Chemistry Department in the determination of elemental composition is also appreciated.

**Registry No.** 1, 81654-47-9; 2, 81654-48-0; 3, 81654-49-1; 4, 85763-09-3; 5, 101566-00-1; 6-HCl, 101566-01-2; 7a, 91374-22-0; 8a, 91374-23-1; 8b, 101566-02-3; 9a, 97351-95-6; 10a, 91374-25-3; 10b, 101566-03-4; 11, 24954-62-9; 12, 101566-04-5; 13, 101566-05-6; 14, 81654-50-4; 14, 81654-50-4; 15, 101566-06-7; 16, 101566-07-8; 17-HCl, 101566-08-9; 18, 101566-09-0; 18-HBr, 101566-10-3; 19, 81654-51-5; 20, 81654-52-6; 21, 81654-54-8; 21-HCl, 81654-53-7; 22, 85763-08-2; 22-HBr, 81654-59-3; 23-HCl, 101566-11-4; 24, 101566-12-5; 24-HBr, 101566-13-6; 25, 85763-10-6; 25-HCl, 81654-56-0; 26, 81654-62-8; 26-HBr, 81654-57-1; 27-HCl, 91374-19-5; 28, 91374-21-9; 28-HCl, 91374-20-8; 29-HCl, 101566-14-7; 30, 101566-15-5; 31, 101566-16-9; 31-HBr, 101566-17-0; 32, 101566-18-1; 33, 101566-19-2; 33-HCl, 101566-20-5; 34, 101566-21-6; 34-HBr, 101566-22-7; 35-HCl, 101566-23-8; 36, 101566-24-9; 37, 101566-25-0; 38, 101566-26-1; 38-HCl, 101566-27-2; 39, 101566-28-3; 39-HCl, 101566-29-4; 40, 101566-30-7; 41, 101566-31-8; 41-HCl, 101566-32-9; 42, 96886-45-2; 43-HBr, 101566-33-0; 44, 96886-47-4; 45-2HCl, 96886-48-5; 46, 101566-34-1; 46-HCl, 101566-35-2; 47, 101566-36-3; 47-HCl, 101566-37-4; 4-methoxybenzeneethanamine, 55-81-2; propionaldehyde, 123-38-6; 1,2-ethanedithiol, 540-63-6; 4-methylphenylacetaldehyde, 5703-26-4; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4; 2-methyl-3-nitrophenylacetic acid, 23876-15-5; 4-methoxybenzeneethanamine, 55-81-2; propionyl chloride, 79-03-8; *N*-[2-(4-methoxyphenyl)ethyl]propanamide, 67191-51-9; phenylpyruvic acid, 156-06-9; 6-(2-hydroxyethyl)-2(3*H*)-indolone, 101566-38-5; 4-methoxyphenylacetyl chloride, 4693-91-8; 4-(benzyloxy)-3-nitro-*N,N*-di-*m*-propylphenethylamine, 96886-51-0.

## Synthesis, Saludiuretic, and Antihypertensive Activity of 6,7-Disubstituted 1(2*H*)- and 3,4-Dihydro-1(2*H*)-phthalazinones

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The synthesis of the isomeric series 6-chloro-7-sulfamoyl- and 7-chloro-6-sulfamoyl-1(2*H*)-phthalazinones (1 and 2) and 6-chloro-7-sulfamoyl- and 7-chloro-6-sulfamoyl-3,4-dihydro-1(2*H*)-phthalazinones (3 and 4), combining structural features characteristic to furosemide and hydralazine, is described, the mechanism of the formation of 1 and 2 is discussed, and their structure-activities relationships are studied. Preliminary screening in the rat shows that series 1 and 3 exhibit diuretic and saluretic activity similar to that of chlorothiazide with, however, Na<sup>+</sup>/K<sup>+</sup> ratios more favorable than chlorothiazide and furosemide. The compounds of series 2 and 4 are practically inactive. All four series show initial antihypertensive activity lower than that of hydralazine. However, compounds 1a, 1c, and 4a show a higher activity at 8 and/or 24 h after administration and thus may offer a unique combination of a "loop" diuresis with direct long-acting peripheral vasodilating effects.

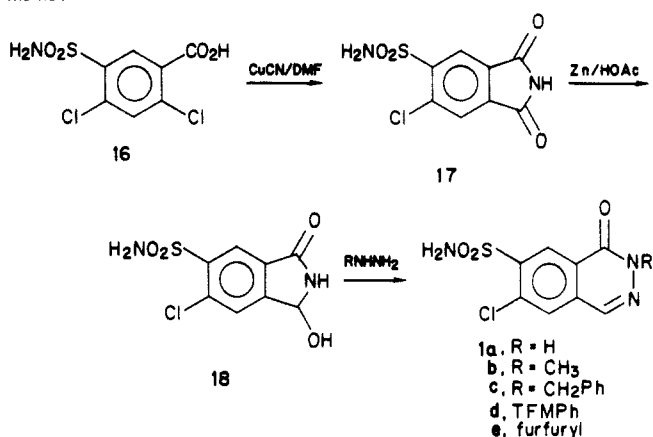
Many diuretics and saluretics possess an aromatic nucleus with a halogen, pseudohalogen, or a phenoxy group in the position ortho to and an electronegative group in the position meta to a sulfonamide group.<sup>1</sup> Among those that have found wide use are furosemide (5), chlorothiazide

(6), hydrochlorothiazide (7), and bumetanide (15) (Figure 1).

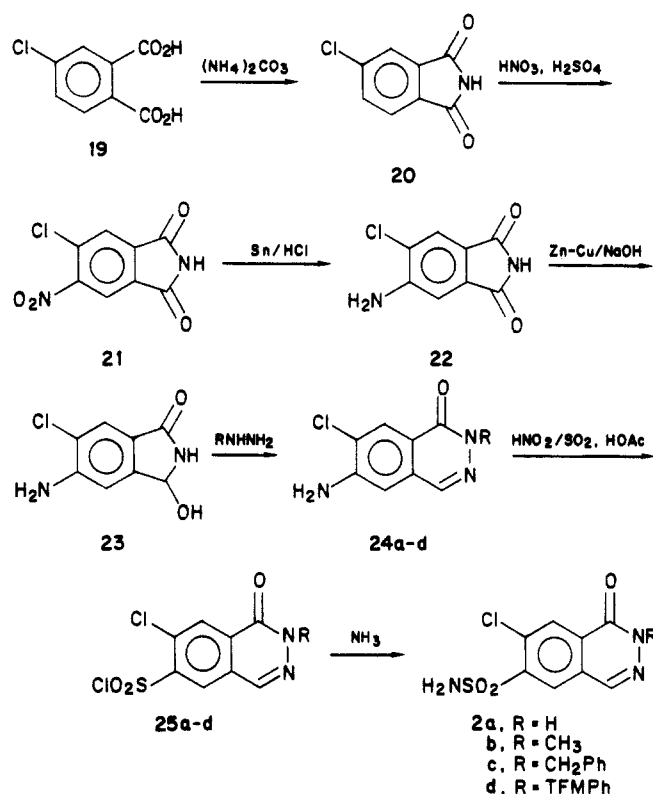
Compounds having cyclic or exocyclic -N-N- moieties (hydralazine, dihydralazine, compounds 11-14<sup>2-4</sup>) are

(1) Feit, P. J. *Med. Chem.* 1971, 14, 432.

(2) Kikuo, A.; Kiyoshi, S. *Jpn. Patent* 7455680; *Chem. Abstr.* 1974, 81, 136167).

**Scheme I.** Synthetic Sequences for Series 1 and 2  
method A

method B

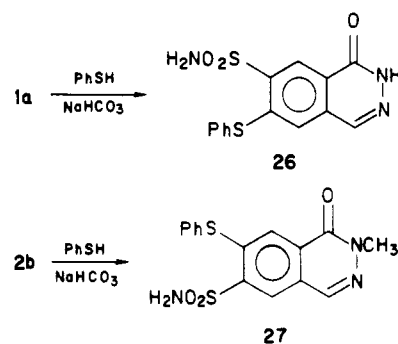
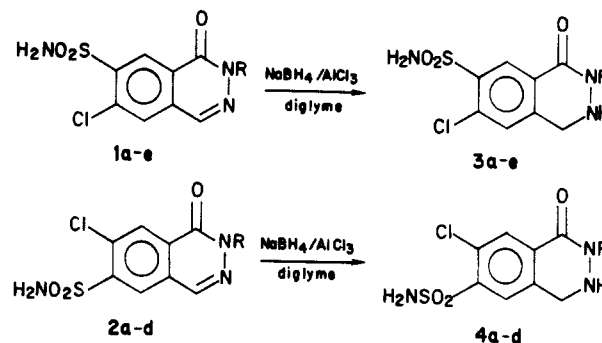


known to possess antihypertensive activity via a peripheral vasodilating effect.

We have synthesized a class of compounds combining structural features of both the furoseamide and the hydralazine type. 1(2*H*)-Phthalazinone, which is one of the metabolites of hydralazine,<sup>5</sup> was selected as the basis for the synthesis of series 1 and 2.

As it is known that reduction of similar diuretic agents often results in enhanced diuretic activity (e.g., hydrochlorothiazide vs. chlorothiazide), we also prepared the analogous series 3 and 4.

As the activity of some diuretics is confined to specific structural isomers, we have examined the structure-activity relationship (SAR) of the two isomeric compounds in both the 1(2*H*)- and 1(2*H*,3*H*,4*H*)-phthalazinone series

**Scheme II****Scheme III**

with respect to their diuretic, saluretic, and antihypertensive activities.

### Chemistry

Two distinct regiospecific pathways have been used for the synthesis of the two isomeric 1(2*H*)-phthalazinone series 1 and 2, as shown in Scheme I. The structure of the two series was unequivocally assigned on the basis of their NMR data and a key intermediate of known structure 18.

**Synthesis.** While the synthetic sequence in series 1 (method A) is short and straightforward, that of series 2 (method B) involves a seven-stage synthesis (Scheme I).

**Method A.** The key intermediate 4-chloro-5-sulfamoylphthalimide 17,<sup>6</sup> obtained by the reaction of 2,4-dichlorosulfamoylbenzoic acid (16) with cuprous cyanide in DMF,<sup>7</sup> was reduced by Zn/acetic acid to the corresponding 3-hydroxyphthalimidine 18. Condensation of the latter with hydrazines afforded the phthalazinones 1a-e.

**Method B.** 4-Chlorophthalimide (20), obtained by fusion of 19 with (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub>, was converted to the phthalimide 22 by nitration and subsequent Sn/HCl reduction. Zn/Cu reduction in basic medium afforded the 3-hydroxyphthalimidine 23, from which, by reaction with hydrazines, the corresponding 6-amino-7-chlorophthalazinones 24a-d were obtained. The amino group was converted to sulfamoyl by applying the Schiemann reaction conditions, followed by treatment with liquid ammonia, thus affording the phthalazinones 2a-d.

It is likely that the reduction step in both sequences determines the regiochemistry of the final products. The electron-withdrawing sulfamoyl group and the electron-donating amino group on the phenyl ring lead to opposite orienting effects and consequently to different courses of reduction.

(3) Delmar Chemicals Ltd, 1974, Brit. Pat. 1417946.

(4) De Ponti, C.; Bardi, U.; Merchetti, M. *Arzneim.-Forsch.* 1976, 26, 2089.

(5) (a) Zimmer, H.; Glaser, R.; Kokosa, J.; Garteiz, D.; Hess, E.; Litwin, A. *J. Med. Chem.* 1975, 18, 1031. (b) Zak, S.; Gilleran, T.; Karliner, J.; Lukas, G. *J. Med. Chem.* 1974, 17, 381.

(6) This compound has been reported to be prepared via a four-step procedure; see ref 7a.

(7) (a) Lee, G. E.; Wragg, W. R. May & Baker, Brit. Pat. 733968, 1961. (b) Cherkez, S.; Herzig, J.; Yellin, H. Teva Pharmaceutical Ind. Ltd Brit. Pat. 1571742, 1977.

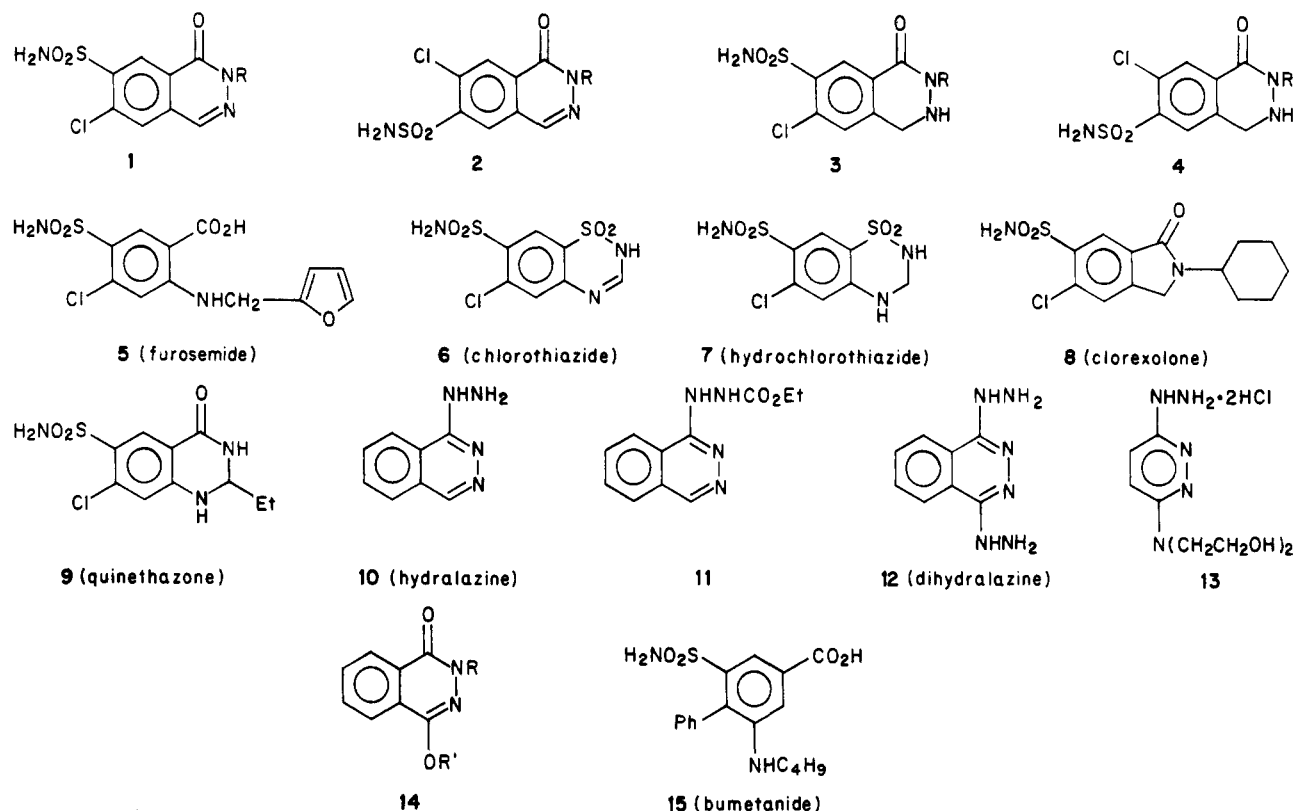


Figure 1.

Two compounds of the (phenylthio)phthalazinone series (26, 27) were prepared by reacting the corresponding chlorophthalazinones with sodium thiophenoxide (see Scheme II). A similar reaction with sodium phenoxide failed, probably due to the lower nucleophilicity of the phenoxide ion.

The compounds of series 3 and 4 were synthesized by the reduction of the two corresponding 1(2H)-phthalazinones 1 and 2 with  $\text{NaBH}_4/\text{AlCl}_3$  in diglyme<sup>8,9</sup> (Scheme III). This reagent was found to effectively reduce the conjugated  $\text{C}=\text{N}$  bond while leaving the carbonyl group intact. The physical, analytical, and spectral properties of phthalazinones 1-4 and of their intermediates are given in Tables I and II.

**Spectral Data.** **NMR.** A detailed discussion of the NMR pattern as a function of the relative position of the substituents is presented below.

**IR.** The  $\text{C}=\text{O}$  absorption bands of 1a and 2a ( $1655$ ,  $1648\text{ cm}^{-1}$ ) are in good agreement with the reported data ( $1658\text{ cm}^{-1}$  for an unsubstituted 1(2H)-phthalazinone<sup>10</sup>). The other compounds have similar absorptions. The two  $\text{SO}_2$  bands appear, as expected,<sup>11</sup> in the  $1330$ – $1360$ - and  $1160$ – $1180\text{ cm}^{-1}$  regions. The  $\text{C}=\text{O}$  absorption bands ( $1636$ – $1668\text{ cm}^{-1}$ ) of 3 and 4 are very similar to those of the corresponding 1(2H)-phthalazinones, the reduction of the  $\text{C}=\text{N}$  bond in the 3,4-position having almost no effect on the absorption of the carbonyl in the 1-position.

**MS.** The mass spectral fragmentation patterns of series 1 and 2 are very similar, both exhibiting a moderate to high intensity molecular ion peak and fragmentations involving the characteristic<sup>12</sup> cleavage of the  $\text{N}-\text{N}$  bond. The frag-

mentation pattern is largely determined by the substituent R. Thus, for  $\text{R} = \text{H}$ ,  $\text{Me}$ , and furfuryl,  $\text{M}^+$  is of high intensity and fragmentations of the pyridazine ring are of moderate intensity. For  $\text{R} = \text{CH}_2\text{Ph}$  and  $\text{CF}_3\text{Ph}$ ,  $\text{R}^+$  is the base peak and all other fragmentations are of minor importance.

Compounds of series 3 and 4 also exhibit a molecular ion peak of moderate to high intensity, depending upon the nature of the substituent R. Both series fragment in similar patterns.

**Reaction of 3-Hydroxyphthalimides with Hydrazines. Mechanism and Intermediates.** The reaction mechanism of 3-hydroxyphthalimide (28) (also described as the open ring tautomer 35)<sup>18</sup> with substituted hydrazines has been widely discussed in the early literature,<sup>14-16</sup> phthalazinone 29, pseudophthalazinone<sup>13</sup> 30, and phthalimidine 31 have all been suggested as possible products (Figure 2). Phthalazinones also have been reported<sup>17</sup> to be obtained from phthalaldehydic acid (or its tautomer 3-hydroxyphthalide 32) via hydrazone or pseudohydrazone intermediates (33 and 34, respectively).

We have proceeded to study the mechanism of phthalazinone formation, giving special attention to (a) the influence of the substituent R on the course of the reaction and (b) possible intermediates. Two types of intermediates have been isolated upon reacting 3-hydroxyphthalimide 18 with the various hydrazines, one for  $\text{R} = \text{H}$  (36) and one

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(17) Vaughan, W. R. *Chem. Rev.* 1948, 43, 447.

(18) (a) Lechat, P. C. R. *Hebd. Seances Acad. Sci.* 1957, 46, 326. (b) Flitsch, W. *Chem. Ber.* 1970, 103, 3205.

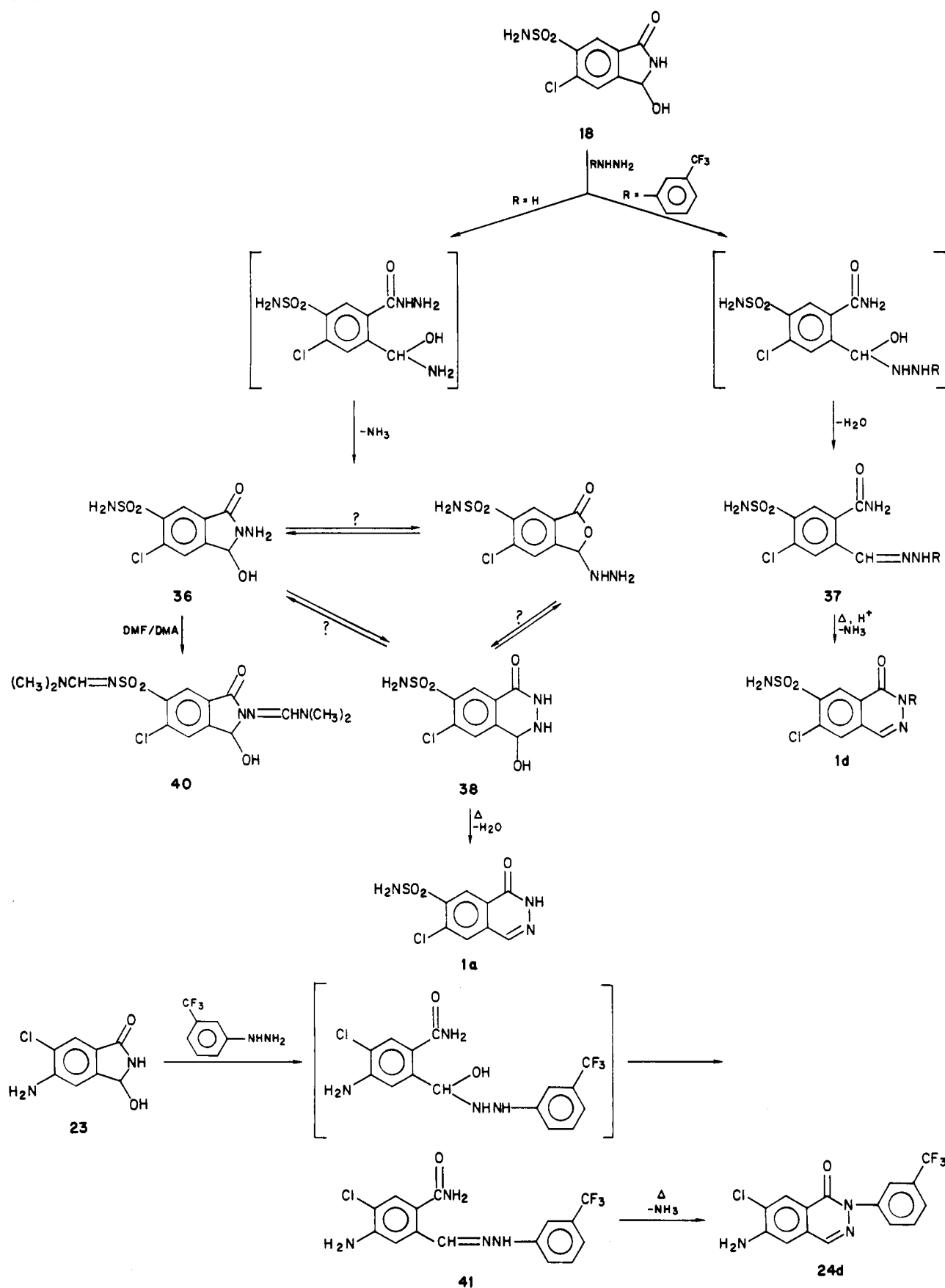
Table I. 1(2H)-Phthalazinones (1a-e, 2a-d, 26, 27) and 1(2H,3H,4H)-Phthalazinones (3a-e, 4a-d)<sup>a</sup>

no.	R	formula <sup>b</sup>	mp, °C	cryst./slurry solvent	yield, %	IR, cm <sup>-1</sup>	MS, m/e	<sup>1</sup> H NMR (Me <sub>2</sub> SO-d <sub>6</sub> ), δ				
								C <sub>4</sub> -H	C <sub>5</sub> -H	C <sub>8</sub> -H	SO <sub>2</sub> NH <sub>2</sub>	other protons
1a	H	C <sub>12</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub> -SCl	>310	H <sub>2</sub> O	46 <sup>d</sup>	3480, 3330, 3200, 1650 (C=O), 1610, 1560, 1470, 1345	259 (M <sup>+</sup> , 100), 243 (7), 202 (5), 179 (39), 151 (11), 124 (48)	8.43 (s)	8.3 (s)	8.78	8.0 (br m)	
1b	CH <sub>3</sub>	C <sub>13</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> -SCl	257-259	H <sub>2</sub> O	33 <sup>d</sup>	3260, 3080, 1645 (C=O), 1633, 1593, 1555, 1427, 1399	273 (M <sup>+</sup> , 75), 245 (100), 202 (15), 193 (9), 165 (25), 122 (35)	8.45 (s)	8.3 (s)	8.8 (s)	8.04 (s)	3.72 (s, 3 H, CH <sub>3</sub> )
1c	CH <sub>2</sub> Ph	C <sub>15</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> -O <sub>3</sub> SCl	236-237	EtOH	30 <sup>d</sup>	3370, 3240, 1638 (C=O), 1579, 1338, 1165	349 (M <sup>+</sup> , 46), 321 (10), 245 (91), 91 (100)	8.5 (s)	8.29 (s)	8.8 (s)	8.0 (s)	5.32 (s, 2 H, CH <sub>2</sub> ), 7.3 (s, 5 H, Ph)
1d	TFMPPh	C <sub>15</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> - <sub>3</sub> SClF <sub>3</sub>	212	H <sub>2</sub> O	48 (88) <sup>e</sup>	3400, 3295, 3090, 1660 (C=O), 1585, 1455, 1387, 1332	403 (M <sup>+</sup> , 33), 323 (4), 202 (6), 145 (100)	8.62 (s)	8.35 (s)	8.8 (s)		7.7-8.1 (m, 6H, SO <sub>2</sub> NH <sub>2</sub> , TFMPPh)
1e		C <sub>13</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> -O <sub>3</sub> SCl	225	Et <sub>2</sub> O	43 <sup>d</sup>	3400, 3300, 3095, 1653 (C=O), 1583, 1386, 1320, 1175	339 (M <sup>+</sup> , 100), 311 (18), 245 (95), 202 (8), 122 (10)	8.47 (s)	8.28 (s)	8.78 (s)	8.0 (s)	5.3 (s, 2 H, CH <sub>2</sub> ), 6.4 (s, 2 H, C <sub>3</sub> '-H, C <sub>4</sub> '-H), 7.58 (s, 1 H, C <sub>5</sub> '-H), 7.62 (s, 5 H, Ph)
26	H	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> -O <sub>3</sub> S <sub>2</sub>	310	Et <sub>2</sub> O	45 <sup>f</sup>	3480, 3260, 3150, 3000, 2900, 1666 (C=O), 1582, 1470, 1440, 1348, 1245	333 (M <sup>+</sup> , 100), 253 (45), 210 (23), 183 (35)	8.22 (s)	7.38 (s)			
2a	H	C <sub>13</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub> -SCl	>300	MeOH	55 <sup>f</sup>	3320, 3240, 3090, 1648 (C=O), 1592, 1448, 1387, 1362, 1330	259 (M <sup>+</sup> , 100), 243 (2), 202 (5), 179 (25), 151 (7), 124 (24)	8.61 (s)	8.65 (s)	8.36 (s)	8.0 (br s)	13.0 (s, 1 H, NH)
2b	CH <sub>3</sub>	C <sub>13</sub> H <sub>9</sub> N <sub>2</sub> O <sub>3</sub> -SCL	280	CHCl <sub>3</sub>	80 <sup>f</sup>	3290, 3200, 3090, 1637 (C=O), 1578, 1542, 1458, 1387, 1367, 1350	273 (M <sup>+</sup> , 100), 245 (94), 202 (13), 193 (12), 165 (35), 122 (20)	8.64 (s)	8.66 (s)	8.4 (s)	8.0 (br s)	3.75 (s, 3 H, CH <sub>3</sub> )
2c	CH <sub>2</sub> Ph	C <sub>15</sub> H <sub>12</sub> N <sub>3</sub> -O <sub>3</sub> SCl	193-195	CHCl <sub>3</sub> /Et <sub>2</sub> O (1:1)	66 <sup>f</sup>	3360, 3230, 3100, 1645 (C=O),	349 (M <sup>+</sup> , 15), 321 (5), 245 (37), 91	8.7 (s, 2H)		8.4 (s)	8.02 (s)	5.32 (s, 2 H, CH <sub>2</sub> ), 7.35 (s, 5 H, Ph)

<b>2d</b>	TFMPPh	$C_{15}H_{14}N_3O_3SClF_3$	172-175	Et <sub>2</sub> O	53 <sup>f</sup>	1577, 1535, 1455, 1387, 1342 3390, 3270, 3100, 1660 (C=O), 1586, 1547, 1495, 1456, 1388 3380, 3280, 1645 (C=O), 1585, 1540, 1364, 1340, 1170 347 (M <sup>+</sup> , 100), 267 (22), 238 (11), 195 (35)	403 (M <sup>+</sup> , 50), 323 (4), 202 (6), 145 (100)	8.76 (s)	8.88 (s)	8.45 (s)	7.7-8.2 (m, 6 H, SO <sub>2</sub> NH <sub>2</sub> , TFMPPh)
<b>27</b>	CH <sub>3</sub>	$C_{15}H_{12}N_3O_3S_2$	279-282	Et <sub>2</sub> O	79 <sup>f</sup>	3380, 3280, 1645 (C=O), 1585, 1540, 1364, 1340, 1170 347 (M <sup>+</sup> , 100), 267 (22), 238 (11), 195 (35)	347 (M <sup>+</sup> , 100), 267 (22), 238 (11), 195 (35)	8.55 (s, 2 H)	7.92 (s)	i	3.1 (s, 3 H, CH <sub>3</sub> ), 7.62 (s, 5 H, Ph)
<b>3a</b>	H	$C_9H_8N_3O_3SCl$	149-151		46 <sup>h</sup>	3200, 1632 (C=O), 1595, 1450, 1348, 1192, 1160 261 (M <sup>+</sup> , 75), 260 (100), 231 (15), 203 (1), 180 (24), 123 (25)	261 (M <sup>+</sup> , 75), 260 (100), 231 (15), 203 (1), 180 (24), 123 (25)	4.02 (s, 2 H)	7.62 (s)	8.38 (s)	7.72 (s)
<b>3b</b>	CH <sub>3</sub>	$C_9H_{10}N_3O_3SCl$	255-257		47 <sup>h</sup>	3260, 3090, 1648, 1632 (C=O), 1595, 1555, 1428, 1372 275 (M <sup>+</sup> , 100), 274 (40), 273 (15), 247 (13), 245 (32), 231 (78), 203 (12), 123 (55)	275 (M <sup>+</sup> , 100), 274 (40), 273 (15), 247 (13), 245 (32), 231 (78), 203 (12), 123 (55)	4.08 (br s, 2 H)	7.6 (s)	8.4 (s)	7.73 (s) 3.07 (s, 3 H, CH <sub>3</sub> )
<b>3c</b>	CH <sub>2</sub> Ph	$C_{15}H_{14}N_3O_3SCl$	232-235	Et <sub>2</sub> O	55 <sup>h</sup>	3320, 3180, 3070, 1631 (C=O), 1595, 1445, 1375, 1330, 1157 351 (M <sup>+</sup> , 20), 349 (2), 260 (2), 247 (8), 245 (7), 231 (5), 218 (3), 123 (5), 91 (100)	351 (M <sup>+</sup> , 20), 349 (2), 260 (2), 247 (8), 245 (7), 231 (5), 218 (3), 123 (5), 91 (100)	4.05 (d, J = 7.5, 2 H)	7.6 (s)	8.45	7.75 (s) 4.72 (s, 2 H, CH <sub>2</sub> ), 6.13 (br t, J = 7.5, 1 H, NH), 7.3 (s, 5 H, Ph)
<b>3d</b>	TFMPPh	$C_{15}H_{11}N_3O_3SF_3Cl$	145-148	Et <sub>2</sub> O	72 <sup>h</sup>	3210, 1668 (C=O), 1595, 1455, 1336, 1170, 1130 405 (M <sup>+</sup> , 90), 403 (90), 231 (35), 145 (100)	405 (M <sup>+</sup> , 90), 403 (90), 231 (35), 145 (100)	4.35 (s, 2 H)	j	8.55 (s)	7.7 (s) 7.5-7.85 (m, 5 H, TFMPPh)
<b>3e</b>	CH <sub>2</sub> Ph	$C_{13}H_{12}N_3O_3SCl$	148-151	Et <sub>2</sub> O	69 <sup>h</sup>	3250, 3060, 1635 (C=O), 1595, 1437, 1340, 1330, 1157 341 (M <sup>+</sup> , 2), 339 (1), 247 (1), 245 (1), 123 (1), 81 (100)	341 (M <sup>+</sup> , 2), 339 (1), 247 (1), 245 (1), 123 (1), 81 (100)	4.05 (d, J = 7.5, 2 H)	7.6 (br s)	8.43 (s)	7.75 (s) 4.7 (s, 2 H, CH <sub>2</sub> ), 6.38 (br s, 2 H, C <sub>3</sub> '-H, C <sub>4</sub> '-H), 7.6 (br s, 1 H, C <sub>5</sub> '-H)
<b>4a</b>	H	$C_9H_8N_3O_3SCl$	152		33 <sup>h</sup>	3220, 1660 (C=O), 1450, 1340, 1195 261 (M <sup>+</sup> , 51), 260 (77), 231 (8), 203 (16), 123 (100)	261 (M <sup>+</sup> , 51), 260 (77), 231 (8), 203 (16), 123 (100)	4.03 (m, 2 H)	7.9 (s, 2 H)		7.6-7.7 (m)
<b>4b</b>	CH <sub>3</sub>	$C_9H_{10}N_3O_3SCl$	255-258		27 <sup>h</sup>	3220, 1642 (C=O), 1455, 1347, 1283, 1193 275 (M <sup>+</sup> , 50), 274 (32), 273 (11), 245 (10)	275 (M <sup>+</sup> , 50), 274 (32), 273 (11), 245 (10)	4.13 (d, J = 8.0, 2 H)	7.92 (s, 2 H)	7.8 (br s)	3.12 (s, 3 H, CH <sub>3</sub> ), 6.11 (t, J = 8.0, 1 H, NH)



Scheme IV



(Scheme IV), depending on the substituent R.

**Structure Assignment.** The correct regiochemistry was assigned to series 1 and 2 on the basis of interpretation of NMR data and on conversion of **18** to a compound of known structure. The regiochemistry of series 3 and 4 is

determined by that of the starting series 1 and 2.

**By  $^1\text{H}$  NMR.** The corresponding deuterio analogues (deuterated at H-4) of **1a** and **2a** have been prepared. By comparison of the NMR spectra of the deuterated and nondeuterated compounds it was found (Figure 3) that the

Table II. Starting Materials 17–23, 6-Amino- and 6-(Chlorosulfonyl)-7-chloro-1(2H)-phthalazinones (24a–d and 25a–d), and Intermediates 36, 37, 40, 41, and 43<sup>a</sup>

no.	mp, °C	cryst./slu-ry solvent	yield, <sup>b</sup> %	IR, cm <sup>-1</sup>	MS, m/e	<sup>1</sup> H NMR (Me <sub>2</sub> SO-d <sub>6</sub> ), $\delta$	remarks
17	290	dioxane	33	3320, 3090, 1793, 1720, 1537, 1390, 1350, 1180, 1150	260 (M <sup>+</sup> , 100), 225 (10), 217 (18), 180 (38)	8.04 (s, 2 H, SO <sub>2</sub> NH <sub>2</sub> ), 8.17 (s, 1 H, C <sub>3</sub> -H), 8.35 (s, 1 H, C <sub>6</sub> -H), 11.75 (s, 1 H, NH)	mp lit. <sup>21</sup> 292 °C
18	272	dil HCl	34	3400, 3310, 3270, 1700 (C=O), 1610	262 (M <sup>+</sup> , 100), 245 (75), 234 (27), 227 (55), 182 (68)	5.96 (d, <i>J</i> = 9 Hz, 1 H, C <sub>3</sub> -H), 6.6 (d, <i>J</i> = 9 Hz, 1 H, OH), 7.82 (m, 3 H, C <sub>4</sub> -H, SO <sub>2</sub> NH <sub>2</sub> ), 8.15 (s, 1 H, C <sub>7</sub> -H), 9.2 (br s, 1 H, NH)	
20	196		91 <sup>c</sup>	1535, 1460, 1345, 3240, 1760, 1725, 1700, 1350, 1300	181 (M <sup>+</sup> , 100), 146 (41), 138 (92), 110 (84), 75 (84)	7.7 (s, 3 H, Ph), 11.3 (br s, 1 H, NH)	
21	192	<i>i</i> -PrOH H <sub>2</sub> O	77 <sup>d</sup> 66			812 (s, 1 H, C <sub>3</sub> -H), 8.35 (s, 1 H, C <sub>6</sub> -H), 11.6 (br s, 1 H, NH)	mp lit. <sup>21</sup> 198 °C
22	312	H <sub>2</sub> O	80			6.4 (s, 2 H, NH <sub>2</sub> ), 6.95 (s, 1 H, C <sub>6</sub> -H), 7.4 (s, 1 H, C <sub>3</sub> -H), 10.5 (br s, 1 H, NH)	mp lit. <sup>21</sup> 314 °C
23	>300	H <sub>2</sub> O	61	3500–3080, 1690, 1622, 1485, 1450	198 (M <sup>+</sup> , 100), 181 (80), 170 (20), 154 (45)	5.85 (br s, 1 H, C <sub>3</sub> -H), 6.2 (br s, 2 H, NH <sub>2</sub> ), 7.05 (s, 1 H, C <sub>4</sub> -H), 7.55 (s, 1 H, C <sub>7</sub> -H), 8.6 (br s, 1 H, NH)	
24a	>310	H <sub>2</sub> O	77	3450–3000, 1680, 1633, 1494, 1385, 1325, 1291	195 (M <sup>+</sup> , 100), 167 (15), 138 (64)	6.55 (br s, 2 H, NH <sub>2</sub> ), 7.1 (s, 1 H, C <sub>3</sub> -H), 8.05 (s, 1 H, C <sub>6</sub> -H), 8.18 (s, 1 H, C <sub>4</sub> -H), 12.3 (m, 1 H, NH)	
24b	>300	H <sub>2</sub> O	60	3500–3200, 1630, 1560, 1490, 1435	209 (M <sup>+</sup> , 60), 181 (100), 138 (59)	3.68 (s, 3 H, CH <sub>3</sub> ), 6.8 (s, 2 H, NH <sub>2</sub> ), 7.34 (s, 1 H, C <sub>5</sub> -H), 8.3 (s, 1 H, C <sub>6</sub> -H), 8.45 (s, 1 H, C <sub>4</sub> -H)	
24c	190–193	Me <sub>2</sub> SO/ H <sub>2</sub> O	37	3500–3200, 1633, 1571, 1492, 1430, 1380	285 (M <sup>+</sup> , 14), 257 (15), 181 (20), 138 (10), 91 (100)	5.3 (s, 2 H, CH <sub>2</sub> ), 6.0–6.9 (m, 2 H, NH <sub>2</sub> ), 7.35 (s, 5 H, Ph), 7.1 (s, 1 H, C <sub>5</sub> -H), 8.1 (s, 1 H, C <sub>6</sub> -H), 8.27 (s, 1 H, C <sub>4</sub> -H)	
24d	148	H <sub>2</sub> O	45 (90) <sup>e</sup>	3550–3200, 1647, 1630, 1572, 1497, 1450, 1375, 1337	338 (65), 145 (81), 138 (100)	6.72 (br s, 2 H, NH <sub>2</sub> ), 7.12, 7.8, 8.0, 8.1, 8.4 (7 H, TFMPh, C <sub>6</sub> -H, C <sub>5</sub> -H, C <sub>4</sub> -H)	
25a	225	H <sub>2</sub> O	68				
25b	189	H <sub>2</sub> O	52				
25c	153–156	H <sub>2</sub> O	61				
25d	105	H <sub>2</sub> O	55				
36	>310	MeOH	47	3310, 3200–3080, 1700 (C=O), 1620, 1424, 1386, 1334	277 (M <sup>+</sup> , 15), 275 (2), 259 (100), 243 (6), 196 (38), 195 (25), 179	4.75 (s, 2 H, NNH <sub>2</sub> ), 5.67 (s, 1 H, C <sub>3</sub> -H), 7.35 (br s, 3 H, SO <sub>2</sub> NH <sub>2</sub> , OH), 7.82 (s, 1 H, C <sub>4</sub> -H), 8.12 (s, 1 H, C <sub>7</sub> -H)	formula C <sub>10</sub> H <sub>9</sub> N <sub>3</sub> O <sub>4</sub> SCl/
37	253	Et <sub>2</sub> O	54	3450, 3220, 3050, 1630 (C=O), 1615, 1535, 1410, 1360, 1330	277 (M <sup>+</sup> , 15), 275 (2), 259 (100), 243 (6), 196 (38), 195 (25), 179	7.05–7.8 (m, 6 H, SO <sub>2</sub> NH <sub>2</sub> , TFMPh), 7.98 (s, 1 H), 8.15 (s, 1 H), 8.22 (s, 1 H), C <sub>3</sub> -H, C <sub>6</sub> -H, benzal), 11.2 (br s, 1 H, NNH)	formula C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> F <sub>3</sub> ClS/
40	220–222	MeOH	38	3260, 2930, 1710, 1692, 1642, 1622, 1425, 1341, 1285	387 (M <sup>+</sup> , 100), 316 (65)	2.95 (s, 9 H, 3 CH <sub>3</sub> ), 3.21 (s, 3 H, CH <sub>3</sub> ), 5.87 (m, 1 H, C <sub>3</sub> -H), 7.0 (m, 1 H, OH), 7.77 (s, 1 H, C <sub>4</sub> -H), 8.0 (s, 1 H, Me <sub>2</sub> NCH=N), 8.17 (s, 1 H, C <sub>7</sub> -H), 8.36 (s, 1 H, Me <sub>2</sub> NCH=NSO <sub>2</sub> )	
41	219	Et <sub>2</sub> O	50	3550–3200, 1626, 1612, 1551, 1480, 1465, 1396, 1337	356 (M <sup>+</sup> , 30), 339 (77), 196 (35), 179 (100), 145 (81)	5.85 (br s, 2 H, NH <sub>2</sub> ), 7.35 (br s, 4 H, TFMPh), 3.5 (s, 2 H, C <sub>6</sub> -H, benzal), 8.5 (s, 1 H, C <sub>3</sub> -H), 10.9 (s, 1 H, NNH)	formula C <sub>13</sub> H <sub>12</sub> N <sub>4</sub> OF <sub>3</sub> Cl/
43	146–147	H <sub>2</sub> O	55	1750 (C=O), 1618,	168 (M <sup>+</sup> , 33), 139 (100),	5.38 (s, 2 H, CH <sub>2</sub> ), 7.8–8.8 (m, 3 H, Ph)	





111 (40)

1590, 1460, 1430,  
1360, 1315, 1273,  
1121, 997, 887,  
830,  
767, 675

<sup>a</sup>For general experimental data, see Experimental Section. <sup>b</sup>Yields were in no case optimized. <sup>c</sup>Prepared from 4-chlorophthalic acid. <sup>d</sup>Prepared from 2,4-dichlorobenzoic acid. <sup>e</sup>The first number refers to the overall yield of 24d based on 23; the number in parentheses indicates the yield of the cyclization of 41. <sup>f</sup>The microanalyses were in satisfactory agreement with the calculated values (C, H, N, O, S, Cl for 36, C, H, N, S, Cl, F for 37, and C, H, N, F, Cl for 41) within  $\pm 0.4\%$ .

Table III. Diuretic and Saluretic Activity<sup>a</sup> in the Rat of Phthalazinone Series 1-4

compd	R	diuretic activity, mL			saluretic activity, <sup>b</sup> mequiv/kg									
		0-5	5-24		0-5					5-24				
			0-5	5-24	0-24	Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>	Na <sup>+</sup> /K <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>	Na <sup>+</sup>	Na <sup>+</sup> /K <sup>+</sup>
1a	H	7.7 $\pm$ 0.6	3.6 $\pm$ 0.5	11.3 $\pm$ 0.8	8.16	2.55	9.87	3.18	3.27	4.21	2.51	4.10	12.37	5.06
1b	CH <sub>3</sub>	6.1 $\pm$ 1.2	2.7 $\pm$ 0.3	8.8 $\pm$ 1.3	8.70	2.67	7.27	3.27	3.27	4.21	2.51	4.10	12.37	5.06
1c	CH <sub>2</sub> Ph	5.9 $\pm$ 1.1	4.9 $\pm$ 1.2	10.8 $\pm$ 0.1	6.40	1.94	7.97	3.29	3.29	5.92	3.36	5.72	12.32	5.3
1d	TFMPH	2.2 $\pm$ 0.7	4.4 $\pm$ 1.4	6.6 $\pm$ 1.9	2.18	1.27		1.72	1.72	4.07	3.04		6.25	4.31
1e		1.8 $\pm$ 0.7	1.0 $\pm$ 0.6	2.8 $\pm$ 1.2	3.68	1.58	3.80	2.83	2.83	2.40	2.16	1.46	6.08	3.74
26	H	2.9 $\pm$ 2.8	4.7 $\pm$ 4.3	7.6 $\pm$ 2.9	2.90	1.45	3.97	2.0	2.44	4.97	4.25	4.47	7.87	5.70
2a	H	5.6 $\pm$ 0.6	3.2 $\pm$ 0.7	8.8 $\pm$ 0.3	6.14	2.51	4.10	2.44	2.44	4.30	3.19	5.02	10.44	5.70
2b	CH <sub>3</sub>	2.2 $\pm$ 0.7	2.6 $\pm$ 1.1	4.8 $\pm$ 1.4	2.58	1.24	2.22	2.10	2.10	5.26	3.92	5.0	7.84	5.16
2c	CH <sub>2</sub> Ph	2.6 $\pm$ 0.9	3.6 $\pm$ 1.8	6.2 $\pm$ 2.5	2.50	1.84	2.90	1.36	1.36	6.29	3.90	6.0	8.79	5.74
2d	TFMPH	0.9 $\pm$ 0.4	4.0 $\pm$ 1.1	4.9 $\pm$ 0.8	0.82	0.49		1.66	1.66	6.59	4.67		7.41	5.16
27	CH <sub>3</sub>	2.1 $\pm$ 0.8	3.8 $\pm$ 1.0	5.9 $\pm$ 1.9	2.05	1.20	2.33	1.70	1.70	6.55	3.42	5.98	8.60	4.62
3a	H	6.5 $\pm$ 1.5	6.2 $\pm$ 1.0	12.7 $\pm$ 0.9	6.55	2.18	8.32	3.0	3.0	4.36	3.45	4.16	10.91	5.63
3b	CH <sub>3</sub>	5.0 $\pm$ 0.7	6.8 $\pm$ 0.7	11.8 $\pm$ 1.3	4.45	2.55	6.20	1.74	1.74	5.98	5.27	3.15	10.43	7.82
3c	CH <sub>2</sub> Ph	6.6 $\pm$ 1.0	6.6 $\pm$ 0.6	13.2 $\pm$ 1.3	6.90	2.61	8.69	2.65	2.65	5.70	4.18	5.0	12.60	6.79
3d	TFMPH	4.9 $\pm$ 1.6	6.7 $\pm$ 1.0	11.6 $\pm$ 1.7	6.17	1.99	7.91	3.10	3.10	4.90	3.42	4.69	11.07	5.41
3e		6.7 $\pm$ 1.8	3.8 $\pm$ 1.6	10.5 $\pm$ 3.4	6.74	2.38	8.45	2.83	2.83	3.09	3.37	2.98	9.83	5.75
4a	H	2.9 $\pm$ 0.5	3.7 $\pm$ 0.8	6.6 $\pm$ 0.3	3.23	1.58	3.49	2.04	2.04	5.84	3.94	6.28	9.07	5.52
4b	CH <sub>3</sub>	2.7 $\pm$ 2.1	3.4 $\pm$ 1.2	6.1 $\pm$ 2.4	2.41	1.35	2.76	1.78	1.78	4.94	3.0	5.29	7.35	4.35
4c	CH <sub>2</sub> Ph	4.0 $\pm$ 1.6	3.6 $\pm$ 0.9	7.6 $\pm$ 1.4	4.01	1.92	5.14	2.10	2.10	5.50	3.29	5.39	9.51	5.21
4d	TFMPH	1.6 $\pm$ 0.1	4.5 $\pm$ 0.9	6.1 $\pm$ 0.8	1.26	0.69	2.07	1.82	1.82	5.60	3.84	6.66	6.86	4.53
furosemide		19.2 $\pm$ 0.6	3.0 $\pm$ 0.2	22.0 $\pm$ 0.8	13.20	4.36	16.2	3.03	3.03	3.02	4.42	1.65	16.22	8.78
chlorothiazide		7.2 $\pm$ 0.3	4.7 $\pm$ 0.2	11.9 $\pm$ 0.6	7.74	3.75	8.80	2.06	2.06	5.03	4.14	4.75	12.77	7.89
saline		2.4 $\pm$ 0.2	3.3 $\pm$ 0.2	5.7 $\pm$ 0.3	2.10	1.38	2.60	1.52	1.52	4.70	3.48	4.03	6.80	4.86

<sup>a</sup>The experimental details of the diuretic and saluretic tests are described in the Experimental Section. <sup>b</sup>Standard deviations for the saluretic data have been calculated and are less than 10% of the mean values.

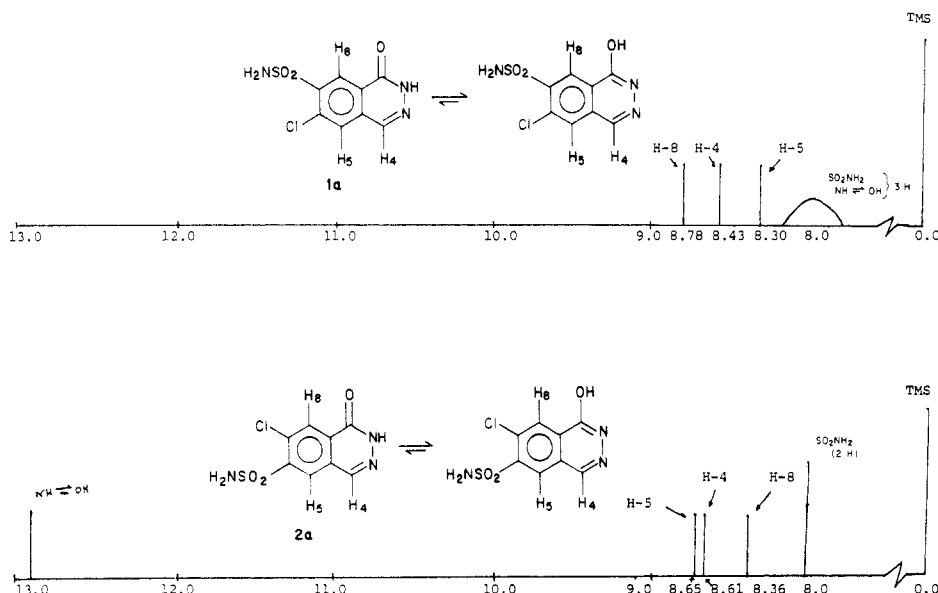


Figure 3.  $^1\text{H}$  NMR spectra (8–13-ppm region) of **1a** and **2a**.

signals of the vinylic protons H-4 are situated between those of the aromatic protons H-5 and H-8. The most downfield signal in both series was assigned to the proton ortho to the powerful electron-withdrawing sulfamoyl group (H-8 in **1a** and H-5 in **2a**).

On the basis of considerations of the electronic effects of the sulfamoyl and carbonyl groups, it may be shown that the difference in chemical shift of the aromatic protons in **1a** should be larger than that of **2a**. Indeed,  $\Delta\delta(\text{H5-H8})$  was found to be 0.48 and 0.29 ppm, respectively. The  $\text{SO}_2\text{NH}_2$  and  $[\text{CONH} \rightleftharpoons \text{C}(\text{OH})=\text{N}]$  signals appear as sharp singlets in the spectrum of **2a**, whereas for **1a** no NH peak can be observed in the 9–14-ppm region and the  $\text{SO}_2\text{NH}_2$  appears as a very broad peak (see Figure 3). This may be explained by the proximity of the carbonyl and the sulfamoyl group in **1a** and subsequent intramolecular exchange.

By changing the nature of the substituent at the 6-position in **1a** from Cl to SPH (a strong electron donating group), an 0.62-ppm upfield shift of the H-5 signal is observed, while H-4 and H-8 remain practically unaffected. The NMR data of **3** and **4** further support the structure assignment presented above. Thus, in series 3, the chemical shift difference  $\Delta\delta(\text{H5-H8})$  is considerable ( $\sim 0.8$  ppm) due to their different magnetic environments, while in **4** both H-5 and H-8 have about the same  $\delta$  value, and in all but one case ( $\text{R} = \text{CH}_2\text{Ph}$ ), the two signals are superimposed. An attempt to assign the three relevant protons (H-4, H-5, H-8) in **1a** and **2a** by determination of the Overhauser effect of two adjacent protons (H-4 and H-5) in **2a** proved unsuccessful and no enhancement was observed. This is probably due to the small separation in chemical shifts (0.04 ppm) between H-4 and H-5.

**By Chemical Synthesis.** By converting **18**, a key intermediate in series 1, to a product of known structure, the regiochemistry of this intermediate and consequently of the series as a whole was unequivocally established. Thus, **18** was treated with Zn–Cu in alkaline medium at elevated temperature, thereby losing the sulfamoyl group and converting the phthalimidine ring to phthalide **43**.

The same phthalide was also obtained from 4-chloro-2-methylbenzoic acid **42** (a commercial compound of known structure) by allylic bromination and spontaneous in situ dehydrobromination (see Scheme V). The identity of the lactones was proved by NMR, MS, IR, and mixture

Scheme V

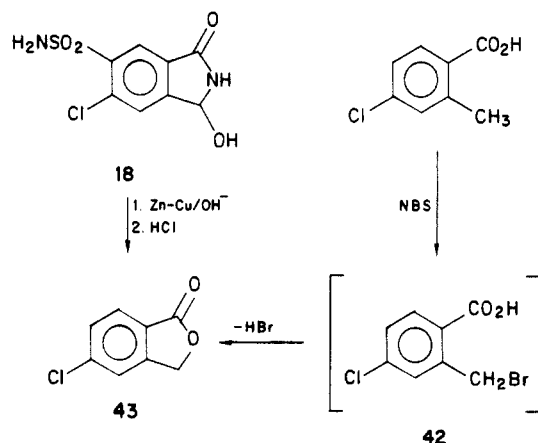


Table IV. Antihypertensive Activity<sup>a</sup> in the Rat of Selected Phthalazinones

compd	drop in systolic blood pressure, mmHg		
	1 h postdose	4 h postdose	24 h postdose
<b>1a</b>	13.7 ± 15.5	33.7 ± 11.0	38.0 ± 10.7
<b>1b</b>	31.7 ± 7.1	47.7 ± 8.7	26.3 ± 23.3
<b>1c</b>	23.0 ± 12.1	36.0 ± 11.1	47.0 ± 11.4
<b>2b</b>	29.7 ± 12.3	47.0 ± 17.8	19.3 ± 10.9
<b>2c</b>	35.3 ± 12.9	54.3 ± 17.3	4.7 ± 19.8
<b>2d</b>	35.6 ± 11.0	54.0 ± 16.5	27.7 ± 23.2
<b>3a</b>	24.7 ± 6.6	31.0 ± 15.6	27.0 ± 6.8
<b>3b</b>	31.3 ± 16.0	45.0 ± 12.1	22.7 ± 20.6
<b>3e</b>	25.3 ± 18.1	31.3 ± 20.3	23.0 ± 15.8
<b>4a</b>	34.7 ± 10.8	51.0 ± 24.9	47.7 ± 25.0
furosemide	35.8 ± 16.3	59.2 ± 16.5	5.3 ± 12.8
hydrochlorothiazide	28.6 ± 9.3	36.7 ± 15.5	18.0 ± 10.1
hydralazine	72.4 ± 33.8	75.1 ± 33.4	35.3 ± 25.0

<sup>a</sup> The experimental details of the tests are described in the Experimental Section.

melting point. Thus, a 7-sulfamoyl structure could be unequivocally assigned to series 1 and subsequently a 6-sulfamoyl structure to series 2.

### Pharmacology

All compounds were subjected to a preliminary screening for diuretic, saluretic, and antihypertensive activity in the

Table V. Antihypertensive Screening of 1c (SHR)

	time following administration, h			
	control (0)	4	8	24
BP <sup>a</sup>	181.2 ± 37.4	163.2 ± 4.6	149.0 ± 1.5	170.2 ± 3.7
ΔBP <sup>a</sup>		23.4 ± 7.9 <sup>c</sup>	40.2 ± 9.2 <sup>c</sup>	14.6 ± 6.6 <sup>d</sup>
heart rate <sup>b</sup>	not measured	399.6 ± 15.2	411.6 ± 8.7	402.0 ± 12.7

<sup>a</sup> Blood pressure, mmHg ± SEM. <sup>b</sup> Beats/minute ± SEM. <sup>c</sup>  $p < 0.05$ . <sup>d</sup>  $0.05 < p < 0.10$ .

rat, and the results are summarized in Tables III–V.

**Diuresis and Saluresis.** Generally, compounds 1a–c and 3a–e exhibited moderate to good diuretic and saluretic activity. When compared to chlorothiazide, compounds 3a and 3c exhibited significantly better diuretic activity ( $p < 0.05$ ), whereas compounds 1a, 3b, 3d, and 3e showed similar activity ( $p > 0.05$ ) at 0–24 h level. The Na<sup>+</sup>/K<sup>+</sup> ratios of 1a–c and 3a,c–e were similar or superior to those of furosemide.

The remaining compounds of series 1, namely, 1d, 1e, and compound 26, showed practically no diuretic or saluretic activity. In series 2, only one compound (2a) exhibited a weak diuretic and a moderate saluretic activity; all the others (2b–d, 27) were, as expected, practically inactive, and thus, this series as a whole may be considered devoid of significant diuretic activity.

All compounds of series 3 exhibited higher diuretic activity than those of series 1, as is the case with the analogous hydrochlorothiazide vs. chlorothiazide.

The compounds of series 4 were moderately saluretic but showed practically no diuretic activity. The results for series 2 and 4 are in agreement with the general observation that a specific regiochemistry (the sulfamoyl and carboxyl groups oriented on the same side of the molecule) is essential for diuretic activity. Substitution of the Cl by the phenylthio group affords no enhancement of activity in series 2 (27) and has an adverse effect on activity in series 1 (26).

**Antihypertensive Activity.** In Table IV are listed those compounds that exhibited significant antihypertensive activity, i.e., comparable to or stronger than that of hydrochlorothiazide at the 1-, 4-, and 24-h time frames. When compared to hydralazine, compounds 1a–c, 2b–d, 3a,b,e, and 4a showed weaker activity at the 1- and 4-h time frames; however, the activity of 1a, 1c, and 4a was stronger at 24-h postdose. Thus, these compounds may offer a unique combination of a "loop" diuresis with direct arterial vasodilating effects of long duration.

Compound 1c was singled out for further screening. Its antihypertensive activity was determined in spontaneously hypertensive rats (SHR; T.N.O., Holland), ranging in weight from 250 to 350 g, and having a spontaneous BP base level of at least 170 mmHg (as measured by the indirect tail cuff plethysmographic method). The test compound was administered po at a single dose of 75 mg/kg to a group of five rats. Both indirect blood pressure and heart rate were recorded prior to and at 4, 8, and 24 h after administration. Their mean group values are presented in Table V, which shows that 1c has significant antihypertensive activity in nonanesthetized SHR, reducing blood pressure by about 40 mmHg with the peak effect occurring about 8 h after administration.

The general profile of compound 1c was determined in groups of three male mice (18–25 g of body weight, starved for 4–6 h) at doses of 50, 100, and 300 mg/kg, by observing motor activity reflexes, sedation, catalepsy, myosis, and mydriasis. No adverse effects have been detected. There was also no apparent difference between controls and ex-

perimental animals at all dose levels in the effect on body weight within 48 h after compound administration.

## Experimental Section

The melting points were obtained on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Analytical Laboratories, Engleskirchen, West Germany. IR spectra were recorded as KBr pellets on a Perkin-Elmer 177 infrared spectrophotometer and are given in reciprocal centimeters. NMR spectra were taken on a JEOL 60 NMR spectrometer; all chemical shifts are given in  $\delta$  units (ppm) downfield from Me<sub>4</sub>Si, and the  $J$  values are given in hertz. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU 6 mass spectrometer at 70 eV and are given as  $m/e$  units with their relative intensity. Monitoring of reactions and homogeneity of intermediates and final products were determined by TLC on Merck silica gel 60-F-254 plates developed with the solvent system CHCl<sub>3</sub>/MeOH.

**4-Chloro-5-sulfamoylphthalimide**<sup>7b</sup> (17). A mixture of 2,4-dichloro-5-sulfamylbenzoic acid (16; 324 g, 1.2 mol); CuCN (123.5 g, 1.2 mol), and DMF (180 mL) was heated gently to 160 °C and kept at this temperature for 2 h. The hot suspension was then poured onto a solution containing FeCl<sub>3</sub> (240 g, 1.49 mol), water (760 mL), and concentrated HCl (100 mL), stirred for 20 min, allowed to cool to room temperature, and filtered. The solid was collected, washed thoroughly with water, and dried to give (after crystallization from dioxane) 102 g (33%) of 17.

**5-Chloro-3-hydroxy-6-sulfamoylphthalimidine** (18). A suspension of 17 (48.0 g, 185 mmol) in MeOH (260 mL) and AcOH (260 mL) was added portionwise to a stirred and cooled mixture of Zn dust (51.0 g, 785 mmol) and water (80 mL), while the temperature was maintained at 10–15 °C. The mixture was stirred at 45 °C for 6 h and filtered. The collected solid was slurried in water (200 mL), filtered, dried, and extracted with MeOH (1.2 L). The methanolic solution was evaporated to dryness, and the residue was purified by slurrying in 10% HCl to remove any residual Zn salts, washed with water, and dried to give 16.5 g (34%) of 18.

**Isolation of Intermediate 5-Chloro-3-hydroxy-6-sulfamoyl-2-aminophthalimidine** (36). A solution of 18 (2.0 g, 7.6 mmol) in hydrazine hydrate (2.0 g, 40 mmol) and water (2 mL) was stirred at room temperature for  $\sim 1/2$  hour. The mixture was poured onto ice, and the solid was collected and washed with water, treated with MeOH, filtered, and dried to give 1.0 g (47%) of 36.

**6-Chloro-7-sulfamoyl-1(2H)-phthalazinone**<sup>14</sup> (1a). A solution of 18 (2.0 g, 7.6 mmol) in hydrazine hydrate (10 g, 200 mmol) and water (10 mL) was stirred at room temperature for 1 h. The solid was collected, slurried in cold water, filtered, and dried to give 0.90 g (46%) of 1a.

**6-Chloro-2-methyl-7-sulfamoyl-1(2H)-phthalazinone** (1b). Methylhydrazine (3.45 g, 75 mmol) was added to a solution of 18 (5.0 g, 19 mmol) in water (10 mL) and 45% NaOH (6.5 mL) and stirred at 40 °C for 5 h under N<sub>2</sub>. The reaction mixture was stirred overnight at room temperature and cooled to 0 °C, and the solid was collected and treated with 10% HCl ( $\sim 2$  mL). The product was washed thoroughly with water and dried to give 1.7 g (33%) of 1b.

**2-Benzyl-6-chloro-7-sulfamoyl-1(2H)-phthalazinone** (1c). A mixture of 18 (1.0 g, 3.8 mmol), benzylhydrazine (2.2 g, 18 mmol), water (4 mL), and EtOH (3 mL) was stirred at 85 °C for 5 h under N<sub>2</sub>. It was then evaporated to dryness and the oily residue was treated with 10% HCl ( $\sim 30$  mL). The resulting suspension was stirred at 10 °C for 1 h and filtered. The solid was washed with water, dried, treated with EtOH, filtered, and dried to give 0.40 g (30%) of 1c.

**6-Chloro-2-furfuryl-7-sulfamoyl-1(2H)-phthalazinone** (1e). To a mixture of 18 (4.0 g, 15.3 mmol) and water (25 mL) was added a solution of furfurylhydrazine (8.8 g, 79 mmol) in EtOH (20 mL). The reaction mixture was stirred at 85 °C for 2 h under N<sub>2</sub>. The mixture was acidified with 10% HCl, and the solid was collected, washed, dried, treated with Et<sub>2</sub>O, filtered, and dried to give 2.2 g (43%) of 1e.

**Isolation of Intermediate 2-(Aminocarbonyl)-5-chloro-4-sulfamoylbenzaldehyde [*m*-(Trifluoromethyl)phenyl]-hydrazine** (37). To a mixture of 18 (3.5 g, 13.4 mmol) and 14

mL of water was added a solution of [*m*-(trifluoromethyl)-phenyl]hydrazine (15.7 g, 89 mmol) in EtOH (21 mL). The mixture was stirred at 85 °C, under N<sub>2</sub>, for 6 h. During this period two additional portions of CF<sub>3</sub>PhNHNH<sub>2</sub> (3.0 g, 17 mmol each) were added. The reaction mixture was cooled to 0 °C, and the yellow solid was collected, washed with water, dried, treated with Et<sub>2</sub>O, filtered, and dried to give 3.03 g (54%) of 37.

**6-Chloro-7-sulfamoyl-2-[*m*-(trifluoromethyl)phenyl]-1-(2*H*)-phthalazinone (1d).** Concentrated HCl (2.5 mL) was added to a solution of 37 (2.5 g, 6 mmol) in DMF (12.5 mL) and the solution was stirred at 100 °C for 10 h. During this period, three additional portions of concentrated HCl (2.5 mL each) were added. The reaction mixture was poured onto ice, and the resulting solid was collected, washed thoroughly with water, and dried to give 2.15 g (88%) of 1d.

**6-(Phenylthio)-7-sulfamoyl-1(2*H*)-phthalazinone<sup>19</sup> (26).** To a suspension of 1a (0.50 g, 2 mmol) in 1 M NaHCO<sub>3</sub> (9 mL) was added thiophenol (0.4 mL). The mixture was stirred at 100 °C for 4 h, cooled to room temperature, and adjusted to pH 8 with dilute HCl. The solid was collected, washed thoroughly with water and ether, and dried to give 0.30 g (45%) of 26.

**4-Chlorophthalimide (20).** (a) **From 4-Chlorophthalic Acid<sup>20</sup> (19).** Compound 19 prepared from its monosodium salt (201.5 g, 1.052 mol) was fused with ammonium carbonate (137.8 g, 1.435 mol), which has been previously ground in a mortar. The mixture was kept at ~300 °C for 2 h, with occasional shaking and reintroduction of the sublimed material. The dark hot melt was poured into an evaporating dish. The brownish solid was ground to a fine dust, 165 g (91%) of 20.

(b) **From 2,4-Dichlorobenzoic Acid.** A mixture of 2,4-dichlorobenzoic acid (573 g, 3 mol), CuCN (322.5 g, 3.6 mol), and pyridine (300 mL) was heated to 130 °C. After a sudden rise of temperature (200 °C), the mixture was cooled to 100 °C and poured into 10% HCl (2 L). Water (~2 L) was added and the mixture was filtered. The solid was refluxed twice with acetone (2 × 1½ L), and the filtrates were evaporated to dryness. The residue was refluxed with 2-propanol (1½ L), and the solid was collected and dried to give 416 g (77%) of 20.

**4-Chloro-5-nitrophthalimide<sup>21</sup> (21).** A solution of 20 (15 g, 82 mmol) in 20% oleum (150 mL) and fuming nitric acid (18 mL) was heated at 80 °C for ½ h. The mixture was cooled to room temperature and poured slowly onto ice (1.5 kg). The solid was collected, slurried twice in water, and dried to give 12 g (66%) of 21.

**4-Chloro-5-aminophthalimide<sup>21</sup> (22).** Compound 21 (8.0 g, 35 mmol) was added to a solution of 28 g of SnCl<sub>2</sub>·2H<sub>2</sub>O in 150 mL of concentrated HCl, and the mixture was heated at 60 °C for ½ h. It was then cooled to 0 °C, and the solid was collected, slurried in water, and dried to give 5.5 g (80%) of 22.

**5-Amino-6-chloro-3-hydroxyphthalimidine<sup>22</sup> (23).** Compound 22 (5.8 g, 29.6 mmol) was added portionwise during ~½ hour to a stirred and cooled mixture of Zn dust (2.2 g, 33.8 mgat), CuSO<sub>4</sub>·5H<sub>2</sub>O (0.03 g), and 2 N NaOH (36 mL). The product was collected, slurried in water, and dried to give 3.6 g (61%) of 23.

**6-Amino-7-chloro-1(2*H*)-phthalazinone<sup>14</sup> (24a).** A mixture of 23 (4.0 g, 20 mmol), 50% hydrazine hydrate (6 mL), and water (20 mL) was stirred at 95 °C for 2 h under N<sub>2</sub>. The mixture was cooled to room temperature and the product was collected, washed with water, and dried to give 3.0 g (77%) of 24a.

**6-Amino-7-chloro-1(2*H*)-phthalazinone (24b).** A mixture of 23 (4.0 g, 20 mmol), methylhydrazine (9 mL), and water (30 mL) was stirred at 90 °C for 3 h under N<sub>2</sub>. The reaction mixture was cooled in an ice bath, and the product was collected, washed with water, and dried to give 2.5 g (60%) of 24b.

**6-Amino-2-benzyl-7-chloro-1(2*H*)-phthalazinone (24c).** A mixture of 23 (8.0 g, 40 mmol), benzylhydrazine (32 g, 260 mmol), water (65 mL), and EtOH (45 mL) was stirred at 95 °C for 20 h under N<sub>2</sub>. During this period an additional portion of benzylhydrazine (10 g, 80 mmol) in water (20 mL) and EtOH (15 mL)

was added. The reaction mixture was filtered hot, the filtrate was cooled to 0 °C, and the solid was collected, slurried first in 10% HCl, then in water, and finally in benzene, and dried, giving 4.3 g of crude product. This was purified by heating in Me<sub>2</sub>SO at 175 °C for 2 h, pouring the hot reaction mixture onto ice and collecting the solid (3.2 g). Another 1.0 g was obtained by evaporation of the filtrate and treatment of the residue with 10% HCl. Overall yield: 4.2 g (37%) of 24c.

**2-(Aminocarbonyl)-4-chloro-5-aminobenzaldehyde [*m*-(Trifluoromethyl)phenyl]hydrazone (41).** A mixture of 23 (10 g, 51 mmol), CF<sub>3</sub>PhNHNH<sub>2</sub> (37 g, 210 mmol), water (60 mL), and EtOH (60 mL) was stirred at 95 °C for 12 h under N<sub>2</sub>. During this period an additional portion of CF<sub>3</sub>PhNHNH<sub>2</sub> (5.0 g, 28 mmol) was added. The reaction mixture was cooled to 0 °C and filtered, and the solid was collected, slurried in ether, and dried to give 8.75 g (50%) of 41.

**6-Amino-7-chloro-2-[*m*-(trifluoromethyl)phenyl]-1-(2*H*)-phthalazinone (24d).** A suspension of 41 (7.0 g, 20 mmol) in Me<sub>2</sub>SO (30 mL) was heated at 180 °C for 3 h. The hot solution was cooled to 100 °C and poured onto ice. The solid was collected, slurried in water, and dried to give 6.0 g (90%) of 24d.

**2-Substituted 7-Chloro-6-(chlorosulfonyl)-1(2*H*)-phthalazinones<sup>21</sup> 25a-d.** General procedure: NaNO<sub>2</sub> solution (20 mmol in 6 mL of water) was added dropwise to a mixture of 24 (10 mmol) in concentrated HCl (23 mL) while the temperature was maintained at 0–5 °C. The mixture was stirred at 5–10 °C for 20 min and poured into glacial acetic acid (15 mL) saturated with SO<sub>2</sub> and containing CuCl (135 mg). The reaction product was collected, slurried in water, and dried. Yields and melting points are listed in Table II.

**2-Substituted 7-Chloro-6-sulfamoyl-1(2*H*)-phthalazinones<sup>21</sup> 2a-d.** General procedure: A mixture of 25 (11 mmol) in liquid ammonia (60 mL) was stirred for 6 h at –60 °C. After allowing the ammonia to evaporate, the residue was triturated with water, collected, and heated with concentrated HCl at 90 °C for 1 h. The mixture was cooled, and the solid was collected, slurried in water, and dried. The crude product was further purified by heating it in an appropriate solvent. Yields and melting points are given in Table II.

**2-Methyl-7-(phenylthio)-6-sulfamoyl-1(2*H*)-phthalazinone<sup>19</sup> (27).** Compound 2b (200 mg, 0.7 mmol) was suspended in 1 N NaHCO<sub>3</sub> (2 mL), and thiophenol (150 mg, 1.5 mmol) was added. The mixture was heated at 100 °C for 6 h, cooled to room temperature, and adjusted to pH 8 by dilute HCl. The solid was collected, washed well with water, and ether and dried to give 200 mg (79%) of 27.

**5-Chloro-6-[[dimethylamino)methylene]sulfamoyl]-3-hydroxy-2-[[dimethylamino)methylene]amino]phthalimidine (40).** *N,N*-Dimethylformamide dimethyl acetal (145 mg, 1.2 mmol) was added to a suspension of 5-chloro-6-sulfamoyl-3-hydroxy-2-aminophthalimidine (36) (75 mg, 0.27 mmol) in absolute MeOH (3 mL). The reaction mixture was stirred for 1 h at room temperature and for 4 h at 50 °C. It was then concentrated under air and the precipitated solid collected and dried to give 40 mg (38%) of 40.

**General Procedure for the Preparation of 3,4-Dihydro-1(2*H*)-phthalazinones 3 and 4.**<sup>8</sup> AlCl<sub>3</sub> (1.6 mmol) was added to dry diglyme (90 mL) with cooling and stirring under N<sub>2</sub>. The mixture was allowed to reach room temperature, and the phthalazinone (1.4 mmol) was added. A solution of NaBH<sub>4</sub> (8 mmol) in dry diglyme (30 mL) was then added dropwise. The mixture was heated for ¾ h at 40 °C (compounds 3b–e, 4c,d); in some cases (3a, 4a,b), additional heating at 70 °C for 1 h was necessary for completion of reaction. The reaction mixture was then cooled to 10 °C, and water (10 mL) followed by 10% HCl (3 mL) was added carefully. The clear yellowish solution was evaporated to dryness. The residue was either extracted with CHCl<sub>3</sub> (in a Soxhlet) for 3 h (R = H, CH<sub>3</sub>) or slurried in an appropriate solvent (R = Bz, CF<sub>3</sub>NHNH<sub>2</sub>, furfuryl). The resulting solid was then slurried in water and dried.

**Preparation of 43.** (1) A suspension of 4-chloro-2-methylbenzoic acid (ICN Pharmaceutical Inc.; 0.5 g, 2.9 mmol), *N*-bromosuccinimide (0.59 g, 2.9 mmol), and dibenzoyl peroxide (7 mg) in carbon tetrachloride (5 mL) was refluxed for 1 h. The reaction mixture was evaporated to dryness and the residue was suspended in a 10% sodium bicarbonate solution. The solid was

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collected, washed, and dried to give 0.2 g (60%) of 43.

(2) **By Reduction of 18.** Compound 18 (500 mg, 2 mmol) was added portionwise to a stirred and cooled mixture of Zn dust (320 mg, 5 mmol),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (2 mg), water (0.5 mL), and 20% NaOH (1 mL). The mixture was stirred in the cold for  $1\frac{1}{2}$  h, diluted with water (2 mL), and heated at 90 °C for 1 h. The Zn was filtered off, and the filtrate was concentrated to about half its volume and acidified (concentrated HCl) in the cold to pH 3. The crude 4-chloro-2-(hydroxymethyl)benzoic acid thus obtained was cyclized by heating in concentrated HCl (1 mL) at 90 °C for  $1\frac{1}{2}$  h. The solid was collected, washed well with water, and dried to give 43 (55%). The spectral data (NMR, IR, MS) of the 5-chlorophthalide prepared in this way are identical with those of the authentic phthalide obtained as described above. No depression was observed in a mixture melting point.

**Pharmacology.** For saluretic screening, all test compounds were prepared as a solution or as a suspension in saline and fed with a stomach tube to male "Sabra" rats (weight 170–200 g) of the Hebrew University, Jerusalem. The animals received 50 mg/kg in a loading volume of 25 mL of saline/kg of body weight. Eight rats were used for testing each compound. Four test compounds and two controls (furosemide or saline, eight rats each) were tested simultaneously on each experimental day. The rats were starved 18 h prior to the feeding and, following administration of the test compounds, were immediately placed in metabolic cages (two animals/cage) in a sound-proof  $22 \pm 1$  °C, well-ventilated, 12:12 h illuminated room. No food or water was supplied during the experimental period. The urine was collected into plastic graduate measuring cylinders (each containing 2 drops of toluene), measured, and analyzed 5 and 24 h after administration of the compound. pH was measured immediately upon collection of the urine. The samples were centrifuged at 2000 rpm, and chlorides were titrated, after acidification with  $\text{HNO}_3$ , by  $\text{Hg}(\text{NO}_3)_2$  in the presence of diphenylcarbazone as indicator.  $\text{Na}^+$  and  $\text{K}^+$  were determined by atomic absorption with a Perkin-Elmer Model 403 spectrophotometer.

For antihypertensive screening, groups of six Sprague-Dawley rats, of 250–350 g of body weight, with a systolic blood pressure

(BP) of minimum 170 mmHg, were treated daily subcutaneously with 10 mg/kg doca and saline. When the BP reached 170 mmHg (usually after 3–4 weeks of doca/saline treatment), the test compounds were given orally in doses of 25 mg/kg in 5 mL/kg of 1% methylcellulose. BP was determined by the tail-cuff method prior to and at 1, 4, and 24 h following administration. Hydralazine (4 mg/kg), hydrochlorothiazide (25 mg/kg), and furosemide (25 mg/kg) served as positive controls.

Summary statistics (mean and standard deviation) for all compounds tested were calculated, and comparisons between compounds analyzed were made by the Student's *t* test for independent samples.

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**Registry No.** 1a, 100448-25-7; 1b, 100448-26-8; 1c, 100448-27-9; 1d, 100448-28-0; 1e, 100448-29-1; 2a, 100448-31-5; 2b, 100448-32-6; 2c, 100448-33-7; 2d, 100448-34-8; 3a, 100448-36-0; 3b, 100448-37-1; 3c, 100448-38-2; 3d, 100448-39-3; 3e, 100448-40-6; 4a, 100448-41-7; 4b, 100448-42-8; 4c, 100448-43-9; 4d, 100448-44-0; 16, 2736-23-4; 17, 3861-99-2; 18, 100448-45-1; 19, 89-20-3; 20, 7147-90-2; 21, 6015-57-2; 22, 5566-48-3; 23, 100448-46-2; 24a, 100448-47-3; 24b, 100448-48-4; 24c, 100448-49-5; 24d, 100448-50-8; 25a, 100448-51-9; 25b, 100448-52-0; 25c, 100448-53-1; 25d, 100448-54-2; 26, 100448-30-4; 27, 100448-35-9; 36, 100448-55-3; 37, 100448-56-4; 40, 100448-57-5; 41, 100448-58-6; 43, 54109-03-4; furfurylhydrazine, 6885-12-7; 4-chloro-2-(hydroxymethyl)benzoic acid, 100448-59-7; hydrazine, 302-01-2; methylhydrazine, 60-34-4; benzylhydrazine, 555-96-4; [*m*-(trifluoromethyl)phenyl]hydrazine, 368-78-5; thiophenol, 108-98-5; 2,4-dichlorobenzoic acid, 50-84-0; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; 4-chloro-2-methylbenzoic acid, 7499-07-2; CuCN, 544-92-3.

## Modified Di- and Tripeptides of the C-Terminal Portion of Oxytocin and Vasopressin as Possible Cognition Activation Agents

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A number of peptides and modified peptides were synthesized and studied for their ability to reverse electroconvulsive shock-induced amnesia in rodents. A few of these peptides were selected for secondary evaluation in tests of short-term memory in rats and aged rhesus monkeys. A number of the peptides and modified peptides were active in the amnesia reversal test. In selected secondary tests, however, the chosen compounds failed to show significant activity in enhancing memory. New methods for preparing methyleneamino and methyleneoxy isosteres of peptides are reported. Other modified peptides also included methylenethio, methylenesulfonyl, and ethylene isosteres in place of the normal peptide amide bond.

The ability of peptides to influence cognitive functions has been the subject of several recent investigations.<sup>1–5</sup> de Wied has shown that lysine vasopressin delays the extinction of active avoidance behavior in the intact rat and Walter et al. have reported on the protective effects of neurohypophyseal hormones and analogues and C-terminal fragments of these hormones on the amnestic action of puromycin in mice.

An interest in the area of pharmacological treatments for cognitive dysfunctions or impairments has been actively

pursued in these laboratories for some time. Previous reports covered the activity of 3-(aryloxy)pyridines<sup>6</sup> and

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