Influence of Lipophilic Character on the Antibacterial Activity of Cephalosporins and Penicillins

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A relationship between lipophilic character, as expressed by the chromatographic R_m value, and biological activity of cephalosporins and penicillins was shown in *Escherichia coli*, *Staphylococcus aureus*, and *Treponema pallidum*. The compounds most active against *E. coli* are more hydrophilic than those most active against *S. aureus*. This was interpreted on the basis of the different lipid composition of the cell walls of Gram-positive and Gram-negative microorganisms. The high lipid content of the cell wall of a Gram-negative microorganism such as *E. coli* could retain the most lipophilic molecules, which would not reach their site of action. Therefore only the most hydrophilic compounds could be able to cross the cell wall and would be the most active ones. In the case of a Gram-positive microorganism such as *S. aureus* the low lipid content of its cell wall would permit the high activity of more lipophilic compounds. *T. pallidum*, which is lacking a cell wall, behaves like *S. aureus*. In fact there is an overlapping of the compounds most active against both microorganisms. The compounds most active against both *E. coli* and *S. aureus* have R_m values which are between those of the compounds most active against Gram-negative and Gram-positive microorganisms, respectively. It is therefore suggested that compounds with intermediate R_m values could be characterized by a broad-spectrum antibacterial activity. The regression analysis of the relationship between R_m values and biological activity of penicillins in *S. aureus* and *T. pallidum* showed evident deviations from the parabolic curve for methicillin, cloxacillin, and dicloxacillin. It is suggested that this could be due to the presence of *ortho* substituents on the aromatic ring of the penicillin side chain.

Hansch, *et al.*,[1] and Lien, *et al.*,[2] by means of two substituent constants π and σ found very good correlations between the chemical structure and the biological activity of several sets of antibacterial agents. The substituent constant π was defined as log (P_X/P_H) where P_H and P_X are the octanol–water partition coefficients for a parent compound H and its derivative X. The lipophilic character, as expressed by the partition coefficient log P or by $\Sigma\pi$, both calculated from π,[3-5] was shown to be the most important factor in determining the biological activity. In particular, the compounds effective against Gram-negative microorganisms were more hydrophilic than those effective against Gram-positive ones. The electron density on aromatic rings as measured by σ or $\Sigma\sigma$ was shown to play a significant role in several series of antibacterial agents,[2] electron withdrawal promoting activity.[2] In the field of antibiotics the activity against *Staphylococcus aureus* in derivatives of phenoxymethylpenicillin and methicillin increased with the hydrophilic character of the substituents.[6] While in the *in vivo* and *in vitro* experiments with derivatives of phenoxymethylpenicillin the electronic effects of substituents were of very little or no importance,[6] in the case of methicillin derivatives, they seemed to play a role.[6] In both cases a positive value of σ seemed to promote activity.

While Hansch, *et al.*,[7] pointed out that the calculated log P $\Sigma\pi$ cannot completely replace the experimental determination of the partition coefficient because of possible group interactions, Bird and Marshall[8] found some anomalies in the calculated $\Sigma\pi$ values of penicillins. On the other hand, in order to avoid the practical difficulties of the direct determination of a partition coefficient, Boyce and Milborrow[9] suggested the use of the chromatographic R_m value, shown to be related to the partition coefficient[10] and calculated from the formula:

$$R_m = \log\left(\frac{1}{R_f} - 1\right)$$

In previous papers it was shown that a reversed-phase tlc method was a suitable technique for the determination of the R_m value of penicillins and cephalosporins.[11] The purpose of the present work was to show that there is a relationship between partition data and antibacterial activity of cephalosporins and penicillins.

Materials and Methods

The antibiotics used in the present study are indicated in Tables I and II. Glaxo Laboratories Ltd. and Eli Lilly and Co. are gratefully acknowledged for the supply of the noncommercial cephalosporins. Some cephalosporins and the penicillins were available in the form of water-soluble compounds. The remaining cephalosporins, in acidic form, were dissolved in 0.1 N $NaHCO_3$.

The compounds were assayed against *S. aureus* Oxford strain and *Escherichia coli* 0-25 by means of the cylinder-plate method.[12] The microorganisms were inoculated into a culture medium consisting of brain-

(1) (a) C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Amer. Chem. Soc.*, **85**, 2817 (1963); (b) C. Hansch and T. Fujita, *ibid.*, **86**, 1616 (1964).

(2) E. J. Lien, C. Hansch, and S. M. Anderson, *J. Med. Chem.*, **11**, 430 (1968).

(3) T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964).

(4) J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.* **8**, 150 (1965).

(5) C. Hansch, A. R. Steward, and J. Iwasa, *ibid.*, **8**, 868 (1965).

(6) (a) C. Hansch and A. R. Steward, *ibid.*, **7**, 691 (1964); (b) C. Hansch and E. W. Deutsch, *ibid.*, **8**, 705 (1965).

(7) C. Hansch, A. R. Steward, J. Iwasa, and E. W. Deutsch, *Mol. Pharmacol.*, **1**, 205 (1965).

(8) E. A. Bird and A. C. Marshall, *Biochem. Pharmacol.*, **16**, 2275 (1967).

(9) C. B. C. Boyce and B. V. Milborrow, *Nature*, **208**, 537 (1965).

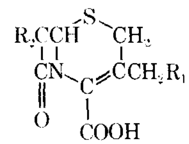
(10) E. C. Bate-Smith and R. G. Westall, *Biochim. Biophys. Acta*, **4**, 427 (1950).

(11) (a) G. L. Biagi and M. F. Gamba, *Boll. Soc. Ital. Biol. Sper.*, **44**, 189 (1967); (b) G. L. Biagi, A. M. Barbaro, M. C. Guerra, and M. F. Gamba, *J. Chromatogr.*, **41**, 371 (1969); (c) G. L. Biagi, A. M. Barbaro, M. C. Guerra, and M. F. Gamba, *ibid.*, **44**, 195 (1969).

(12) D. C. Grove and W. A. Randall, "Assay Methods of Antibiotics," Medical Encyclopedia Inc., New York, N. Y., 1955.

TABLE I

STRUCTURE–ACTIVITY RELATIONSHIP IN CEPHALOSPORINS AGAINST *E. coli*, *S. aureus*, AND *T. pallidum*



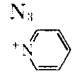
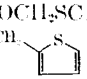
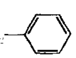
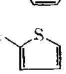
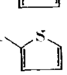
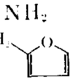
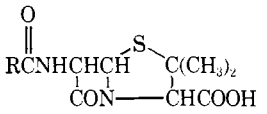
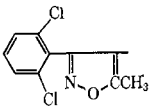
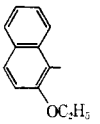
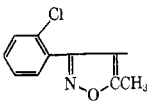
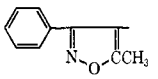
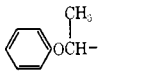
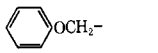
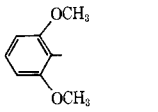
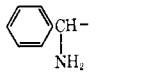
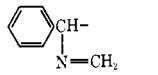
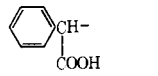
Compd	Structure R₁	Structure R₂	R_m value	*E. coli* log 1/c obsd	*E. coli* log 1/c calcd	*S. aureus* log 1/c obsd	*S. aureus* log 1/c calcd	*T. pallidum* log 1/c obsd	*T. pallidum* log 1/c calcd
I Acid	OAc	$NHCO(CH_2)_6CH_3$	1.60	0.60	0.11	4.27	4.23	3.60	3.81
II Acid	OAc	NHCOCH 	1.32	0.79	0.89	4.53	4.49	4.54	4.24
III Na salt	OAc	$NHCOCH_2SCH_2C_6H_5$	1.08	0.81	1.41	4.70	4.59	4.56	4.47
IV Na salt	N_3	$NHCOCH_2SCH_2C_6H_5$	1.08	0.83	1.41	4.59	4.59	4.24	4.47
V Cephaloridine acid		$NHCOCH_2$ 	0.98	1.86	1.59	4.36	4.59	4.52	4.53
VI Cephaloram Na salt	OAc	$NHCOCH_2$– 	0.54	2.06	2.13	4.23	4.37	4.51	4.53
VII Cephalotin Na salt	OAc	$NHCOCH_2$ 	0.40	2.48	2.20	4.24	4.22	4.52	4.44
VIII Acid	N_3	$NHCOCH_2$ 	0.37	2.16	2.22	4.15	4.18	4.78	4.42
IX Cephaloglycin acid	OAc	$NHCOCHC_6H_5$ (CH bearing NH_2)	0.29	2.85	2.24	4.00	4.07	4.50	4.35
X Acid	OAc	$NHCOCH_2$ 	0.16	2.39	2.24	4.00	3.87	3.88	4.20
XI Acid	OH	$NHCOCH_2C_6H_5$	−0.07	2.21	2.15	3.73	3.42	3.84	3.84
XII Acid	OAc	$NHCOCH_2Cl$	−0.31	1.95	1.93	3.61	2.83	3.36	3.35
XIII (7-Aminocephalosporanic acid)	OAc	NH_2	−0.39	1.22	1.83	1.56	2.61	2.56	3.16
XIV (Cephalosporin C K salt)	OAc	$NHCO(CH_2)_3CH(NH_2)CO_2H$	−0.71	1.44	1.29	1.71	1.60	2.66	2.25

Table II
Structure–Activity Relationship in Penicillins against *E. coli*, *S. aureus*, and *T. pallidum*



Compd	Structure R	R_m value	*E. coli* log 1/c obsd	*E. coli* log 1/c calcd	*S. aureus* log 1/c obsd	*S. aureus* log 1/c calcd	*T. pallidum* log 1/c obsd	*T. pallidum* log 1/c calcd
Dicloxacillin		1.63	0.66	0.42	4.23		4.89	
Nafcillin		1.39	0.72	0.74	3.72	3.77	4.54	4.51
Cloxacillin		1.34	0.86	0.80	4.10		4.85	
Oxacillin		1.05	0.93	1.18	3.98	4.48	4.84	5.15
Phenethicillin		1.03	1.06	1.21	4.80	4.52	5.10	5.18
Phenoxymethylpenicillin		0.89	1.72	1.39	5.14	4.70	5.78	5.37
Benzylpenicillin	$C_6H_5CH_2$	0.55	2.09	1.83	4.85	4.89	5.76	5.64
Methicillin		0.47	0.85	1.94	3.15		4.50	
Ampicillin		0.08	3.10	2.45	4.35	4.57	5.43	5.62
Methylenampicillin		−0.29	2.94	2.93	3.87	3.85	5.14	5.26
Carbenecillin		−0.46	3.12	3.15	3.45	3.37	5.16	5.00

heart agar from Difco. The antibiotic solutions (0.1 ml) were allowed to diffuse from holes cut in the agar layer. At the end of a 16-hr incubation period at 37° the diameter of the zone of inhibition was measured. Each antibiotic was tested at various concentrations. There was a range of linear relationship between inhibition diameters and the log of drug concentrations. From the equations of the straight lines the log of the concentration giving an inhibition diameter of 20 mm was calculated. The significance of b for each equation was shown by means of a t test. The biological activity was finally expressed as log $1/c$ where c is the molar ($mM \times 10^{-2}$) concentration of each antibiotic, which gives an inhibition diameter of 20 mm.

Penicillins and cephalosporins were assayed against *Treponema pallidum* Reiter strain by means of the turbidimetric method.[12] Reiter strain was grown in Fluid Thioglycollate Medium (Difco) with addition of 1% human serum. Minimal inhibitory concentrations (mic) were determined after a 4-day incubation and reported as log $1/c$, where c is the molar concentration ($mM \times 10^{-2}$) of each antibiotic, which prevents the growth of spirochetes.

The lipophilic character of the molecules was expressed as R_m value. This was measured by means of a reversed-phase tlc. The polar mobile phase was represented by acetone and water in various proportions. The nonpolar stationary phase consisted of silicone oil, which impregnated a silica gel G layer. The R_m values were linearly related to the concentration of acetone in the mobile phase. In this way it was possible to obtain, by interpolation or extrapolation, an R_m value for each compound in a standard system, *i.e.*, silicone oil–H_2O. Higher and/or positive R_m values indicate compounds more lipophilic than those represented by a lower and/or negative R_m value. The details of the method have been described previously.[11]

The structure–activity relationships were analyzed by means of multiple regression analysis. The multiple correlation coefficient r was obtained by computing the correlation between observed and calculated log $1/c$ values. The fraction of the variance of log $1/c$ attributable to the multiple regression is indicated by r^2.[13]

(13) G. W. Snedecor and W. G. Cochran "Statistical Methods," The Iowa State University Press, Ames, Iowa, 1967, p 402.

Table III
Regression Analysis of Cephalosporins and Penicillins on *E. coli*, *S. aureus*, and *T. pallidum*[a]

No.	Equation	n	r	s
	Cephalosporins *vs. E. coli*			
1	$\log 1/c = 1.928 - 0.527R_m$	14	0.497	0.662
2	$\log 1/c = 2.189 + 0.483R_m - 1.113R_m^2$	14	0.853	0.416
	Cephalosporins *vs. S. aureus*			
3	$\log 1/c = 3.327 + 1.120R_m$	14	0.788	0.628
4	$\log 1/c = 3.566 + 2.044R_m - 1.017R_m^2$	14	0.919	0.419
	Cephalosporins *vs. T. pallidum*			
5	$\log 1/c = 3.709 + 0.653R_m$	14	0.623	0.589
6	$\log 1/c = 3.964 + 1.637R_m - 1.084R_m^2$	14	0.925	0.298
	Penicillins *vs. E. coli*			
7	$\log 1/c = 2.551 - 1.304R_m$	11	0.899	0.463
	Penicillins *vs. S. aureus*			
8	$\log 1/c = 3.978 + 0.245R_m$	11	0.285	0.618
9	$\log 1/c = 4.053 + 0.880R_m - 0.562R_m^2$	11	0.468	0.604
10	$\log 1/c = 4.454 + 1.644R_m - 1.537R_m^2$	8	0.881	0.344
	Penicillins *vs. T. pallidum*			
11	$\log 1/c = 5.232 - 0.204R_m$	11	0.321	0.429
12	$\log 1/c = 5.277 + 0.170R_m - 0.330R_m^2$	11	0.458	0.430
13	$\log 1/c = 5.567 + 0.732R_m - 1.072R_m^2$	8	0.847	0.270

[a] n, number of the tested compounds; r, multiple correlation coefficient; s, standard deviation.

Results

Antibacterial Activity of Cephalosporins against *E. coli* and *S. aureus*.—The R_m values and the observed log $1/c$ values of cephalosporins against *E. coli* and *S. aureus* are indicated in Table I. The equations, which correlate the structure-activity relationship in *E. coli* and *S. aureus*, were calculated from the data of Table I by means of multiple regression analysis and reported in Table III. In the Gram-negative *E. coli* and in the Gram-positive *S. aureus* the best rationalization of the relationship between structure and activity is provided by eq 2 and 4, respectively. These show a parabolic relationship between lipophilic character and biological activity and explain 73 and 84%, respectively, of the variance in the biological activity instead of the 25 and 62% of eq 1 and 3. An F test showed that the introduction of the R_m^2 term into eq 2 and 4, from which the calculated log $1/c$ values of Table I were obtained, significantly improved the correlations provided by eq 1 and 3. The negative sign associated with the R_m^2 term in both equations means that the activity of cephalosporins against *E. coli* and *S. aureus* increases and decreases as the R_m values change and pass through an optimum.

Antispirochetal Activity of Cephalosporins against *Treponema pallidum* Reiter Strain.—The observed log $1/c$ values of cephalosporins against *T. pallidum* are reported in Table I. A parabolic relationship between R_m values and biological activity, is shown by eq 6, which explains 86% of the variance in the biological activity. The calculated log $1/c$ values of Table I were obtained from eq 6.

Antibacterial Activity of Penicillins against *E. coli* and *S. aureus*.—The R_m values and the observed log $1/c$ values of penicillins against *E. coli* and *S. aureus* are reported in Table II. The structure-activity relationship in *E. coli* is best rationalized by eq 7, from which the calculated log $1/c$ values of Table II were obtained. Part (81%) of the variance in the biological activity is explained. The negative sign associated with the R_m term means that the activity against *E. coli* increases linearly with the hydrophilic character of the molecules. The introduction of the R_m^2 term does not improve, in a significant way, the correlation.

The relationship between R_m values and the antibacterial activity of penicillins against *S. aureus* is first described by eq 8 and 9. Equation 9 indicates a parabolic relationship, but the correlation is very poor ($r = 0.468$) and only 22% of the variance of log $1/c$ is explained by the regression. As the most evident deviations from the parabolic curve were presented by methicillin, cloxacillin, and dicloxacillin, these compounds were not used in calculating eq 10. The calculated log $1/c$ values of Table II were obtained from eq 10 which shows a clear improvement of the correlation coefficient.

Activity of Penicillins against *T. pallidum* Reiter Strain.—The experimental data are reported in Table II. The relationship between R_m values and antispirochetal activity is described by eq 11 and 12. However the correlation coefficients are very low. As in the case of *S. aureus*, the noninclusion of methicillin, cloxacillin, and dicloxacillin in eq 13 resulted in an improvement of the correlation. The calculated log $1/c$ values of Table II were obtained from eq 13.

Discussion

The data of the present work show the influence of lipophilic character on the biological activity of cephalosporins and penicillins. There is a parabolic dependence of log $1/c$ on the R_m values of cephalosporins for *E. coli*, *S. aureus*, and *T. pallidum*. This is in agreement with the postulate of the parabolic relationship between the penetration rate of compounds through biological membranes and their lipophilic character.[2,14] The penetration rate increases

(14) J. T. Penniston, L. Becker, D. L. Bentley, and C. Hansch, *Mol. Pharmacol.*, **5**, 333 (1969).

and decreases as the lipophilic character increases progressively and passes through an optimum. In the case of chemotherapeutic agents the penetration rate is related to their antibacterial activity, as the penetration through the cell wall or the cell membrane is a prerequisite for their activity.

The log $1/c$ values of Table I show that the cephalosporins most active against *E. coli* are more hydrophilic (lower R_m values) than those most active against *S. aureus*. This confirms the results of Hansch, *et al.*,[1] and Lien, *et al.*,[2] and supports the view that also in the field of antibiotics the compounds active against Gram-negative microorganisms are more hydrophilic than those active against Gram-positive ones. As suggested by Lien, *et al.*[2] the reason of the different lipophilic character of the molecules active against Gram-positive or Gram-negative organisms may be in the different lipid composition of the cell wall. It is known[15] that the cell wall of the Gram-negative microorganisms is richer in lipid than that of the Gram-positive ones. The lipophilic molecules could be retained by the cell wall of Gram-negative microorganisms more strongly than the hydrophilic ones. Therefore only the latter could be able to reach the cell and exert their toxic effects.

The calculated log $1/c$ values of Table I show that cephaloridine and compounds III and IV are the most active compounds against *S. aureus*. This can be considered to be in agreement with the results of several investigators, as reported by Van Heyningen.[16] In particular it was pointed out that cephaloridine shows a greater activity than cephalothin against staphylococci.[17]

The same data show that cephaloglycin and compound X with lower R_m values are the most active cephalosporins against *E. coli*.

The products of the calculated log $1/c$ values for each compound on *S. aureus* and *E. coli* indicate that cephaloram and cephalothin are the most active cephalosporins against both microorganisms. This agrees with the data of other investigators pointing out the broad-spectrum antibacterial activity of cephalothin.[16] It is interesting to note that the R_m value of cephalothin is between those of cephaloridine and cephaloglycin. This could suggest that above a certain degree of lipophilicity or hydrophilicity the compounds are mainly active against Gram-positive microorganisms or, respectively, Gram-negative ones. A compound with an intermediate R_m value could be the most active against both type of microorganisms. However, if the present data seem to support such a suggestion, it must be pointed out that they were obtained only from *E. coli* and *S. aureus*. Moreover a survey of the literature concerning the assay of the above cephalosporins against several species of Gram-positive and Gram-negative organisms seems to indicate a broad-spectrum antibacterial activity also for cephaloridine and cephaloglycin.[16,18]

The calculated log $1/c$ values regarding the activity of the tested cephalosporins against *T. pallidum* show that the most active compounds are cephaloram and cephaloridine. This result, which practically confirms the data of Ferrari, *et al.*,[19] means that there is an overlapping of the R_m values of the compounds most active against *S. aureus* and *T. pallidum*. This supports the hypothesis that the different lipophilic character of the compounds active against Gram-positive or Gram-negative microorganisms may depend on the different lipid composition of the cell wall. In fact, *T. pallidum*, which lacks a cell wall, seems to be most sensitive to those lipophilic compounds which are not trapped by the low lipid content of the cell wall of a Gram-positive microorganism such as *S. aureus*. Finally 7-aminocephalosporanic acid is consistently less active than expected by its R_m value. This could indicate that, as regards the antibiotic activity of cephalosporins, the side chain exerts a steric effect.

The data regarding the activity of penicillins against *E. coli* show a significant linear relationship between R_m values and antibacterial activity. In particular the most active compounds against *E. coli* are the most hydrophilic ones. The absence of a parabolic dependence of log $1/c$ on R_m values for *E. coli* is likely to be due to the lack of more hydrophilic compounds, which should show a progressive decrease in activity.

In the case of *S. aureus* and *T. pallidum* the interpretation of the data is much more difficult. Equations 9 and 12 seem to indicate a parabolic relationship between R_m values and biological activity. However they provide very low correlation coefficients ($r = 0.468$ in eq 9 and 0.458 in eq 12). An explanation could be in the fact that all the data of the present work were obtained from experiments carried out in the absence of serum in the culture medium (*T. pallidum* was only a partial exception because it was grown in the presence of 1% bovine serum). Hansch, *et al.*,[6] by examining the relationship between π values and antibacterial activity of penicillins on *S. aureus*, found very poor correlations when human serum had not been added to the culture medium. A striking improvement in the correlations was obtained when the serum binding was taken into consideration.[6] In any case the present data would suggest the influence of serum only in the case of penicillins on *S. aureus* and *T. pallidum*. Equations 10 and 13, calculated without methicillin, cloxacillin, and dicloxacillin, show a better correlation. The fact that methicillin, cloxacillin, and dicloxacillin have substituent groups on the *ortho* positions of the aromatic ring might suggest a role of these groups. They could exert an electronic effect and this would be in agreement with the findings of Lien, *et al.*,[2] that electron withdrawal promoted activity in their series of antibacterial agents. In the field of penicillins Hansch, *et al.*,[6] also noted some evidence indicating the role of positive σ values. However in the present case, if it was possible to express the electronic effects of the *ortho* substituents by means of the Hammett constant (σ values), the lack of available data in the literature did not permit evaluations of the electronic effects of substituents in other sites of the side chain, as expressed by the Taft constant (σ^* values).

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The *ortho* substituents could also exert a steric effect, the evaluation of which is very difficult at the present time. Finally both electronic and steric effects may play a role. It is well known that methicillin, although not susceptible to penicillinase, is much less active than benzylpenicillin and ampicillin against Gram-positive and Gram-negative microorganisms.[20] In particular, a comparative study of Barber and Waterworth[21] on the activity of 8 penicillins against 5 Gram-positive microorganisms and 15 Gram-negative ones clearly showed, as reported by Garrod,[22] that methicillin is by far the least active compound. The deviations of methicillin, cloxacillin, and dicloxacillin from the parabolic curve could mean that the enzymic system or membrane system with which the penicillins interact in the *S. aureus* and *T. pallidum* are different or that metabolism is involved in some way which causes the difference. The calculated log $1/c$ values for *S. aureus* and *T. pallidum* show that also in the case of penicillins the R_m values of the active compounds on these organisms are fairly overlapping and indicate compounds more lipophilic than those active against *E. coli*. The most active compounds against *S. aureus* and *E. coli* are benzylpenicillin ($R_m = 0.55$) and carbenecillin ($R_m = -0.46$), respectively. The products of the calculated log $1/c$ values for *S. aureus* and *E. coli* indicate that methylenampicillin and ampicillin with R_m values between the above limits are the most active against both microorganisms. This is in agreement with the literature attributing such a characteristic to ampicillin.[20]

In conclusion, both in the case of cephalosporins and penicillins there is a relationship between lipophilic character and spectrum of antibacterial activity. This could suggest that differences in the activity of a given antibiotic on different species of microorganisms may depend on its chance to cross their cell wall rather than on metabolic features of the bacterial cells. To this purpose, it was found that Gram-positive microorganisms grown under conditions of increased cellular lipid content showed also an increase in their resistance to penicillins.[23]

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Agents Acting on the Central Nervous System. XIII. 2,3,4,4a,5,6-Hexahydro-1(*H*)-pyrazino[1,2-*a*]quinolines. A New Class of Hypotensive Agents[1]

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The synthesis and pharmacological evaluation of a number of 3-substituted 2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinolines are reported. These compounds in general show hypotensive and adrenergic-receptor blocking activity. The hypotensive activity is particularly marked in 3-β-phenethyl- and 3-γ-(*p*-fluorobenzoyl)-propyl-2,3,4,4a,5,6-hexahydro-1(*H*)pyrazino[1,2-*a*]quinolines.

N-Phenylpiperazines possess CNS and cardiovascular activities, and substitution of the second imino group greatly modulates and modifies these activities.[2] *N*-Phenylpiperazines have also served as a side chain in a number of pharmacologically important molecules.[3] In general *O*-alkyl substitution in the phenyl residue of these *N*-phenylpiperazines greatly enhances the effect on the cardiovascular activities,[4] and, in fact, a number of 1-substituted 4-*o*-tolylpiperazines are known to be strong adrenolytics.[5] It therefore seemed of interest to incorporate this molecular framework into a rigid structure such as is present in 3-substituted 2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinolines (I, R = H). In this paper we report the synthesis and pharmacological activities of a number of 3-substituted derivatives of I, substituted 2-aminomethylquinolines (II), and the corresponding 1,2,3,4-tetrahydro compounds (III).[6]

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