TABLE I
N,N′-DIALKYLAMIDES (1c)

N-Substituent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	221–222.5	$C_{11}H_{18}N_2O_6$	48.17	48.29	6.62	6.82	10.21	9.91
Ethyl[a]	166–167	$C_{13}H_{22}N_2O_6$	51.64	51.70	7.34	7.05	9.27	9.39
Propyl[a]	161–162	$C_{15}H_{26}N_2O_6$	54.53	54.30	7.93	8.08	8.48	8.60
Butyl	146–147	$C_{17}H_{30}N_2O_6$	56.96	57.07	8.43	8.36	7.82	7.57
Amyl	151–152	$C_{19}H_{34}N_2O_6$	59.04	59.30	8.87	9.13	7.25	7.26
Hexyl	154–155	$C_{21}H_{38}N_2O_6$	60.82	60.66	9.24	9.16	6.76	7.01
Heptyl	160–160.5	$C_{23}H_{42}N_2O_6$	62.41	62.39	9.57	9.66	6.33	6.36
Octyl	154–155	$C_{25}H_{46}N_2O_6$	63.81	63.79	9.85	9.87	5.95	5.87
Nonyl	157–158	$C_{27}H_{50}N_2O_6$	65.02	65.02	10.11	10.16	5.62	5.68
Decyl	152–153	$C_{29}H_{54}N_2O_6$	66.12	66.26	10.33	10.41	5.31	5.05

[a] Recrystallized from ethyl acetate; all others from ethyl acetate–ether.

TABLE II
N,N′-DIALKYLAMINOALKYLAMIDES (Id)

N-Substituent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Dimethylaminoethyl	106–107	$C_{17}H_{32}N_4O_6$	52.55	52.56	8.30	8.37	14.42	14.22
Dimethylaminopropyl	117–118	$C_{19}H_{36}N_4O_6$	54.79	54.77	8.71	8.77	13.45	13.14
Pyrrolidinopropyl	105–106	$C_{23}H_{40}N_4O_6$	58.95	58.65	8.60	8.56	11.96	11.62
Piperidinoethyl	135–136.5	$C_{23}H_{40}N_4O_6$	58.95	59.28	8.60	8.97	11.96	11.67
Diethylaminopropyl	Oil	$C_{23}H_{44}N_4O_6$	58.44	57.66	9.38	9.68	11.85	11.51
Dibutylaminopropyl	Oil	$C_{31}H_{60}N_4O_6$	63.66	63.18	10.34	10.43	9.58	9.39

N,N′-Bismethyl-3,9-dicarboxamido-2,4,8,10-tetraoxaspiro[5.5]-undecane.—To 5.52 g. (0.02 mole) of 3,9-dicarbomethoxy-2,4,8,-10-tetraoxaspiro[5.5]undecane in 75 ml. of methanol was added 0.06 mole of a 25% aqueous methylamine solution. The mixture was refluxed for 1 hr. and stripped of all solvents. The bisamide was obtained quantitatively as a white powder that melted at 220–222° and at 221–222.5° on recrystallization from methanol–ether. The product was soluble in water.

N,N′-Bis(3-dimethylaminopropyl)-3,9-dicarboxamido-2,4,8,-10-tetraoxaspiro[5.5]undecane.—To a solution of 5.52 g. (0.02 mole) of the diester Ib dissolved in 100 ml. of absolute methanol, was added 4.08 g. (0.04 mole) of 3-dimethylaminopropylamine in 50 ml. of methanol. The solution was refluxed 1 hr. and all solvents were stripped at the aspirator. A clear oil resulted which solidified on slurrying with anhydrous ether. There was obtained 7.6 g. (91%) of material melting at 117–118°, unchanged on recrystallization from ethyl acetate–ether. This product was water soluble.

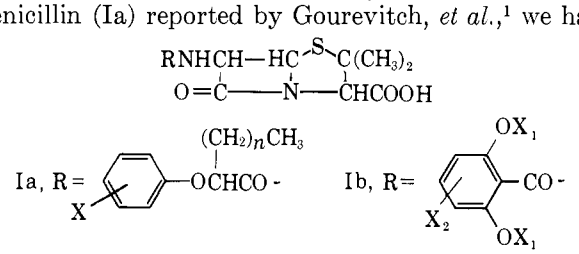
The Structure–Activity Relationship in Penicillins

CORWIN HANSCH AND EDNA W. DEUTSCH

Department of Chemistry, Pomona College, Claremont, California

Received April 6, 1965

In a recent study of the activity of 22 derivatives of penicillin (Ia) reported by Gourevitch, *et al.*,[1] we have



shown, using substituent constants and regression analysis,[2] that variation in activity against resistant *Staphylococcus aureus* in the presence of serum is well correlated by eq. 1 and 2. In these equations, C is

	n	r	s		
$\log \frac{1}{C} = -0.445\pi + 5.673$	20	0.909	0.191	*in vivo*	(1)
$\log \frac{1}{C} = -0.468\pi + 6.437$	20	0.857	0.267	*in vitro*	(2)

the molar concentration for CD_{50} with Smith strain *S. aureus* in the *in vivo* mice experiments and the minimum inhibitory molar concentration for the *in vitro* tests on bacteria. Human serum was used in the *in vitro* experiments. The number of points used in obtaining the constants *via* the least-squares method is represented by n; r is the correlation coefficient, and s is the standard deviation. It was shown by regression analysis that electron density on the ring as measured by $\Sigma\sigma$ for the substituents had no detectable effect on the biological activity.

Comparison of eq. 1 and 2 reveals that the slopes of the curves have the same dependence on the lipophilic character of the substituent (π). By definition,[3] a negative value of π for a substituent X indicates a preference with respect to H for the aqueous phase, and a positive value indicates a preference for the lipophilic phase. The negative sign associated with the π terms in eq. 1 and 2 means that increasing the hydrophilic character of the substituent increases its activity. Thus, as we pointed out,[2] using substituents such as $-SO_2CH_3$, $-CN$, or $-CH_2OH$ which are quite hydrophilic and possess negative values[4,5] for π would result in higher activity for compounds in the series Ia.

Recently, Sheehan[6] has published a summary of the activity of penicillins related to methicillin (Ib). These derivatives were also tested on resistant and nonresistant *S. aureus* in the presence and absence of

(1) A. Gourevitch, G. A. Hunt, and J. Lein, *Antibiot. Chemotherapy*, **10**, 121 (1960).
(2) C. Hansch and A. R. Steward, *J. Med. Chem.*, **7**, 691 (1964).
(3) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
(4) T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175 (1964).
(5) J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965).
(6) J. C. Sheehan, "Molecular Modification in Drug Design," American Chemical Society, Washington, D. C., 1964, p. 15.

serum. Unfortunately, quantitative results were given for the resistant series only in the presence of serum. From his data (Table I) we have derived the following

TABLE I

OBSERVED AND CALCULATED ACTIVITY OF 2,6-DIALKOXYPHENYLPENICILLINS IN THE PRESENCE OF SERUM

No.	X_1[a]	X_2[a]	$\Sigma\pi$[b]	σ	*S. aureus* (resistant) log (1/*C*) Obsd.[c]	Calcd.[d]
1	CH_3	H	1.00	0	1.945	1.531
2	C_2H_5	H	2.00	0	1.395	1.287
3	C_6H_5	H	4.26	0	0.609	0.734
4	$C_6H_5CH_2$	H	5.80	0	0.638	0.357
5	$C_6H_5(CH_2)_2$	H	6.32	0	0.063	0.230
6	CH_3	3-Cl	1.76	0.34	1.709	1.930
7	CH_3	3-OCH_3	1.12	0.12	1.702	1.708
8	CH_3	4-OCH_3	0.96	−0.27	0.795	1.077

[a] See structure I. [b] See text for calculation of $\Sigma\pi$. [c] Taken from data of Sheehan. His values reported as γ/ml. were converted to moles/l. [d] Calculated from eq. 4.

equations for the tests on resistant bacteria in the presence of serum. Since substituent constants are

$$\log \frac{1}{C} = -0.249\pi + 1.828 \qquad n = 8,\ r = 0.823,\ s = 0.412 \qquad (3)$$

$$\log \frac{1}{C} = -0.245\pi - 1.720\sigma + 1.776 \qquad n = 8,\ r = 0.929,\ s = 0.295 \qquad (4)$$

$$\log \frac{1}{C} = +0.010\pi^2 - 0.316\pi + 1.76\sigma + 1.853 \qquad n = 8,\ r = 0.930,\ s = 0.328 \qquad (5)$$

not available for all of the functions in Table I, we have had to make certain assumptions. It is assumed that all of the OX_1 groups (Ib) have the same electronic effect on the ring and carbonyl group. Since all molecules have two such groups, σ was given a reference value of zero for these groups and only σ for X_2 was used in the calculations. The only group likely to be slightly out of line with this assumption is OC_6H_5.

For π-values we have used those taken from phenoxyacetic acids[4] except for benzyl and phenylethyl which were developed from data in a later report.[5] To calculate the value of π for the benzyl and phenethyl groups we have subtracted the value of −1.80 for π for aliphatic OH from log P for benzyl alcohol (1.10) and log P for phenethyl alcohol[5] (1.36). Thus, $\Sigma\pi$ for derivative 5 in Table I was calculated as follows.

$$\Sigma\pi = 2(1.36 + 1.80) = 6.32 \qquad (6)$$

From the data in Table I we have derived eq. 3–5 by the method of least squares. Of these equations, 4 provides the simplest rationalization of the variance in biological activity. Most interesting is the fact that biological activity shows a similar dependence on π in eq. 1–4.

The fact that the π-term has a negative coefficient in each series of penicillins shows that the parent side chains [$C_6H_5OCH(CH_3)CO$ in Ia and 2,6-$(CH_3O)_2$-C_6H_3CO in Ib] are already too lipophilic for maximum activity. Unfortunately, both Gourevitch, *et al.*, and Sheehan were concerned only with functions having positive values for π. The above equations clearly indicate the disadvantage of such groups in the presence of serum.

In eq. 1 and 2, the addition of the σ-term did not result in improved correlation; however, σ does seem to play a role in the benzoic acid derivatives where the substituents are not insulated from the carbonyl group. A positive value for the σ-term indicates that groups which decrease the electron density on or in the region of the carbonyl group promote activity. The importance of σ must be accepted with some reservation since only three derivatives were used to evaluate this effect.

Our previous analysis[2] leads to the conclusion that bulky substituents in the side chain serve to prevent opening of the lactam ring. Keeping in mind that large groups will help shield both the amide linkage and the lactam ring, and that these groups should be much more hydrophilic than phenyl, a number of new approaches for improving the activity of these two classes of penicillins are evident. Of course, functions such as $-SO_2CH_3$ ($\pi = -0.50$, $\sigma = +0.60$) could be used to advantage. However, the phenyl group has such a large π-value ($\sim$2) that stable heterocyclic functions would make much better starting points. Pyridine (log P = 0.65), imidazole, or other nitrogen or oxygen heterocycles would be much more hydrophilic, and should give derivatives of much greater activity in the presence of serum.

Increasing the hydrophilic character of the penicillins will be even more important when they are being designed for use against gram-negative bacteria. Analysis of the mechanism of action of phenols[3] against gram-positive and gram-negative bacteria showed that optimal lipophilic character for the phenol coefficient for the latter group is very much lower than for the former.

Acknowledgment. This research was supported under Research Grant 07492 from the National Institutes of Health.

Dihydrazides, a New Class of Anthelmintics[1a]

RAYMOND CAVIER

Chaire de Parasitologie, Faculté de Pharmacie, Paris

AND RICHARD RIPS[1b]

Institut d'Anesthesiologie de la Faculté de Médecine, Paris, France

Received April 26, 1965

More than half a century ago, Curtius[2] described the synthesis of hydrazides of dicarboxylic acids. Such derivatives were studied later for their sweet taste, in the search for a saccharin substitute.[3] More recently, it appeared that hydrazides of malonic and other dicarboxylic acids might have tuberculostatic

(1) (a) This work was supported by a grant given by the Institut National de la Santé et de la Recherche Médicale. (b) To whom inquiries should be addressed.

(2) (a) T. Curtius, *J. prakt. Chem.*, [2] **91**, 1 (1915); (b) T. Curtius and H. Clemm, *ibid.*, **62**, 189 (1900); (c) T. Curtius, G. Schöfer, and N. Schwann, *ibid.*, **51**, 180 (1895).

(3) (a) J. J. Blanksma and H. A. Bakels, *Rec. trav. chim.*, **58**, 497 (1939); (b) J. J. Blanksma and H. de Graaf, *ibid.*, **57**, 3 (1938).