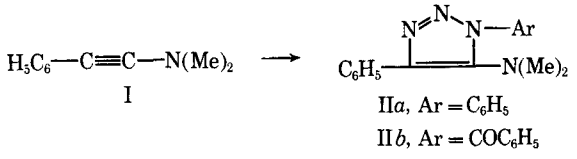
Antimetabolite Activity of Some *N,N*-Dialkylamino-1,2,3-triazoles and α-Diazoamidines

Keyphrases □ *N,N*-Dialkylamino-1,2,3-triazoles—synthesis □ α-Diazoamidines—synthesis □ Antibacterial activity—*N,N*-dialkylamino-1,2,3-triazoles, α-diazoamidines

Sir:

A number of 1,3-dipolar additions to ynamines or *N,N*-disubstituted-1-amino-1-alkynes have been reported to produce a series of five-membered heterocycles (1–3). For instance, the additions of both aryl and aroyl azides to *N,N*-dimethylaminophenylacetylene (I) gave the corresponding 1,2,3-triazoles II*a* and II*b*, respectively (Scheme I). From the 1,3-dipolar additions of a number of substituted benzenesulfonyl azides to the ynamine (I) and *N,N*-diethylaminoprop-1-yne, we have isolated crystalline *N,N*-dialkylamino-1,2,3-triazoles (X and XI) and α-diazoamidines (III–IX). Details about the preparation and characterization of Compounds III–XI (Table I) will be published (4).



Scheme I

Compounds III–XI were subjected to *in vitro* screening for antimetabolites (5). In this method, the detection system utilizes the Gram-positive *Bacillus subtilis* (UC-564) and Gram-negative *Escherichia coli* (ATCC 26). Both of these organisms were grown in two types of agar: (*a*) nutrient agar—a complex medium containing 0.3% beef extract, 0.5% peptone, and 1.5% agar; and (*b*) a completely synthetic medium with glucose as the only source of carbon. Acetone solutions of Compounds III–XI at concentrations of 1 mg./ml. were applied onto 13-mm. paper disks, and they were placed on the surface of the seeded agar. The trays containing these paper disks, seeded with *E. coli* and *B. subtilis*, were incubated at 37° for 18 hr., and the zones of inhibition were measured. The results are given in Table I. None of the compounds inhibited the growth of *E. coli*. All the compounds inhibited the growth of *B. subtilis* in synthetic agar but not (or inhibited much less) in nutrient agar. This indicated that some of them could be potential antimetabolites. Furthermore, most of the α-diazoamidines (Compounds III–IX) showed more pronounced activity than the triazoles (X and XI). Compounds IV–VI and IX were further tested by the technique of specific reversal against *B. subtilis*, and the results of these experiments are included in Table II. Once again, all the samples inhibited *B. subtilis* more strongly on synthetic agar than on nutrient agar. However, none of the samples was reversed by amino acids, vitamins, purines, and pyrimidines. Therefore,

Table I—Inhibition of *B. subtilis* Grown in Two Different Media (Zones of Inhibition in Millimeters)

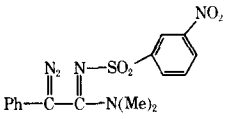
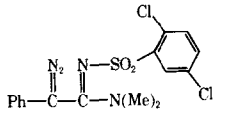
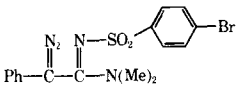
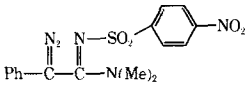
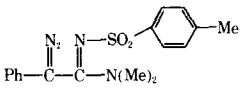
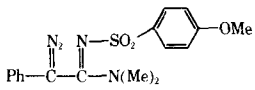
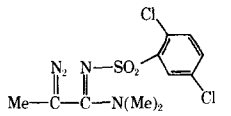
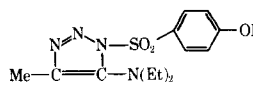
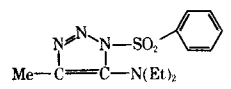
Compound Number	Compound Structure	Nutrient Agar	Synthetic Agar
III		Trace	25
IV		0	41
V		0	25
VI		22	39
VII		0	18
VIII		0	17
IX		Trace	38
X		0	15
XI		0	16

Table II—Specific Reversal Studies against *B. subtilis*

Compound	Nutrient	Synthetic Agar Further Implemented with: No Supplements (Control)	Amino Acids	Combined Vitamins	Combined Purines and Pyrimidines
III	0	35	25	26	30
IV	0	59	41	51	50
V	0	25	37	Trace	21
VI	22	40	38	36	21
IX	15	32	28	28	35

these compounds do possess significant antibacterial activity, but this activity is noncompetitive in nature.

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Solubility Relationships in Urea–Water Systems

Keyphrases □ Urea–water systems—solubilization mechanism □ Solute–urea interaction effect—solubility □ Transfer, standard free energy—solute in urea solution, water

Sir:

Interpretations regarding the mechanisms of solution in cosolvent systems are facilitated if one can rely on various simplifying assumptions. In urea–water mixtures, for example, it would be convenient to assume that the interactions of the cosolvent with a given solute moiety are specific and predictable. Further, it would be of immeasurable aid if explanations of observed solubility phenomena were possible in terms of purely basic theoretical concepts. Therefore, as part of a larger study of solution properties, we investigated the potential usefulness of certain of these assumptions relative to compounds of intrinsic pharmaceutical interest.

The solubilities of compounds having various moieties in common were determined in water and in 5 *M* urea solutions at 30°. After equilibrating excess drug in both solvent systems, samples of the resulting solutions were withdrawn, and solubilities were determined spectrophotometrically. The standard free energies of transfer, $\Delta G_t°$, were then calculated according to the equation used by Wetlaufer *et al.* (1):

$$\Delta G_t° = -RT \ln C_u/C_w + RT \ln N_u/N_w \qquad \text{(Eq. 1)}$$

where C_u and C_w are the molar concentrations of drug in the urea and water solutions, respectively; and N_u and N_w represent the moles/liter summed over all components of solvent and solute for the urea and water solutions, respectively. In the present investigation, the free energy change is that which accompanies the transfer of 1 mole of drug from water to a 5 *M* urea solution. These data, along with the aqueous solubilities, are shown in Table I.

Table I—Standard Free Energy of Transfer, $\Delta G_t°$, from Water to 5 *M* Urea Solutions at 30°

Solute	Aqueous Solubility, moles/l. × 10^3	$\Delta G_t°$, cal./mole
Methyl *o*-methoxybenzoate	41.6	+621
Methyl paraben	19.2	−690
Methyl benzoate	17.8	−480
Methyl salicylate	6.27	−612
Ethyl paraben	5.85	−781
n-Propyl paraben	2.78	−645
n-Butyl paraben	1.34	−792

The results strongly suggest the following:

1. Moieties having the same chemical structure may not be expected to exhibit parallel interactions in solvent systems of similar composition. In all likelihood, these interactions are also a function of the chemical entity to which a given moiety is attached. This is in contrast to the interpretation by Nozaki and Tanford (2), who reported additive solubility effects for the hydrocarbon groups attached to various amino acids. The data in Table I show that this is not the case. For example, the difference in the standard free energy of transfer between methyl benzoate and methyl paraben is 210 cal./mole. The difference between phenylalanine and tyrosine is only 85 cal./mole for the same conditions of transfer (2).

2. The use of a simple homologous series gives no assurance of success in obtaining consistent resolution of solute–solvent interactions. As might be expected, the interactions observed on transferring alkanes from water to urea solutions vary as methane, ethane, propane, and butane (1). In contrast, the interactions of the parabens vary as propyl, methyl, ethyl, and butyl.

3. Relative hydrophobicity, as determined by a comparison of aqueous solubilities, may not be used to explain differences in enhanced solubilities in urea solutions. The data in Table I illustrate this point. For example, the aqueous solubility of methyl paraben is three times greater than methyl salicylate and seven times greater than propyl paraben, yet the transfer of methyl paraben to a 5 *M* urea solution is thermodynamically favored over either of these compounds.

4. Direct urea–solute interaction is a significant factor in altering the solubility of drug species. Although this has been shown (3, 4), reports persist in which attempts are made to explain observations solely on the basis of solvent structuring. The latter approach was taken by Feldman and Gibaldi (5) in rationalizing the increased solubility of benzoic and salicylic acids in