Pharmacology. Cats of both sexes, weighing between 2.6 and 3.2 kg, were starved for 24 h and pretreated with reserpine (Serpasil, 2.5 mg/mL), 5 mg/kg of body weight, 18 h before experimentation in order to provoke neuronal noradrenaline depletion, thereby inducing a chemical sympathetectomy. The animals were anesthetized by a pentobarbital (Mebumal, 60 mg/mL ACO) injection, 30 mg/kg of body weight, intraperitoneally and maintained at a constant level of anesthesia by a continuous infusion of pentobarbital sodium (Mebumal), 0.1 mg min^{-1} (kg of body weight).$^{-1}$

Artificial respiration was given by means of a respiratory pump (Braun) connected to a tracheal cannula.

The cats were vagotomized bilaterally and the right carotid artery was catheterized for recording of the mean arterial blood pressure via a Statham P 23 strain gage pressure transducer. The heart rate was recorded via a Grass 7P4 cardiotachograph, which was triggered by the blood-pressure oscillations.

The pharmacological effects on the peripheral vascular resistance in one hind leg were estimated as follows: A plastic catheter loop was introduced into the left femoral artery in the inguinal region and connected to a peristaltic pump (Watson Marlow) which delivered a constant flow of >10 mL/min. The hind leg was thus perfused with the cat's own blood at a constant flow rate. Alterations in vascular resistance measured as changes in perfusion pressure were recorded via a Statham P 23 strain gage pressure transducer connected to the loop distal to the roller pump.

The left jugular and right femoral veins were catheterized for barbiturate and test compound administration, respectively.

All recordings were made on a Grass 7D polygraph. The blood gas status and hematocrit values of the animal were controlled continuously throughout the experiment and were regarded as normal within the following ranges: pH, 7.38 ± 0.06; pCO_2, 4.1 ± 0.2 kPa; HCO_3, 19.0 ± 1.0 mequiv/L; hematocrit, 30 ± 10%.

A standard fluid therapy (Ringer acetate, ACO, 20 mL/kg of body weight, + Macrodex, Pharmacia, 5 mL/kg of body weight, infused at 0.5 mL/min) was used to compensate for the fluid loss due to the reserpine pretreatment.

Maximal heart rate and peripheral vascular effects were obtained by iv and ia injection of supramaximal doses of isoprenaline (IPR).

The test compounds were infused iv for 10 min at a rate of 1.0 mL/min in five stepwise raised concentrations. Each infusion was followed by an iv and an ia injection of IPR in concentrations which in the absence of test compounds induced control responses equal to about 80% of the maximal IPR effects.

Knowing that the submaximal IPR concentration used induces a response which may be identified at the top of the linear part of the IPR dose–response graph and assuming that any antagonistic property of the test compound represents a perfectly competitive interaction with IPR at the receptor site, any decrease in the response to the IPR standard concentration will reflect a parallel rightward shift of the IPR dose–response curve.

Dissociation constants characteristic of the affinity for the receptors were calculated for agonistic (K_A) and antagonistic (K_B) effects of the test compounds.

The doses of the test compounds producing semimaximal excitatory effects on the heart rate were taken as estimates of K_A. The K_B values for antagonistic effects on heart rate and peripheral vascular dilatation were calculated according to Åblad et al.[14]

The formula used provided us with a series of K_B values, one for each dose of test compound, in every experiment. These values, which theoretically should be identical with each other within one experiment, were, however, widely scattered due to a possible nonlinearity of the dose–response curve segment at its extreme points (i.e., around the 20–30% and the 70–80% levels).

For calculation of the "mean" K_B of each experiment, a "weighing" formula[14] was used.

Acknowledgment. We thank Drs. Peder Berntsson and Arne Brändström for valuable discussions and Hans Thorin for the mass spectra.

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Notes

Structure-Activity Relationships in Dihydropteroate Synthase Inhibition by Sulfanilamides. Comparison with the Antibacterial Activity

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A set of 12 acidic, 5 imidic, and 5 amidic sulfanilamides (SA) were tested for their inhibitory activity on dihydropteroate synthase of *Escherichia coli*. The enzyme inhibition indexes (EII_{50}) were compared with the growth inhibition indexes (GII_{50}), and electronic structures of SA and cell permeability effects were discussed as possible determinant factors of the observed variation of the activity in the SA set. The results strongly support the following conclusion: (a) permeability factors are highly effective in depressing the activity of SA in growth inhibition with respect to enzyme inhibition, but they do not appear to contribute significantly to the activity variation; (b) the activities of the different SA, both in growth and enzyme inhibition experiments, are well accounted for by the electronic features of these compounds.

Studies[1-3] on the synthesis of dihydropteroate and folate in several bacterial species, and particularly in *E. coli*, have definitively shown that sulfanilamides (SA) carry out their antibacterial action by inhibiting, competitively with respect to *p*-aminobenzoate, the enzyme dihydropteroate

(1) G. M. Brown, *Adv. Biochem.*, **35**, 35 (1971), and references cited therein.

(2) L. Jaenicke and P. C. Chan, *Angew. Chem.*, **72**, 752 (1960).

(3) T. Shiota, M. N. Disraely, and M. P. McCann, *J. Biol. Chem.*, **239**, 2259 (1964).

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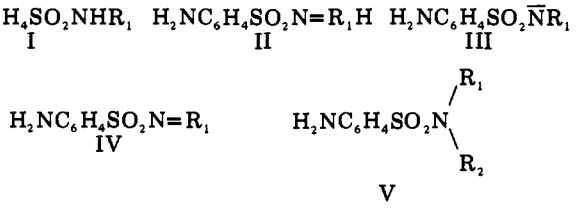
synthase, which catalyzes the formation of dihydropteroate from *p*-aminobenzoate and (hydroxymethyl)dihydropteridine pyrophosphate.

The inhibitory potency of a number of sulfanilamides has been studied and found to be generally proportional to the efficiency of the antibacterial activity of these compounds. This result was obtained by Miller et al.[4] with two homologous series of N^1-phenyl- and N^1-pyridylsulfonamides and by Brown[5] and Thijssen[6] with heterogeneous series of SA, containing very different substituents. In these researches, however, the inhibitory effects of acidic SA have been essentially considered.

Previous results[7-10] have pointed out the importance of studying the biological effects of a large series of SA, including not only isomeric acidic forms I and II, which can



dissociate to give the common anion III, but neutral forms also, as blocked imidic IV and blocked amidic V forms.

In such a series, indeed, there is a significant variation of spectroscopic parameters[11] and of theoretical electronic indexes[10] of the common moiety *p*-$NH_2C_6H_4SO_2$ of SA; this allows to a comparison of these structural features with the biological effects of SA, in which their common moiety is involved.

On the other hand, a study of the biological effects of both acidic and neutral SA can represent an approach to the problem of the role of cell-membrane permeation in the antibacterial activity of these compounds, which appears to be, at present, still an open question.

In the present research, the inhibitory effects of 12 acidic, 5 imidic, and 5 amidic sulfanilamides on the dihydropteroate synthase of *E. coli* have been studied. The results have been related to the spectroscopic parameters of these compounds and compared with their antibacterial activity, which has been recently evaluated.[10]

Experimental Section

The sulfanilamides were either obtained from commercial sources or synthesized by methods described elsewhere.[12] *p*-Amino[7-^{14}C]benzoic acid (specific activity 53 μCi/mg) was purchased from the Radiochemical Centre, Amersham, U.K. 2-Amino-4-hydroxy-6-(hydroxymethyl)pteridine was prepared according to Thijssen[13] from the corresponding 6-formyl derivative, prepared in turn from folic acid. Reduction to 2-amino-4-hydroxy-6-(hydroxymethyl)-7,8-dihydropteridine was accomplished with sodium dithionite[14] (2 g/200 mg of pteridine) in 0.5 N NaOH at room temperature for 5 h.

E. coli $K_{12}J_{53}$ (pro$^-$ met$^-$ Nal) strain, kindly supplied by the Istituto di Igiene dell'Università di Modena, was used as the enzyme source. This strain was already employed for measurements of growth inhibition indexes.[10] The cells were grown on a solid medium ("brain–heart infusion agar", DIFCO), at 37 °C with aeration, and then harvested and disrupted with Alcoa A 305 (bacteriological grade alumina, obtained from Aluminum Company of America). The paste was extracted with cold 0.05 M Tris-HCl buffer, pH 8.0, and ammonium sulfate fractionation was carried out, according to Richey and Brown,[15] on the clear supernatant, obtained by centrifugation at 27000*g* for 40 min. The protein fraction, precipitated between 30 and 70% saturation, was retained and dissolved in cold 0.05 M Tris-HCl buffer, pH 8.0. The protein content of the final preparation was about 40 mg/mL, as determined by the method of Lowry et al.[16] This preparation contains both (hydroxymethyl)dihydropteridine pyrophosphokinase (EC 2.7.6.3) and dihydropteroate synthase (EC 2.5.1.15), the two enzymes which catalyze the synthesis of dihydropteroate from 2-amino-4-hydroxy-6-(hydroxymethyl)-7,8-dihydropteridine and ATP. The enzyme preparation could be stored at −25 °C for many months without appreciable activity loss.

The enzymatic formation of dihydropteroate was measured by the method described by Richey and Brown,[15] which is based on the determination of the radioactivity of dihydropteroate synthesized from *p*-amino[7-^{14}C]benzoate. Complete reaction mixtures contained, in a final volume of 1 mL, 0.1 M Tris-HCl buffer, pH 8.6; 0.01 M $MgCl_2$; 0.05 M mercaptoethanol; 0.25 mM ATP; 0.06 mM (hydroxymethyl)dihydropteridine; 0.05 mL of the enzyme preparation; 5 μM *p*-amino[7-^{14}C]benzoic acid (16000 cpm); and different concentrations of SA, when present. The values of the SA concentrations giving 50% inhibition of enzyme activity were calculated by interpolation from plots of 1/dpm vs. SA concentration. These values divided by *p*-aminobenzoate concentration give the enzyme inhibition indexes, EII_{50}.

Results and Discussion

The values of the enzyme inhibition indexes (EII_{50}) measured in the present research are reported in Table I. In the case of some acidic SA, a comparison with the values obtained by other authors is possible; the values reported here are in good agreement with those obtained by Brown[5] but proportionally higher than those measured by Thijssen.[6] This discrepancy could be due to differences in the experimental conditions, such as the enzyme preparation utilized for the experiments, the pH of the reaction mixtures, and the method used to measure enzyme activity.

The activity parameters (ap_E), reported in Table I, were calculated as the logarithms of the inverses of the EII_{50} values, after correction of these values, in the case of acidic SA, according to the approximation that the whole activity of these compounds can be ascribed to the anionic forms only, by ignoring the contribution of the corresponding molecular forms.[7] In order to carry out this correction, the concentrations of the anionic forms of acidic SA tested were calculated from the value of the pH, at which the experiments have been accomplished, and the pK_a values reported in Table I.

For comparison purposes, the values of the growth inhibition indexes (GII_{50}) determined in a previous work,[10] and the corresponding ap_G values, calculated as described above for the ap_E values, are also reported in Table I, together with the measured symmetric stretching fre-

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Table I. Activity Parameters and Physicochemical Indexes of Sulfanilamides

no.	X	pK_a	EII_{50}	ap_E	GII_{50} [a]	ap_G	ν_S (SO_2), [b] cm^{-1}	δ (NH_2), [b] ppm
	Acids: p-$NH_2C_6H_4SO_2$—NHX							
1	CH_3	10.77[c]	32.4	0.66	60 000	−1.01	1113	5.31
2	H	10.43[c]	25	0.44	25 000	−0.97	1115	5.25
3	2-pyridinyl	8.56[d]	4.20	−0.34	1 500	−1.60	1125	5.36
4	2-(4,6-dimethylpyrimidinyl)	7.51[e]	1.92	−0.25	500	−2.07	1116 1133[f]	5.35
5	2-thiazolyl	7.23[d]	0.90	0.06	200	−1.87	1127	5.42
6	2-pyrimidinyl	6.37[d]	2.56	−0.40	350	−2.45	1129	5.37
7	6-(2,4-dimethoxypyrimidinyl)	5.98[d]	0.85	0.07	300	−2.44	1130	5.44
8	$CONH_2$	5.42[c]	8.40	−0.92	25 000	−4.39	1114 1137[f]	5.40
9	$COCH_3$	5.38[c]	4.44	−0.65	3 800	−3.57	1130	5.47
10	2-(5-methyl-1,3,4-thiadiazolyl)	5.22[d]	0.40	0.40	750	−2.88	1126	5.51
11	COPh	4.57[c]	5.20	−0.72	3 300	−3.52	1128	5.48
12	CN	2.92[c]	8	−0.90	>50 000	<−4.70	1135	5.61
	Imides: p-$NH_2C_6H_4SO_2$—N=X							
13	2-(N-methylpyrimidinyl)		31.20	−1.49	>100 000	<−5	1146	5.71
14	2-(N-methyl-4,6-dimethylpyrimidinyl)		26	−1.41	52 000	−4.72	1143	5.63
15	2-(N-methylthiazolyl)		13.40	−1.13	>>10 000	<<−4	1140	5.89
16	$C(NH_2)_2$		10.20	−1.01	38 500	−4.58	1135	5.71
17	2-(N-methylpyridinyl)		8	−0.90	30 000	−4.48	1136	5.74
	Amides: p-$NH_2C_6H_4SO_2$—N(CH_3)X							
18	CH_3		82	−1.91	>>35 000	<<−4.54	1154	6.07
19	2-thiazolyl		35.40	−1.55	>>10 000	<<−4	1159	6.31
20	2-pyridinyl		30	−1.48	40 000	−4.60	1152	6.14
21	2-(4,6-dimethylpyrimidinyl)		10.80	−1.03	NA[g]	NA[g]	1154	6.07
22	2-pyrimidinyl		9.20	−0.96	10 000	−4	1155	6.15

[a] Reference 10. [b] These values refer to the anionic forms of acidic SA (ref 11). [c] Reference 19. [d] M. Yoshioka, K. Hamamoto, and T. Kubota, *Yakugaku Zasshi*, 84, 90 (1964). [e] A. V. Willi and W. Meier, *Helv. Chim. Acta*, 39, 54 (1956). [f] Double band: the assignment of the main peak is uncertain. [g] NA, not active at the highest testable concentration (5×10^{-5} M).

quency values of the SO_2 group [ν_S (SO_2)][11] and the proton chemical shifts of the p-NH_2 group [δ (NH_2)].[11] It must be pointed out that, in the case of acidic SA, the ν_S (SO_2) and δ (NH_2) values were measured on the anionic forms.

Simple correlation analysis allows the establishment of some significant relationships between the data of Table I.

Enzyme and growth inhibition indexes fulfill the linear regression eq 1 and 2, where n represents the number of

$$\log 1/EII_{50} = 0.58 \log 1/GII_{50} + 1.42 \quad (1)$$

$$n = 16;\ r = 0.902;\ s = 0.26;\ F = 61.44$$

$$\log 1/EII_{50} = 0.53 \log 1/GII_{50} + 1.19 \quad (2)$$

$$n = 15;\ r = 0.936;\ s = 0.19;\ F = 91.99$$

data, r is the correlation coefficient, s is the standard deviation from the regression, and F is the significativity Fisher test. In formulating eq 2, compound **10** has been discarded because of its very large deviation from eq 1. No explanation appears possible, at present, for this fact.

The good correlation between enzyme and growth inhibition indexes represents a remarkable result, in consideration of the broad heterogeneity of the chemical structures of the SA tested; together with nonacidic SA, the series embraces acidic SA almost nonionized as well as SA ionized up to 99%, under the experimental conditions of both enzyme and growth inhibition experiments.

In eq 1 and 2, compounds **12**, **13**, **15**, **18**, and **19** could not be considered; for these compounds, indeed, because of their poor solubility, only limit GII_{50} values could be obtained experimentally. Equation 2, however, allows one to estimate for compounds **12**, **13**, **15**, **18**, and **19** GII_{50} values of 8900, 116 000, 23 500, 718 000, and 147 000, respectively, which are in agreement with the limit values of Table I, with the only exception being compound **12**.

As already observed by Brown,[5] GII_{50} values are 10^2–10^3 times higher than EII_{50} values. This suggests that SA may have some difficulties in getting to the intracellular site involved in the enzymatic synthesis of dihydropteroate. These difficulties can be ascribed to a limited permeability of the bacterial cell toward these compounds, which, however, appears to be actually independent of the chemical nature, molecular or ionic, of the forms existing in the growth medium. The results do not agree with the theory of SA action proposed by Brueckner[17] and Cowles,[18] which stated that only the ionic forms are active, but cannot permeate the bacterial cell; actually, a number of neutral (amidic and imidic) SA show both antibacterial and enzyme inhibitory activity, and permeability factors appear to affect the antibacterial efficiency of SA, but no evidence emerges of a selective role toward the different forms.

A good correlation was also observed between the activity parameters ap_E and ap_G, in spite of the further approximations introduced in the related calculations. These values fulfill eq 3 and 4. Here again, compound **10** was

$$ap_E = 0.44ap_G + 0.88 \quad (3)$$

$$n = 16;\ r = 0.890;\ s = 0.29;\ F = 53.48$$

$$ap_E = 0.43ap_G + 0.81 \quad (4)$$

$$n = 15;\ r = 0.937;\ s = 0.21;\ F = 93.95$$

not considered in eq 4.

Whereas compounds **1** and **2**, according to their EII_{50} and GII_{50} values, appear to be the less active ones in the group of acidic SA, the corresponding anions actually result

(17) A. H. Brueckner, *Yale J. Biol. Med.*, 15, 813 (1943).
(18) P. B. Cowles, *Yale J. Biol. Med.*, 14, 599 (1942).

to be the most active inhibitors in the whole series of SA. This result is in full agreement with the hypothesis of Bell and Roblin,[19] which affirms that the lower the acidity of the sulfonamide, the higher the antibacterial (and, in our case, the enzyme inhibitory) activity of both the anionic and the molecular forms.

Actually, the activity parameters of the anions of compounds 1 and 2 could be somewhat overestimated because of the approximation which assigns the whole activities of these compounds to their anionic forms, whose fractions are rather small in these cases. This point has been already discussed in a previous work,[9] and it can be concluded that a reasonable correction of ap_E and ap_G values, made by considering the contributions of the neutral forms of compounds 1 and 2, should be within the limits of the approximations introduced in the calculation of the anionic fractions.

The correlation between ap_E and ap_G and the relationships previously observed[7,9] between the antibacterial potencies of the different forms of SA and the measured spectroscopic values ν_s (SO_2) and δ (NH_2) suggest the occurrence of similar relationships between the enzyme inhibitory activities of the same forms and the spectroscopic indexes.

The correlation between ap_E and ν_s (SO_2) values results from eq 5, where compounds 4 and 8 are not considered

$$ap_E = -0.048\nu_s\ (SO_2) + 53.44 \quad (5)$$

$$n = 20;\ r = 0.871;\ s = 0.35;\ F = 56.47$$

because of the uncertain assignment of their ν_s (SO_2) frequencies, and from eq 6, where compounds 10, 21, and 22 are also discarded because of their large deviations from eq 5. Actually, amides 21 and 22 show too large inhibitory potencies (both in growth and enzymatic activity measurements) in relation to their structural indexes.

$$ap_E = -0.054\nu_s\ (SO_2) + 60.54 \quad (6)$$

$$n = 17;\ r = 0.932;\ s = 0.26;\ F = 99.08$$

The correlation between ap_E and δ (NH_2) values is shown by eq 7 and 8. Here again, compounds 10, 21, and 22 are not considered in eq 8.

$$ap_E = -1.68\delta\ (NH_2) + 8.81 \quad (7)$$

$$n = 22;\ r = 0.757;\ s = 0.42;\ F = 26.88$$

$$ap_E = -1.92\delta\ (NH_2) + 10.03 \quad (8)$$

$$n = 19;\ r = 0.818;\ s = 0.40;\ F = 34.42$$

Equations 5-8 point out the relationship between the enzyme inhibitory potency of SA and their electronic features, represented by spectroscopic indexes.[10,11] The negative slopes of these equations assign the highest activity to those SA forms which show the highest electronic richness both on the SO_2 oxygens and on the p-NH_2 group.

Conclusion

It appears possible to conclude that, as in the case of the antibacterial activity[9] of SA, high activity of these compounds as inhibitors of dihydropteroate synthase is related to the following electronic features: (a) high polarization of the S-O bonds (i.e., high negative charges on the oxygens) and (b) low conjugation within the common moiety p-$NH_2C_6H_4SO_2$, due to (c) low engagement of the p-NH_2 lone pair to the aromatic system.

Moreover, it appears that permeability factors, while highly effective in depressing the antibacterial activity (GII_{50} with respect to EII_{50}) of all the SA, do not contribute significantly to the activity variation in this class of compounds, which appears to be mainly determined by the electronic structure of the different forms of SA.

Acknowledgment. This work was carried out with financial support of the Consiglio Nazionale delle Ricerche, Roma.

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Synthesis and Pharmacological Properties of 1,2,3,4,5,6-Hexahydro-1,6-methano-2-benzazocines

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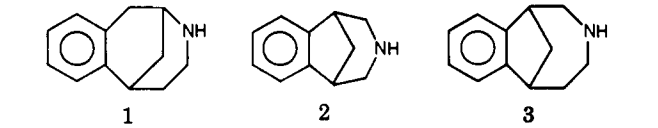
1,2,3,4,5,6-Hexahydro-1,6-methano-2-benzazocine, 2'-methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine, and *N*-alkyl derivatives of 2'-hydroxy-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine have been synthesized in order to evaluate their analgesic activities. These compounds show only slight antinociceptive activities in the mouse hot-plate assay.

Structural modifications of the benzomorphan ring system (1) have produced a number of interesting new



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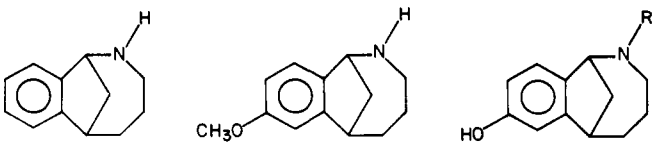

4a 5a 6

compounds; for example, *B*-norbenzomorphan (2) is a morphine-like analgesic with one-third the activity of codeine.[1] Benzazocine 3 is an active analgesic (ED_{50} = 4.9 mg/kg) which does not support morphine dependence in rats and monkeys.[2] As part of a long-term program to investigate the structure-activity relationships of potential analgesics structurally related to 6-7-benzomorphans, we have synthesized the related system 1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (**4a**), its methoxy analogue (**5a**), and appropriate *N*-alkyl derivatives of **4a**, **5a**, and the hydroxy analogue **6**.

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