ings[18,19] and after treatment with an anticholinesterase agent in order to eliminate effects mediated by inhibition of this enzyme or differences in substrate specificity. Although these precautions do not eliminate an indirect mechanism, they make it unlikely. A second possible explanation lies in the highly directional nature of the H bond in comparison with a simple ionic bond; thus considerably greater constraints could be placed on the "fit" with the remainder of the molecule, particularly in the case of less flexible compounds. Third, intramolecular interactions in dilute solution may be sufficiently strong to preclude the adoption of a conformation appropriate for interaction with the receptor. In the present study the basis hydrolysis kinetics have been examined to provide an assessment of intramolecular interactions in a paired series of tertiary and quaternary ammonium compounds with muscarinic activity. There was a significant negative correlation (Figure 3) between an anchimeric effect on hydrolysis and muscarinic potency of the tertiary amine relative to its *N*-Me quaternary analog, and the data support the view that intramolecular interactions restricting conformational flexibility are responsible for the low muscarinic activity of tertiary amines such as dimethylaminoethyl acetate.

There are several conformational studies of ACh from which inferences have been drawn regarding the structure of the cholinergic receptor. The techniques employed have included X-ray diffraction studies in the solid state,[20] ir spectral studies in EtOH,[21] and the biological activity of derivatives of ACh with fixed stereochemistry.[22] The first 2 studies demonstrated a cyclic structure for ACh with a cisoid relationship between C-N and C-O bonds, and postulated that this conformation is important for interaction with the receptor. More recent pmr and ir studies have yielded similar data.[23] In a study with rigid cyclopropyl analogs of ACh, Chiou, *et al.*,[22] concluded that a transoid relationship between the C-N and C-O bonds is important for muscarinic activity. Those cyclopropyl derivatives cannot alter their conformation and only the trans isomer was active. If ACh must assume a transoid conformation to interact with the muscarinic receptor and produce an effect, structural and electronic features of ACh analogs which favor a cyclic or cisoid conformation should reduce the pharmacological potency. The intramolecular interactions inferred from the present study presumably lower muscarinic activity by this mechanism.

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Correlation of Antihypertensive Activity with Structure in a Series of 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides Using the Substituent Constant Approach†

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The relationship of the antihypertensive properties of an extensive series of substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides to lipophilic, electronic, and steric effects has been examined using multiple regression analysis and the substituent constant approach of Hansch. A high degree of correlation was observed between activity and the π values of substituents at certain positions in the nucleus. Electronic effects appeared to be of minor significance. The activities of several compounds not included in the regression analyses could be calculated within satisfactory limits and structural requirements for compounds of maximum activity in the series were established. Some implications with regard to possible receptor site interactions are considered.

Following the discovery of the antihypertensive agent, diazoxide, 7-chloro-3-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (I, $R_3 = CH_3$, $R_7 = Cl$, $R_5 = R_6 = R_8 = H$),[1] many analogs were prepared in order to study structure-activity relationships.[2,3] The development and wide application of the substituent constant method to structure-activity problems by Hansch[4] prompted us to examine this approach in the antihypertensive benzothiadiazine series.

The 1,2,4-benzothiadiazine 1,1-dioxide system is capable

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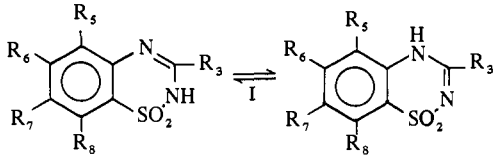


IA, 2*H* tautomer IB, 4*H* tautomer

of existing in two tautomeric forms, IA and IB. On the basis of ultraviolet spectral measurements with N_2- and N_4-alkylated derivatives and the corresponding unsubstituted NH compounds, Novello, *et al.*,[5] tentatively concluded that the 4*H* tautomer (IB) predominates in alcohol solution. This conclusion has been supported by a similar study using different compounds.‡ Molecular orbital calculations using the extended Huckel technique have been employed to compute the energy differences between forms IA and IB for a series of substituted 1,2,4-benzothiadiazines.[6] This study indicated IB to be the preferred form. Since the present study is concerned with the action of these compounds in solution in biological systems they will be depicted in the 4*H* tautomeric form although the 2*H* nomenclature in naming the compounds is retained, consistent with past practice by Chemical Abstracts.

Method. The approach formulated by Hansch[4] was utilized in which the effect of a substituent X on the free energy change in a rate or equilibrium process characterized by K is factored as in eq 1. In eq 1 C_X is the molar concentration

$$\delta X \log K = \log 1/C_X = a\pi_X + b\sigma_X + cE_{SX} + d \qquad (1)$$

of compound with substituent X producing an equivalent biological response such as ED_{50} under the assay conditions used in the experiment. The parameter π is defined as $\pi_X = \log P_X - \log P_H$ where P_X is the octanol-water partition coefficient of a derivative and P_H is that of a parent molecule. Electronic effects of X, which may be represented by Hammett's σ or similar parameters, are related to highly specific electronic effects not contained in π. For steric effects of X the E_S parameter of Taft or E_S^c, the Hancock modification of the Taft parameter may be used. As with π and σ there is overlap between π and E_S so that steric effects represented by E_S (or E_S^c) will be highly specific effects such as those involved in the formulation of that parameter. Other free energy related parameters such as polarizability may also be employed in eq 1 and those parameters which are significant in terms of the biological response are determined by regression analysis.

For the series under investigation, the activity measure used in the correlations is based on the ability of a compound to block the norepinephrine-induced contractile response of the rat aortic ring and is determined experimentally as an ED_{50} (μl/ml) value.§ This provides a measure of the effect of the compound on vascular reactivity which, according to the accepted mechanism of action of diazoxide, is directly related to its antihypertensive properties.[7,8] The ED_{50} (μl/ml) value *vs.* norepinephrine may be viewed as an *in vitro* measure of antihypertensive activity in this series of compounds. For the purposes of the correlations a logarithmic value was computed from eq 2. The factor 2

$$A = \log\left[\frac{2 \times \text{molecular weight}}{ED_{50}}\right] \qquad (2)$$

which appears in eq 2 is used merely for convenience of scale. Since 1,2,4-benzothiadiazine 1,1-dioxides are weak acids and may be partially ionized under the test conditions employed for the determination of biological activity, a correction factor C was calculated for this effect according to eq 3,[9,10] where K_a is the dissociation constant and H^+

$$C = \log\frac{K_a + [H^+]}{[H^+]} \qquad (3)$$

is the hydrogen ion concentration in the test medium. The actual activity value used in the correlations was A^* given by eq 4.

$$A^* = A + C \qquad (4)$$

Another activity value, pA_2, which is a measure of the competitive antagonism of Ba^{2+}-induced contractile response of the rat aortic ring, has been used in other structure-activity correlations with this series of compounds.[11] These values, corrected for ionization and designated pA_2^*, are highly correlated with A^* values for the corresponding compounds as shown by eq 5. Since A^* values were available

$$pA_2^* = 3.40(\pm 0.30) + 1.03(\pm 0.13)A^*$$
$$n = 33, r = 0.95, r^2 = 0.89, s = 0.38, p < 0.005 \qquad (5)$$

for a larger series of compounds, these were used in preference to pA_2^* values for the present study. For most compounds in the study the magnitude of C was small compared to A reflecting the fact that these compounds were largely undissociated at the pH (7.4) of the biological test medium. All highly active compounds were essentially present as the neutral form under test conditions. Compounds with appreciable concentrations of both neutral and ionized forms present under test conditions were well accounted for in the correlations by assuming that only the neutral form was responsible for activity. Very highly ionized compounds (>95%) had minimal activities.

The various substituent constants utilized in the correlations[4] consisted of π values as a measure of possible penetration effects and hydrophobic bonding, σ values (of the Hammett and Taft types) for electronic effects, and E_S^c values (Taft steric values as modified by Hancock[12]) for steric effects. The π values were determined experimentally, using the *n*-octanol-water system for the 1,2,4-benzothiadiazine 1,1-dioxide series.[13] The σ values were determined experimentally from pK_a measurements in 33% DMF-water, on substituted 1,2,4-benzothiadiazine 1,1-dioxides.§

Data correlations were carried out using a stepwise multiple regression analysis performed on an IBM-360-40 computer with variables entered and removed at the $p < 0.10$ level.

Results and Discussion

From the data pertaining to twenty 3-methyl-1,2,4-benzothiadiazine 1,1-dioxides (Table I, **1-20**), differing only in substitution at the 6 and 7 positions, eq 6 and 7 were formulated. In these equations the figures in parentheses are the 95% confidence intervals, the values under the variables are the significance levels for those variables, n is the number of data points employed, r is the correlation coefficient, s is the standard deviation from regression, and p is the significance level. It is apparent that the preferred equation is 6 where activity correlates well with a combination of π and σ terms. From a comparison of eq 6 and 7 it can be seen that π is the dominant term in the correlation since omission of

‡M. D. Yudis, unpublished work.

§The biological data was furnished by Dr. A. Wohl, Department of Pharmacology, Schering Corporation. See Wohl, *et al.*[16]

$$A^* = 0.81(\pm0.26) + 0.80(\pm0.32)\,\pi_{R_{6\text{-}7}} + 0.30(\pm0.25)\sigma_{R_{6\text{-}7}}$$
$$(p < 0.005) \qquad (p < 0.025)$$
$$n = 20, r = 0.92, r^2 = 0.84, s = 0.29, p < 0.005 \qquad (6)$$

$$A^* = 0.83(\pm0.29) + 1.05(\pm0.28)\pi_{R_{6\text{-}7}}$$
$$n = 20, r = 0.88, r^2 = 0.78, s = 0.33, p < 0.005 \qquad (7)$$

the σ variable in eq 7 results in only a small loss of fit.

Adding nine compounds with substituents at the 5 or 8 positions to the 20 6- and 7-substituted compounds provided a total of 29 compounds (Table I, **1-29**) which form the basis of eq 8-10. In this set of compounds activity cor-

$$A^* = 0.79(\pm0.27) + 0.99(\pm0.24)\pi_{R_{5\text{-}8}}$$
$$n = 29, r = 0.86, r^2 = 0.73, s = 0.35, p < 0.005 \qquad (8)$$

$$A^* = 0.90(\pm0.21) + 0.62(\pm0.34)\pi_{R_{6\text{-}7}} + 0.44(\pm0.30)\sigma_{R_{6\text{-}7}}$$
$$(p < 0.005) \qquad (p < 0.005)$$
$$n = 29, r = 0.91, r^2 = 0.82, s = 0.29, p < 0.005 \qquad (9)$$

$$A^* = 0.86(\pm0.23) + 1.04(\pm0.23)\pi_{R_{6\text{-}7}}$$
$$n = 29, r = 0.87, r^2 = 0.76, s = 0.33, p < 0.005 \qquad (10)$$

relates only with the $\pi_{R_{5\text{-}8}}$ term in eq 8; the $\sigma_{R_{5\text{-}8}}$ term is not significant in this case. Moreover, the overall fit of the data, although satisfactory, is not as good as for 6,7-sublower using eq 9 and 10 than for eq 8. In addition using compounds **2**, **22**, **23**, **24**, and **25**, which differ only with respect to 5 substitution, no correlation of activity with π and/or σ was observed. Thus in the limited group of such compounds studied there is no evidence of correlation between activity and the π and σ values of 5 and 8 substituents.

Data on a large number of substituents at the 3 position were available for study. In addition to possible hydrophobic bonding and electronic effects accounted for by π_{R_3} and σ_{R_3}, steric effects of 3 substituents, represented as E_S^c were seen as possibly affecting activity. Since E_S^c values are known for many fewer substituents than π and σ values, a study was devised involving substituents for which E_S^c values were available to see if this term was significant in the correlation. Since there tends to be a rather good correlation between π and E_S^c for many substituents,[14] it is necessary to select examples so as to minimize this covariance problem, for otherwise a possible correlation with E_S^c might be masked entirely by a better overall correlation with π. It has been shown that the σ^* values employed in this study are independent of steric effects as represented by E_S^c.# The π terms, $\pi_{R_{6\text{-}7}}$ and π_{R_3}, were examined as separate variables[15] rather than as a combined single π variable since the degree of possible hydrophobic bonding at these different regions in the molecule may differ significantly. Table II lists data on 15 compounds (**1-15**) from which eq 11 was derived. This equation accounts for 84% of the variance in the data and contains only π terms; neither

$$A^* = 0.44(\pm0.67) + 1.24(\pm0.57)\pi_{R_{6\text{-}7}} + 0.92(\pm0.66)\pi_{R_3} - 0.28(\pm0.29)\pi_{R_3}{}^2 \qquad (p < 0.005) \qquad (p < 0.025)$$
$$(p < 0.10)$$
$$n = 15, r = 0.91, r^2 = 0.84, s = 0.24, p < 0.005 \qquad (11)$$

Table I. Observed and Calculated *in Vitro* Vascular Reactivity Effects of 3-Methyl-1,2,4-benzothiadiazine 1,1-Dioxides Substituted at the 5, 6, 7 and 8 Positions

						Activity data										
No.	Compound	$\pi_{R_{6\text{-}7}}$[a]	$\pi_{R_{5\text{-}8}}$[a]	$\sigma_{R_{6\text{-}7}}$[b]	$\sigma_{R_{5\text{-}8}}$[b]	A_{obsd}[c]	C[d]	A^*_{obsd}[e]	A^*_{calcd}[f]	ΔA^*[f]	A^*_{calcd}[g]	ΔA^*[g]	A^*_{calcd}[h]	ΔA^*[h]	A^*_{calcd}[i]	ΔA^*[i]
1	H	0	0	0	0	0.41	0.00	0.41	0.81	−0.40	0.79	−0.38	0.90	−0.49	0.52	−0.11
2	7-Cl	0.91	0.91	0.77	0.77	1.79	0.04	1.83	1.76	0.07	1.69	0.14	1.81	0.02	1.68	0.15
3	6-Cl	0.89	0.89	0.89	0.89	1.66	0.04	1.70	1.78	−0.08	1.67	0.03	1.85	−0.15	1.67	0.03
4	6,7-Cl_2	1.90	1.90	1.66	1.66	2.64	0.17	2.81	2.82	−0.01	2.57	0.25	2.75	0.06	2.82	−0.01
5	6-CH_3	0.45	0.45	−0.11	−0.11	1.06	0.01	1.07	1.13	−0.06	1.23	−0.16	1.13	−0.06	1.10	−0.03
6	6-OCH_3	0.27	0.27	0.15	0.15	1.74	0.01	1.75	1.07	0.68	1.05	0.70	1.13	0.62	0.87	0.88
7	6-CF_3	1.30	1.30	1.31	1.31	1.91	0.11	2.02	2.24	−0.22	2.07	−0.05	2.29	−0.27	2.20	−0.18
8	7-Br	1.08	1.08	0.57	0.57	1.53	0.02	1.55	1.84	−0.29	1.85	−0.30	1.82	−0.27	1.90	−0.35
9	6-CF_3, 7-Cl	2.21	2.21	2.08	2.08	2.80	0.33	3.13	3.20	−0.07	2.97	0.16	3.20	−0.07	3.35	−0.22
10	7-F	0.33	0.33	0.47	0.47	1.22	0.02	1.24	1.21	0.03	1.11	0.13	1.31	−0.07	0.95	0.29
11	6-Br	1.08	1.08	0.87	0.87	1.87	0.07	1.94	1.93	0.01	1.85	0.09	1.96	−0.02	1.91	0.03
12	7-CF_3	1.22	1.22	1.22	1.22	2.01	0.09	2.10	2.15	−0.05	1.99	0.11	2.20	−0.10	2.08	0.02
13	7-I	1.32	1.32	0.70	0.70	1.96	0.03	1.99	2.07	−0.08	2.09	−0.10	2.03	−0.04	2.21	−0.22
14	6-C_2H_5	0.96	0.96	−0.09	−0.09	1.51	0.01	1.52	1.55	−0.03	1.73	−0.21	1.45	0.07	1.75	−0.23
15	6-OCH_3, 7-Cl	1.18	1.18	0.92	0.92	2.60	0.03	2.63	2.03	0.60	1.95	0.68	2.75	−0.12	2.03	0.60
16	7-CH_3	0.52	0.52	−0.27	−0.27	1.00	0.00	1.00	1.14	−0.14	1.30	−0.30	1.10	−0.10	1.19	−0.19
17	6-NO_2, 7-Cl	1.13	1.13	2.16	2.16	2.09	0.50	2.59	2.35	0.24	1.90	0.69	2.56	0.03	1.97	0.62
18	7-NO_2	0.36	0.36	1.79	1.79	0.97	0.27	1.24	1.62	−0.38	1.14	0.10	1.28	−0.04	0.99	0.25
19	6-NH_2, 7-Cl	0.34	0.34	−0.01	−0.01	1.02	0.01	1.03	1.08	−0.05	1.12	−0.09	1.10	−0.07	0.96	0.07
20	6-NHAc, 7-Cl	0.24	0.24	0.82	0.82	1.44	0.04	1.48	1.24	0.24	1.02	0.46	1.41	0.07	0.83	0.65
21	5-Cl	0	0.43	0	1.67	0.58	0.22	0.80			1.21	−0.41	0.90	−0.10		
22	5,7-Cl_2	0.91	1.23	0.77	2.44	0.95	0.51	1.46			2.00	−0.54	1.81	−0.35		
23	5-Br, 7-Cl	0.91	1.36	0.77	2.22	2.04	0.53	2.57			2.13	0.44	1.81	0.76		
24	5-I, 7-Cl	0.91	1.52	0.77	2.20	1.64	0.53	2.17			2.29	−0.12	1.81	0.36		
25	5-CH_3, 7-Cl	0.91	1.14	0.77	0.52	1.58	0.04	1.62			1.91	−0.29	1.81	−0.19		
26	8-Cl	0	0.35	0	0.76	0.96	0.03	0.99			1.13	−0.14	0.90	0.09		
27	6,8-Cl_2	0.89	1.24	0.89	1.65	1.53	0.16	1.69			2.01	−0.32	1.85	−0.16		
28	7,8-Cl_2	0.91	1.26	0.77	1.53	1.66	0.11	1.77			2.03	−0.26	1.81	−0.04		
29	6,7,8-Cl_3	1.80	2.15	1.66	2.42	2.44	0.19	2.63			2.91	−0.28	2.75	−0.12		

[a]Ref 13. [b]See footnote #. [c]Eq 2. [d]Eq 3. [e]Eq 4. [f]Eq 6. [g]Eq 8. [h]Eq 9. [i]Eq 13.

stituted compounds alone in eq 6, 7. In fact, if π and σ are given the value zero for all 5 and 8 substituents in compounds **1-29** a better correlation is obtained (eq 9, 10). An examination of the individual observed *vs.* calculated activity values for 5- and 8-substituted compounds, grouped separately, reveals that for both groups the aggregate difference between observed and calculated activity values is

#M. D. Yudis and J. G. Topliss, unpublished results.

Table II. Observed and Calculated *in Vitro* Vascular Reactivity Effects of 3-Substituted-1,2,4-benzothiadiazine 1,1-Dioxides

								Activity data								
No.	R_3	R_6	R_7	π_{R_3}[a]	σ_{R_3}[b]	$E_s{}^cR_3$[c]	$\pi_{R_{6-7}}$[a]	A_{obsd}[d]	C[e]	A^*_{obsd}[f]	A^*_{calcd}[g]	ΔA^*[g]	A^*_{calcd}[h]	ΔA^*[h]	A^*_{calcd}[i]	ΔA^*[i]
1	H	Cl	H	0.00	0.00	1.24	0.89	1.19	0.24	1.43	1.54	−0.11	1.56	−0.13	1.57	0.14
2	CH_3	H	Cl	0.15	−0.79	0.00	0.91	1.79	0.04	1.83	1.70	0.13	1.69	0.14	1.70	0.13
3	$(CH_2)_2CH_3$	Cl	H	1.03	−0.92	−0.67	0.89	2.21	0.04	2.25	2.20	0.05	2.10	0.15	2.11	0.14
4	$CH(CH_3)_2$	Cl	H	0.99	−1.00	−1.08	0.89	1.97	0.04	2.01	2.19	−0.18			2.08	−0.07
5	$CH_2CH(CH_3)_2$	Cl	H	1.34	−0.93	−1.24	0.89	2.06	0.04	2.10	2.28	−0.18			2.19	−0.09
6	$CH(CH_3)CH_2CH_3$	H	Cl	1.40	−1.03	−1.74	0.91	2.37	0.01	2.38	2.32	0.06			2.22	0.16
7	$C(CH_3)_3$)	H	Cl	1.33	−1.15	−2.46	0.91	2.31	0.01	2.32	2.31	0.01	2.21	0.11	2.22	0.10
8	Cyclobutyl	H	Cl	1.26	−1.03	−0.67	0.91	2.67	0.02	2.69	2.29	0.40			2.19	0.50
9	$(CH_2)_4CH_3$	H	Cl	1.76[j]	−0.93	−0.71	0.91	2.30	0.02	2.32	2.33	−0.01			2.26	0.06
10	$CH(CH_2CH_3)_2$	Cl	Cl	1.72	−1.05	−2.59	1.80	3.29	0.18	3.47	3.44	0.03			3.40	0.07
11	$CH_2C(CH_3)_3$	H	Cl	1.64	−0.97	−2.05	0.91	1.77	0.02	1.79	2.34	−0.55			2.25	−0.46
12	$CH_2C_6H_5$	Cl	H	1.73	−0.25	−0.69	0.89	2.37	0.16	2.53	2.31	0.22	2.23	0.30	2.25	0.28
13	$(CH_2)_2C_6H_5$	Cl	H	2.11[j]	−0.75	−0.69	0.89	2.36	0.04	2.40	2.26	0.14	2.23	0.17	2.24	0.16
14	CH_2Cl	Cl	H	0.67	0.96	−0.55	0.89	1.17	0.89	2.06	2.04	0.02	1.96	0.10	1.96	0.10
15	$CH(CH_2CH_2CH_3)_2$	Cl	Cl	2.48[j]	−1.06	−2.72	1.80	3.07	0.15	3.22	3.25	−0.03	3.38	−0.16	3.36	−0.14
16	$CH{=}CH{-}CH_3$	Cl	H	0.95	−0.55		0.89	1.84	0.08	1.92			2.07	−0.15	2.08	−0.16
17	Δ^1-Cyclopentenyl	Cl	Cl	1.53	−0.32		1.80	2.06	0.15	2.21			3.42	−1.21	3.40	−1.19
18	Δ^2-Cyclopentenyl	Cl	Cl	1.40[j]	−0.70		1.80	3.55	0.13	3.68			3.40	0.28	3.37	0.31
19	Δ^3-Cyclopentenyl	Cl	Cl	1.37	−0.80		1.80	4.02	0.05	4.07			3.40	0.67	3.37	0.70
20	Δ^2-Cyclopentenylmethyl	H	Cl	1.90[j]	−0.87		0.91	2.24	0.03	2.27			2.26	0.01	2.28	−0.01
21	C_6H_5	Cl	H	1.62	0.26		0.89	1.73	0.33	2.06			2.22	−0.16	2.24	−0.18
22	$CH_2C_6H_4pOCH_3$	Cl	H	1.74[j]	−0.25[j]		0.89	1.75	0.01	1.76			2.23	−0.47	2.25	−0.49
23	$CH_2C_6H_4pCl$	Cl	H	2.43[j]	−0.25		0.89	2.67	0.09	2.76			2.18	0.58	2.20	0.56
24	2-Thienyl	Cl	H	1.52	0.50		0.89	1.55	0.52	2.07			2.21	−0.14	2.22	−0.15
25	2-Thienylmethyl	Cl	H	1.63[j]	−0.17		0.89	2.03	0.18	2.21			2.23	−0.02	2.24	0.03
26	2-(2-Thienyl)-ethyl	Cl	H	2.01[j]	−0.72		0.89	2.01	0.06	2.07			2.24	−0.17	2.22	−0.15
27	2-Furyl	Cl	H	0.90	0.65		0.89	1.41	0.13	2.04			2.05	−0.01	2.06	−0.02
28	CH_2OCH_3	Cl	H	0.11	0.22		0.89	1.13	0.35	1.48			1.63	−0.15	1.64	−0.16
29	$CH_2SCH_2C_6H_5$	Cl	H	2.41[j]	0.17		0.89	1.97	0.32	2.29			2.19	0.10	2.20	0.09
30	$CH(CH_2CH_2CH_3)$-cyclopentyl	Cl	Cl	3.07[j]	−1.08		1.80	2.96	0.14	3.10			3.18	−0.08	3.16	−0.06
31	Cyclohexyl	Cl	H	2.04	−1.06		0.89	1.84	0.02	1.86			2.23	−0.37	2.25	−0.39
32	Cyclopentyl	Cl	Cl	1.67	−1.13		1.80	3.69	0.05	3.74			3.44	0.30	3.41	0.33
33	$CH(CH_3)CH_2CH_3$	Cl	Cl	1.40	−1.06		1.80	3.41	0.18	3.59			3.40	0.19	3.37	0.22
34	CH_2CH_3	H	Cl	0.57	−0.89		0.91	2.02	0.03	2.05			1.93	0.12	1.94	0.01
35	H	H	H	0.00	0.00		0.00	0.24	0.04	0.28					0.42	−0.14
36	CH_3	CF_3	H	0.15	−0.79		1.30	1.91	0.11	2.02					2.20	−0.18
37	CH_3	Br	H	0.15	−0.79		1.08	1.87	0.07	1.94					1.91	0.03
38	CH_3	H	F	0.15	−0.79		0.33	1.22	0.02	1.24					0.95	0.29
39	CH_3	H	CH_3	0.15	−0.79		0.52	1.00	0.00	1.00					1.19	−0.19
40	CH_3	H	NO_2	0.15	−0.79		0.36	0.97	0.27	1.24					0.99	0.25

[a]Ref 13. [b]See footnote #. [c]Ref 12. [d]Eq 2. [e]Eq 3. [f]Eq 4. [g]Eq 11. [h]Eq 12. [i]Eq 13. [j]Estimated.

σ_{R_3} nor $E_s{}^cR_3$ are significant at the $p < 0.10$ level indicating the lack of influence on activity of both electronic and steric effects of the 3 substituent. The presence of the $-\pi_{R_3}{}^2$ term shows that an increase in the lipophilicity of the 3 substituent beyond an optimum value results in a decrease in activity.

Expanding the range of 3 substituents studied (Table II, **1-3, 7, 12-34**) leads to eq 12. The general relationships seen previously in eq 11 are confirmed by eq 12 which was

$$A^* = 0.37(\pm0.57) + 1.33(\pm0.39)\pi_{R_{6-7}} + 0.72(\pm0.62)\pi_{R_3} - 0.19(\pm0.21)\pi_{R_3}{}^2 \quad (p < 0.005) \quad (p < 0.01) \quad (p < 0.10)$$
$$n = 27, r = 0.87, r^2 = 0.75, s = 0.37, p < 0.005 \qquad (12)$$

derived from a broader data base. The electronic term σ_{R_3} again is not significant. The correlation of σ_{R_3} with π_{R_3} in this data set has a coefficient of −0.30 so a covariance problem is an unlikely reason for the lack of significance of σ_{R_3}. It may therefore be concluded that an electronic effect from the 3 substituent does not influence the observed activity (corrected for ionization effects) of 3-substituted compounds.

In the foregoing sections the effects on activity of substituent variation in the benzenoid portion of the benzothiadiazine molecule and at position 3 have been separately analyzed. From Table II there were selected 33 compounds (**1-3, 7, 12-40**) encompassing representative substituent variation at positions 3, 6, and 7 which leads to the more general eq 13 for the series. The compounds in this set were selected with a view to obtaining a balanced representation of substituent variation in the different positions. Inclusion of all available compounds would risk a possible statistical distortion through overweighting of certain substituents, particularly the 3-methyl substituent. It can be seen that eq 13, which accounts for 84% of the variance in

$$A^* = 0.42(\pm0.33) + 1.28(\pm0.31)\pi_{R_{6-7}} + 0.72(\pm0.47)\pi_{R_3} - 0.19(\pm0.16)\pi_{R_3}{}^2 \quad (p < 0.005) \quad (p < 0.005) \quad (p < 0.05)$$
$$n = 33, r = 0.91, r^2 = 0.84, s = 0.35, p < 0.005 \qquad (13)$$

the data, is very similar to previous eq 11 and 12 derived from studies of 3-substituent variation. Of 33 compounds, 29 have activity values computed according to eq 13 which are close to the experimental values. Compounds **19**, **22**, and **23** (Table II) show fairly wide discrepancies between calculated and observed activities. In the case of the 3-Δ^1-

cyclopentenyl compound (Table II, **17**), however, there is an order of magnitude difference. Compounds **1-6**, **8-9**, **12-15**, **17**, and **19-20** from Table I and **4-6** and **8-11** from Table II which were not included in the set from which eq 13 was derived, had calculated activity values according to eq 13 in generally good agreement with the experimental values.

It is interesting to consider the poor fit in the regression analysis of the 3-Δ^1-cyclopentenyl compound (Table II, **17**) in the light of the calculated difference in conformation[6] of this substituent with respect to the benzothiadiazine nucleus as compared with the Δ^2 and Δ^3 isomers and the cyclopentyl substituent. If the 3 substituent is considered to interact in terms of hydrophobic bonding with a receptor region, perpendicular to the plane of the benzothiadiazine nucleus (see later discussion), then the degree of the interaction will depend on that portion of the substituent which is in a position to interact at the receptor surface. Thus, the Δ^3-cyclopentenyl and cyclopentyl substituents both can present a full face to the receptor for maximum interaction according to their calculated conformations. There will be minimum effective interaction ($\hat{=}$ 2 CH_2 groups) in the case of the Δ^1 isomer and an intermediate one for the Δ^2 isomer. It is immediately clear by inspection that this might explain the poor fit of the Δ^1 isomer. To allow for this effect a modified π value (π') was estimated and assigned to the appropriate 3 substituents as determined from an examination of molecular models. As applied to the 33 compounds on which eq 13 was based this did reduce somewhat the error of estimation of the Δ^1 isomer and improve slightly, but significantly, the overall fit in the regression analysis. However, if the Δ^1 isomer was left out and the results compared with those obtained from the remaining compounds, there was no statistically significant difference in the correlations using either π or π' values. Thus, it would be equally valid to regard the Δ^1 isomer as an outlyer as far as the correlations are concerned.

Differentiating eq 13 with respect to π_{R_3} leads to a value π_{R_3} (max), which provides a maximum activity contribution in the equation. The value of π_{R_3} (max) obtained from eq 13 is 1.95. Equation 13, a simple expression involving only terms from readily available π values, represents a very satisfactory general equation for a series of compounds encompassing a 4000- to 5000-fold variation in activity. From this it is possible to state in simple terms the substituent requirements for maximum activity: (1) highly lipophilic groups at positions 6 and 7, (2) a group at position 3 with a π value of close to 2. In addition, because of the effects of ionization previously discussed, the pK_a of the compound should be >8.0.

A test of eq 13 was carried out by comparing the found and estimated activity values of six compounds which had not been included in the regression analysis (Table III). The deviation between the found and calculated activities of the compounds was well within satisfactory limits.

In all the correlations discussed so far activity data has been based on *in vitro* measurements of vascular reactivity. Since this activity measure should relate to antihypertensive activity it would clearly be of great interest to see what kind of correlation could be obtained with the *in vivo* data. A well-known problem with *in vivo* data in mathematical correlations of this type is poor quantification of activity data. Fortunately, we did have available *in vivo* antihypertensive activity data on 14 compounds[§] determined in the DOCA rat[7] (Table IV) which was thought to be of sufficient precision for use in the correlations. The activity value A' is defined as log (1000/MED) where MED is the minimum effective dose which produces a significant lowering of blood pressure. From these data eq 14 was derived which is of the same general form as eq 13. The π_{R_3} (max) value in this equation is 0.88.

$$A' = 1.23(\pm0.40) + 0.43(\pm0.22)\pi_{R_{6-7}} + 1.42(\pm1.14)\pi_{R_3} - 0.81(\pm0.78)\pi_{R_3}^2 \quad (p < 0.005) \quad (p < 0.05) \quad (p < 0.05)$$
$$n = 14, r = 0.85, r^2 = 0.73, s = 0.25, p < 0.005 \qquad (14)$$

The results of the correlations obtained in the main studies using *in vitro* data provide a basis for speculation on some aspects of the drug-receptor interactions in this series. An examination of the coefficients of the $\pi_{R_{6-7}}$ and π_{R_3} terms in eq 13 shows that the $\pi_{R_{6-7}}$ terms are much more heavily

Table III. Comparison of Found and Estimated Activity Values of Compounds not Included in Regression Analysis

Compound	A_{obsd}[a]	C[b]	A^*_{obsd}[c]	A^*_{calcd}[d]	
3-$(CH_3)_2CH$, 6,7-di-Br	3.18	0.15	3.33	3.71	−0.38
3-Cyclopentyl, 6-CF_3, 7-Cl	4.07	0.10	4.17	3.92	+0.25
3-$(CH_3)_2CH$, 6-CH_3, 7-Cl	2.55	0.01	2.56	2.68	−0.12
3-(2-Thienylmethyl), 6-CF_3	2.06	0.29	2.35	2.75	−0.40
3-NH_2, 7-Cl	1.63	0.00	1.63	1.46	+0.17

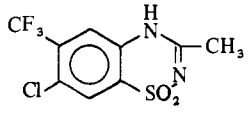
[a]Eq 2. [b]Eq 3. [c]Eq 4. [d]Eq 13.

Table IV. Observed and Calculated *in Vivo* Antihypertensive (Doca Rat) Activities of 3,6,7-Substituted-1,2,4-benzothiadiazine 1,1-Dioxides

No.	R_3	R_6	R_7	π_{R_3}[a]	σ_{R_3}[b]	$\pi_{R_{6-7}}$[a]	A' Obsd	A' Calcd[c]	$\Delta A'$
1	CH_3	H	Cl	0.15	−0.79	0.91	1.92	1.81	0.11
2	CH_3	CF_3	H	0.15	−0.79	1.30	1.82	1.98	−0.16
3	CH_3	H	CF_3	0.15	−0.79	1.22	1.82	1.94	−0.12
4	CH_3	H	F	0.15	−0.79	0.33	1.40	1.56	−0.16
5	CH_3	OCH_3	Cl	0.15	−0.79	1.18	2.22	1.93	0.29
6	CH_3	NO_2	Cl	0.15	−0.79	1.13	2.00	1.90	0.10
7	$CH(CH_3)_2$	CF_3	Cl	0.99	−1.00	2.21	2.40	2.78	−0.38
8	$CH(CH_2CH_3)_2$	Cl	Cl	1.72	−1.05	1.80	1.74	2.03	−0.29
9	Cyclopentyl	H	H	1.67	−1.05	0.00	1.12	1.33	−0.21
10	Cyclopentyl	Cl	Cl	1.67	−1.05	1.80	2.15	2.10	0.05
11	Cyclopentyl	CF_3	Cl	1.67	−1.05	2.21	2.52	2.27	0.25
12	Δ^3-Cyclopentenyl	H	H	1.37	−0.80	0.00	1.82	1.65	0.17
13	Δ^3-Cyclopentenyl	Cl	H	1.37	−0.80	0.89	2.10	2.03	0.07
14	Δ^3-Cyclopentenyl	Cl	Cl	1.37	−0.80	1.80	2.70	2.41	0.29

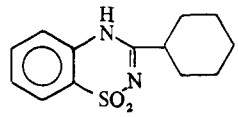
[a]Ref 13. [b]Footnote #. [c]Eq 14.

weighted than the π_{R_3} term. This would indicate that the π terms relate principally to hydrophobic bonding effects rather than to penetration effects since if the latter were dominant then approximately equal weighting of $\pi_{R_{6-7}}$ and π_{R_3} would be expected. The point is illustrated by a comparison of compounds II and III. These have about the same



II

$\log P = 2.24$
$A^* = 3.13$



III

$\log P = 2.20$
$A^* = 1.15$

partition coefficients and should thus be about equally efficient in penetrating to the receptor site. However, II, the lipophilic character of which is mainly accounted for by the 6 and 7 substituents, has an activity 100-fold that of III whose lipophilic character arises mostly from its 3 substituent. The situation is similar in the case of the *in vivo* data (eq 14). Here a greater sensitivity to penetration effects might have been expected. However, the correlation of activity with $\Sigma\pi - (\Sigma\pi)^2$ for all substituents is poor ($r = 0.60$, $s = 0.37$).

It is suggested that hydrophobic bonding takes place at R_6 and R_7 to a lipophilic area of the receptor and that weaker hydrophobic bonding of R_3 occurs at a second lipophilic area of the receptor. If R_3 is too lipophilic additional hydrophobic bonding may result which is unfavorable to the drug-receptor interaction, perhaps through receptor perturbation which disturbs the optimum drug-receptor fit. This would account for the presence of the $-\pi_{R_3}^2$ term in eq 13.

The fact that methylation of the 4-nitrogen atom in this series results in a marked reduction of potency[2] suggests the possibility of a hydrogen bonding type interaction of the 4-hydrogen atom (NH) with the receptor. An alternative explanation is a steric effect in that a group larger than hydrogen located on the 4-nitrogen might interfere with the approach of the molecule to the optimum receptor site position. Wohl[11] has proposed that 4-N-methylation creates an adverse effect on the charge type interactions of the molecule with an anionic site located off the 4,4a and 5 positions in the plane of the nucleus.

An attachment to the receptor through the negatively charged oxygens of the sulfonyl group also seems plausible, particularly since removal of one of these oxygens, as in the 1-oxide analog of diazoxide, results in a significant loss of activity.[11] This picture, however, is at variance with the proposal,[11] based on MO calculations, that the molecule interacts with an anionic center in the region of the sulfonyl oxygens and asymmetrically placed between them.

It seems appropriate at this juncture to attempt to make some comparison between the results obtained in this investigation and those reported[11] from a molecular orbital treatment of the same series. In the latter study, although the fit in the regression equation was excellent, more variables were required, fewer compounds were employed, and the range of substituents studied was much more limited. However, a number of ring-modified compounds were included in the MO study which were not in the Hansch correlations. Thus, the MO work was broader in its treatment of different nuclei but narrower in its examination of substituent variation in the 1,2,4-benzothiadiazine 1,1-dioxide system.

Our study shows a marked dependency of activity on the π values of substituents at the 6 and 7 positions. It is not obvious how this relates to the key regression equation (4) in the MO study. In this connection it may be noted that of 7 hypothetical "receptor sites" selected for intermolecular force calculations in the latter study, none was located in the plane of the molecule adjacent to the 6 and 7 substituents.

With regard to substitution at the 3 position, the present study has revealed a parabolic dependence on π ($\pi - \pi^2$), but no significant correlation with σ^* (electronic effect). In the MO work it was shown that activity increases with increasing net positive charge on the 3 substituent and a charge-charge type interaction of this substituent with a hypothetical anionic center on the receptor located at site [E] was proposed.[11] If the findings between the two analytical approaches were consistent with regard to the 3 substituent then some dependency in the Hansch analysis on $\sigma_{R_3}^*$ might have been expected, since this term should roughly correlate with net positive charge.

This difference could originate in the different sampling of 3 substituents utilized in the two studies since, when the compounds listed in Table I in the MO study were subjected to the analytical procedure utilized in the present study, a highly significant correlation with σ^* was found denoting increased activity with increased electron release ($\triangleq$ net positive charge) of the 3 substituent. Considering the more numerous and diverse 3 substituents utilized in the primary Hansch analysis, the significance of the role of the positive charge on the 3 substituent as discussed in the MO correlations may be questioned. Thus, the interesting basis presented[6] for the differences in activity of a series of 3-cyclic substituents in which conformational preference is related to regional charge on the 3-substituent group may be fortuitous.

In this regard it may be noted that the inactive compound with a 3-trifluoromethyl substituent cited as supporting the conclusions of the MO study because of the high negative charge of the CF_3 group is, in fact, >99.9% ionized at the pH under which the activity measurements were made. Such a compound would not be capable of crossing the necessary membrane barriers to arrive at the receptor site in meaningful concentration and no activity would be expected for this reason.

It appears likely that the compounds exert their action by occupying a receptor site at which Ca^{2+} is normally the operative stimulus in inducing arterial contraction.[8] Wohl has postulated a receptor model[11] in which the drug molecule forms weak molecular bonds at three anionic sites on the receptor, two of which may be part of an organic phosphate, with subsequent disengagement following donation of a partial negative charge from the compound to the receptor. The implied picture of two strategically located electron-deficient regions of the drug molecule substituting for the Ca^{2+} ion at the receptor is a convenient and direct one but is difficult to reconcile with the results of the present study with respect to bonding interactions of the 3 substituent as previously discussed.

Inferences with regard to drug-receptor interaction which follow from the present study suggest the importance of the role of hydrophobic bonding at regions of the drug molecule adjacent to the 6, 7 and 3 positions. The contributions of other types of bonding interactions involving the 4-NH and SO_2 functions were also suggested. Conceivably the action of the drug may be indirect in that access of Ca^{2+} to its normal site of action may be prevented without direct interaction of the drug with this particular site. Attach-

ment of the drug molecule could occur, with a major contribution from hydrophobic bonding, at proximal sites with consequent steric blocking of the normal Ca^{2+} site either directly or perhaps following an induced receptor perturbation.

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π-Substituent Constants for the 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxide System

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Partition coefficients for a series of substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides were measured in the system *n*-octanol-H_2O from which π values for a variety of substituents at different positions in the heterocyclic nucleus were calculated. There were marked variations in π for the same substituent depending on its position of attachment to the nucleus. Low values were obtained for the 3,5 and 8 positions due to the proximity of polar atoms. The additivity of π values in some polysubstituted compounds was examined.

In recent years the value of the substituent constant approach in structure-activity correlations has been amply demonstrated. It has been shown that π, a free energy related constant, derived from partition coefficient data, which relate to penetration and hydrophobic bonding effects, is particularly useful in such work.[1] The π value for a substituent X is defined by the relationship $\pi_X = \log P_X - \log P_H$, where P_H is the partition coefficient of the parent nucleus and P_X that of an X-substituted derivative.[2] As in the case of the analogous Hammet σ constants, π values are additive except where strong group interactions are present.

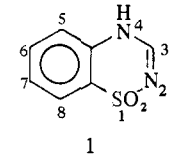
In connection with structure-activity correlations using the substituent constant approach in a series of 2*H*-1,2,4-benzothiadiazine 1,1-dioxide† antihypertensive agents,[3] we were faced with the problem of obtaining suitable π values for substituents in various positions in the nucleus. Previous work[4,5] on π values did not utilize heterocyclic systems as the parent molecule and did not appear therefore, to offer an adequate basis for selection in this case. Accordingly, it was necessary to obtain π values for substituents in the 2*H*-1,2,4-benzothiadiazine 1,1-dioxide series directly from partition coefficient measurements of the appropriate compounds.

Method. Partition coefficients, between *n*-octanol and water, of a series of substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides were measured (Table I) from which π values for a variety of substituents at different positions in the nucleus were calculated (Table III) using the relationship $\pi_X = \log P_X - \log P_H$. In addition to the parent 2*H*-1,2,4-benzothiadiazine 1,1-dioxide (Table I, **1**), the 3-methyl, 6-chloro, 7-chloro, and 7-chloro-3-methyl compounds (Table I, **2**, **8**, **19**, and **20**) were required to provide reference values ($\log P_H$) for the determination of some π_X values. Where a π value for a substituent could be computed in more than one way from different reference compounds with comparable accuracy an averaged value was used. In these cases the individual values before averaging, were usually very similar. Reference (parent) compounds used in the determination of individual π values are noted in Table II.

†These compounds are designated 2*H* consistent with Chemical Abstracts practice although in solution they probably exist as the 4*H* tautomers and are depicted as such in structural formulas in this paper (see ref 5).

Results and Discussion

Large differences in π values for the same substituent at different positions in the nucleus were found. In the benzenoid portion of the nucleus (I) highest π values were observed for the 6 and 7 positions; these values were close to those reported by Fujita, *et al.*,[3] for the meta and para positions in the phenol system. There is a sharp drop in the π values at the 5 and 8 positions reflecting the proximity of the polar NH and SO_2 functions, respectively, with attendant possibilities for hydrogen bonding to water molecules. This drop is more pronounced, particularly at the 8 position, than that experienced in the change from the meta or para to the ortho position in the phenol system. A good illustration is afforded by comparing π values for the Cl function at the 5,6,7, and 8 positions in the benzothiadiazine system and the ortho, meta, and para positions in the phenol system (Chart I).



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