Conformational and Structural Relationships among Antipeptic Ulcer Compounds

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A model is presented which defines a necessary criterion for activity in several classes of compounds which are active in preventing peptic ulcers. Specifically, the model pertains to drugs which inhibit the formation of peptic ulcers in the pylorus-ligated rat and which also inhibit gastric secretion by nonanticholinergic mechanisms. The model is supported by structural data, qualitative conformational arguments, and conformational analysis performed theoretically through use of extended Hückel theory (EHT). Drug conformation is discussed in relation to drug–receptor complex formation by appeal to elementary collision theory.

Many drugs have been claimed to be useful in peptic ulcer therapy,[1,2] but comparatively little effort has been directed toward establishment of models for their mode of action at the molecular level. A pharmacological subclass of these drugs, which has been described in a recent review,[2] is composed of those drugs which are antisecretory and act by a nonanticholinergic mechanism. With the aid of molecular orbital theory, one can qualitatively relate the electronic and conformational characteristics of these drugs, not only to one another, but also to the secretogogues[3] histamine and gastrin. The relationships observed tentatively define a necessary condition for antiulcer compounds which are nonanticholinergic and gastric antisecretory.

The Model. The specific compounds under consideration are: 2-phenyl-2-(2-pyridyl)thioacetamide[4] (**1**), 3-(methylamino)-2,1-benzisothiazole[5] (**2**), 2,2′-bipyridine[6] (**3**), milid[2] (*N*-benzoyl-*N*,*N*-di-*n*-propyl-DL-isoglutamine) (**4**), benzyltris(2-propoxyethyl)ammonium iodide[2] (**5**), and prostaglandin (PGE_1)[7] (**6**), all of which inhibit ulcer formation in pylorus-ligated rats or stress-induced ulcers in rats. Recent publications on compounds related to **1**[8] and **2**[9] substantiate the model to be presented.

It was not possible to devise a single, unified model which incorporates compounds **1**–**6**. Table I summarizes the activities of these compounds *vs.* various secretory stimulants, from which it appears that 2,2′-bipyridine (**3**) is unique in that it does not inhibit insulin- or histamine-stimulated secretory response. If all compounds related to **3**[10] behave similarly to **3**, omission of these compounds from the model is justified. Compound **5** has also been omitted from consideration, since it has been suggested to have a selective anticholinergic action on the stomach,[2] even though it is not manifest systemically.

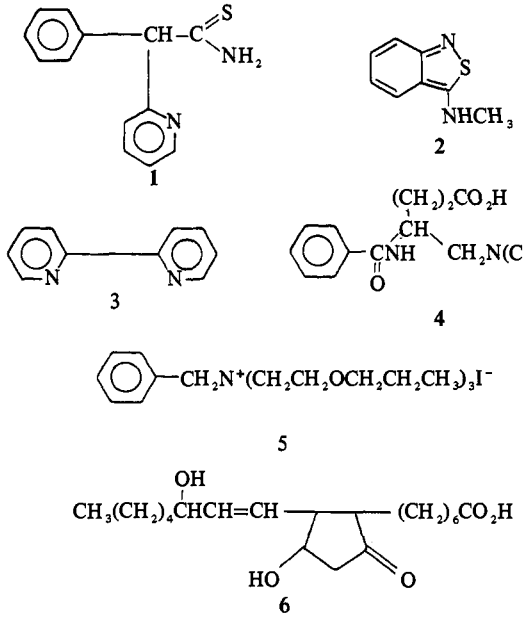


Table I. Response to Secretory Stimulants[a]

Drug	Insulin	Gastrin	Histamine
1[b]	I	I	I
2[c]	I	–	I
3[d]	NE	–	NE
4[e]	I	I	I
6[f]	–	I	I

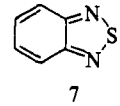
[a] I = inhibition of secretion, NE = no effect, (–) = results are unavailable. [b] Ref 4. [c] Ref 5. [d] Ref 6. [e] Ref 2. [f] Ref 7.

The model now proposed is that a necessary condition for antisecretory and/or antiulcer activity, based on compounds **1**, **2**, **4**, and **6**, is the presence of two heteroatoms separated by 3.7 ± 0.2 Å in a low energy conformation.†

One of these atoms has its lone-pair electrons in a σ-type hybrid orbital, while the other atom is involved in a π-electron system. Figure 1 illustrates the structural requirements for the above molecules and also for phenylalaninamide and histamine, which will be discussed later.

Foundation for the Model. Compounds **1**, **2**, **4**, and **6** clearly have the required electronic characteristics, which leaves the interheteroatomic distance requirement to be established. In doing so, possible insight into the secretory response and considerable support for the model may be gained by examination of the relationship between the two secretogogues histamine (**17**) and gastrin and the compounds under discussion.

Since the benzisothiazole **2** is a rigid compound, its internitrogen distance (r_{NN}) can be estimated easily. Unfortunately, a structural analysis of **2** has not been reported; however, X-ray crystallographic results are available on benzo-2,1,3-thiazole[11] (**7**). With the addition of an amino group to one of the nitrogens of **7** and the assumption that the C=N–S geometry in **7** is similar to the C=C–S geometry in **2**, the required r_{NN} in **2** is calculated to lie between 3.8 and 3.9 Å.



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PGE_1 (**6**) also has the two heteroatoms rather rigidly fixed around the five-membered cyclopentanone ring. Cyclopentanone exists preferentially in a half-chair form;[12] however, the 3-hydroxycyclopentanone moiety of PGE_1 can exist in either of two half-chair conformers, one with the hydroxyl

†Much of the stimulus for this study was provided by Kier's work on histamine, in which he associated a 3.6-Å internitrogen distance in a preferred conformation with secretory activity (ref 21).

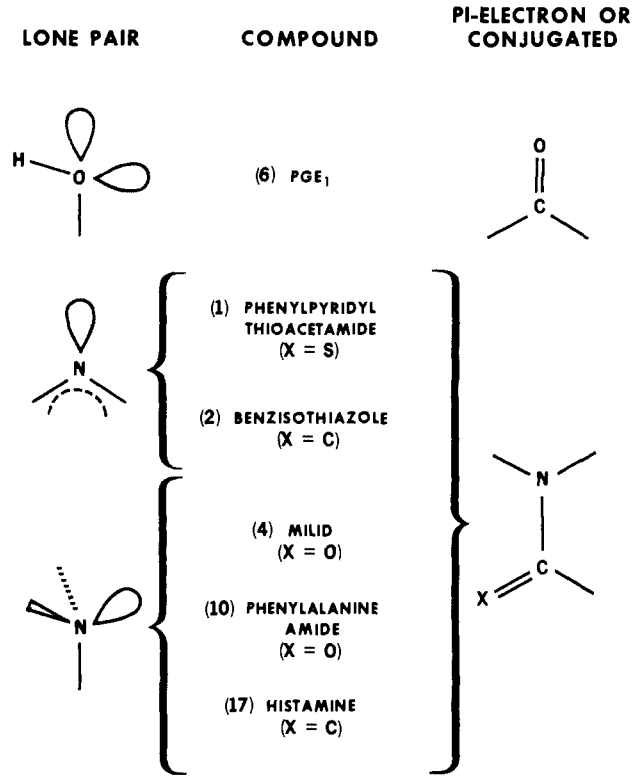
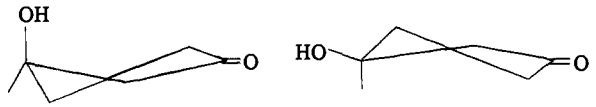


Figure 1. Lone pair and π electron or conjugated parts of the proposed model.



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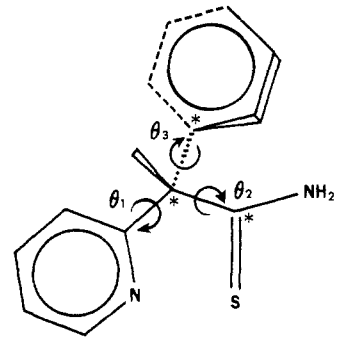
group approximately axial (**8**), the other approximately equitorial (**9**). A recent theoretical determination of the conformational preference of PGE_1 indicates that the energies of the two half-chair forms are rather close,[13] thus appreciable populations of both conformers should exist in solution. However, only the axial conformer (**8**) has an interoxygen distance of roughly 3.9 Å as determined from Dreiding models.

The thioacetamide (**1**) is conformationally mobile; hence r_{NN} may assume many values. Since extended Hückel theory (EHT)[14] has been successful in the calculation of preferred conformations of molecules,[15] this method was applied to **1**. Energy minimization was performed with respect to rotations of the phenyl, pyridyl, and thioacetamide groups. The EHT parameterization for H, C, N, and O atoms was that of Adam, *et al.*,[16] except that the Slater exponent on hydrogen was set equal to 1.2 instead of 1.3. For sulfur, 3s, 3p, and 3d orbitals were considered and the parameters of Jordan, *et al.*,[17] were used. Molecular coordinates were derived from structural data[18] on pyridine, thioacetamide, and benzene. The reference conformation is indicated by **10**, in which the pyridyl and thioamide groups are coplanar and the phenyl ring makes a 100° dihedral angle with the plane defined by the starred atoms.

Rough scans of the energy surface at 45 or 60° intervals indicated two equally preferred conformations. These minima were subsequently refined using rotational increments of 24–30°. Finally, the true EHT minima were estimated by fitting a parabola through three calculated points around the approximate minima.

The refined calculations indicate two equal energy con-



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formations, each with the phenyl ring within 10° of its initial position. The rotation angles, θ_1 and θ_2, and the internitrogen distances at these two conformations are shown in Table II. Two substantially higher energy conformations corresponding to those in Table II, but with the pyridyl rotated by 180°, were also found. Thus it has been established that conformation number 2 (Table II) is a preferred one. Tables of total energies (Tables III–VI) as a function of θ_1, θ_2, and θ_3 and Appendix A summarize the computational results upon which the conformational analysis has been based.

Compound **4** is also conformationally mobile but is larger and much more rotationally complex than **1**. For these reasons, a conformational analysis *via* EHT was not possible within the limits of our computer (Univac 1108/

Table II. Conformational Parameters at the Minima for 2-Phenyl-2-(2-pyridyl)thioacetamide

Minimum	θ_1, deg	θ_2, deg	r_{NN}, Å
1	24	103	2.9
2	24	277	3.5

Table III. Energy as a Function of $CS(NH_2)$ Rotation at $\theta_1 = \theta_3 = 0°$

θ_2, deg	E, kcal/mole
0	69.2
45	3.5
90	−8.3
135	−3.4
180	45.0
225	1.6
270	−8.4
315	−2.0

Table IV. Energy as a Function of Pyridyl Rotation at $\theta_2 = 103°$ and $\theta_3 = 0°$

θ_1, deg	E, kcal/mole
0	−8.9
24	−11.0
48	−8.2
100	39.2
150	3.2
180	−5.6
210	−2.3
300	83.0

Table V. Energy as a Function of Pyridyl Rotation at $\theta_2 = 277°$ and $\theta_3 = 0°$

θ_1, deg[a]	E, kcal/mole
0	−8.9
24	−11.0
48	−8.2

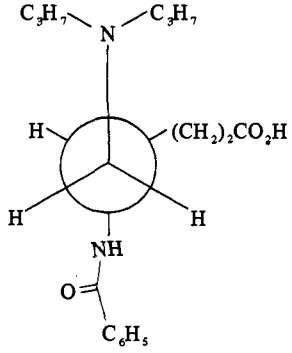
[a] E behaves similarly to that in Table IV through the complete range of θ_1.

Table VI. Energy as a Function of Phenyl Rotation at $\theta_1 = 24°$ and $\theta_2 = 277°$

θ_3, deg[a]	E, kcal/mole
0	−11.0
45	8.2
90	74.6
135	−2.8
180	−11.0

[a] E behaves similarly when $\theta_2 = 103°$.

65K). Molecular models were thus used to qualitatively establish likely low energy rotamers which satisfy the proposed distance criterion. This distance is a function of rotation about the intervening carbon–carbon single bond, consideration of which leads to conformers **11** and **12** as likely low energy forms. Appreciable populations of each form are expected; however, only **11** has the requisite r_{NN}, estimated to be 3.8 Å.



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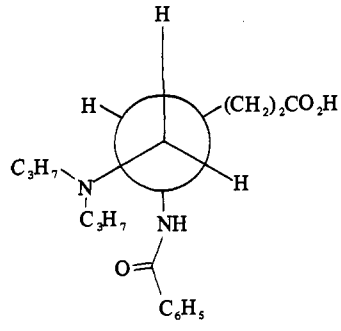

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Since the inhibition of gastric secretion produced by gastrin or its C-terminal tetrapeptide amide (**13**), which has the same range of physiological activity as gastrin,[19] is one of the pharmacological properties of several of the compounds under consideration, one may postulate a structural rela-

Try-Met-Asp-Phe-NH_2

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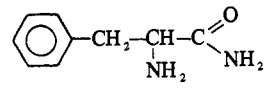

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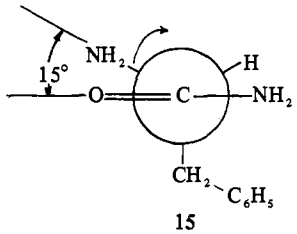

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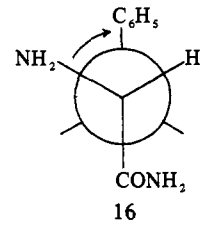

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tionship between this secretogogue and its antagonists. It has recently been suggested[4] that the antigastrin activity of the thioamide (**1**) is due to its similarity to the C-terminal amino acid amide in **13**, phenylalaninamide (**14**). EHT calculations have therefore been performed on **14**. The geometrical data for **14** were taken from a review by Scheraga.[20] The energy minimizations considered rotations of the $CONH_2$ and $CH(NH_2)CONH_2$ groups, which yield global energy minimum conformations defined by structures **15** and **16**. This broad minimum has an r_{NN} of approximately 3.6 Å, but two local minima within 2 kcal/mole of it also exist which have an r_{NN} of about 3.5 Å. The total energies as a function of the two angles implied by **15** and **16** are given in Tables VII–IX and Appendix B.

Table VII. Energy as a Function of $CH(NH_2)(CONH_2)$ Rotation at $\theta_1 = 240°$

θ_2, deg	E, kcal/mole
0	−1.7
60	6.4
120	5.2
180	10.9
240	−1.2
300	2.4

Table VIII. Energy as a Function of $CO(NH_2)$ Rotation at $\theta_2 = 0°$

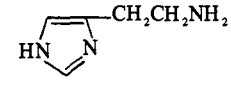
θ_1, deg	E, kcal/mole
0	5.6
60	−1.0
120	0.5
180	−0.7
240	−1.7
255	−2.5
300	−2.5

Table IX. Energy as a Function of $CO(NH_2)$ Rotation at $\theta_2 = 240°$

θ_1, deg	E, kcal/mole
0	92.4
60	−0.1
120	5.8
180	16.6
240	−1.2
255	−1.8
300	21.5

The fact that **1** and **14** are structurally similar and have an r_{NN} in the range 3.7 ± 0.2 Å supports the hypothesis that the r_{NN} is a critical factor not only for antipeptic ulcer activity but also in antigastrin secretory activity. Morley, *et al.*,[19] have concluded that the phenylalanine part of **13** is binding rather than functionally active, which implies that the thioamide **1** may antagonize **13** by preferentially binding to the receptor.

The role of histamine (**17**) has long been discussed with regard to its possible action in the peptic ulcer disease and particularly with respect to its role as a secretogogue.[3] EHT calculations[21] and nmr studies[22] reveal that in one of its



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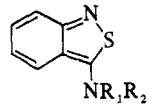
two nearly equally preferred conformations, histamine has an r_{NN} of 3.6 Å. The model may thus provide a rationale for histamine's secretory activity but may also explain why compounds (**1**, **2**, **4**, and **6**) antagonize this activity.

Discussion

The structural evidence presented has established the basis of the model for the antipeptic ulcer drugs under discussion. Even though these compounds are structurally diverse and have differing degrees of conformational flexibility, their activities appear to be related by a single structural feature. This feature represents a necessary criterion in the logical sense that *only* if a molecule contains two heteroatoms with the electronic characteristics as shown in Figure 1 and separated by 3.7 ± 0.2 Å will it be a nonanticholinergic antisecretory peptic ulcer drug with a pharmacological profile as indicated in Table I. It does not follow that the structural feature proposed is solely responsible for activity, only that activity is absent without it. Additionally, the model pro-

vides a rationale for the pharmacological activities of the secretogogues histamine (**17**) and gastrin or its C-terminal tetrapeptide amide (**13**).

One should not conclude from the model that the particular substituent effects which commonly affect drug activity[23] are inoperant in the structural classes here. On the contrary, such an analysis is required to order to rationalize the wide variations in activity observed in these compounds. For example, the variation in the antisecretory activities of benzisothiazoles (**18**) with respect to amine substitution ap-



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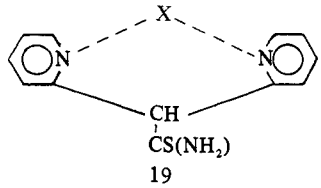
pears to be a parabolic function of the partititon coefficient (Table X). Other variations within the series can be similarly rationalized.

Table X. Relationship between Activity and Partition Coefficient of N-Substituted 3-Amino-2,1-benzisothiazoles[a]

R_1	R_2	$\Delta \log P$[b]	ED_{50}, mmoles/kg sc
H	H	−2.04	0.42
H	Me	−0.52	0.01
H	Et	−0.19	0.02
Me	Me	−0.38	0.03
H	*i*-Pr	−0.03	0.02
H	*n*-Pr	0.37	>0.14
$(CH_2)_2$	$(CH_2)_2$	0.53[c]	>0.26
H	*sec*-Bu	0.57[d]	0.10
H	*i*-Bu	0.70	0.12
H	Phenyl	0.94	>0.12
H	Benzyl	1.09	>0.22

[a] See ref 9. [b] Based on log *P* values for the amines R_1R_2NH in Leo, *et al.*[24] [c] Log *P* (cyclobutylamine) = log *P* (diethylamine) − 0.09. [d] Estimated to lie 0.13 below *i*-Bu based on log *P* for the corresponding alcohols.

The substituted thioacetamides, $R_1R_2CHCS(NH_2)$, in which R_1 = H or alkyl and R_2 = 2-pyridyl, 2-pyrimidyl, 2-pyrazinyl, or HN = $C(CH_3)$, are all very active antisecretory agents[8] ($16.2 \geq ED_{50}$ (mg/kg id) ≥ 1.42 in pylorus-ligated rats), in full accord with the model. The model's most significant failure is the prediction of activity for R_1 = 2-pyridyl or 2-pyrazinyl and R_2 = 2-pyridyl, when in fact no antisecretory activity is observed. A possible rationale for this apparently anomalous behavior is the formation of a structure such as (**19**), which restricts the pyridyl or pyrazinyl to lie in an unfavored conformation through metal chelate or hydrogen bridge formation.



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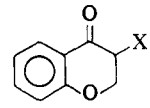
Additionally, the low or marginal activities of the compounds in which $R_1 = R_2$ = phenyl (ED_{50} = 82 mg/kg id) and thioacetamide itself (ED_{50} = 35 mg/kg ip) suggest that the $CS(NH_2)$ moiety has some intrinsic antisecretory activity. Support for this latter assertion derives from recent observations that methyl and butyl thiocyanate and phenyl isothiocyanate inhibit H^+ secretion in the isolated gastric mucosae of bullfrogs (*Rana catesbeiano*).[25] It is noteworthy that the distances between S and N atoms (r_{NN}) in methyl thiocyanate and methyl isothiocyanate[26] are 2.78 and 2.82 Å, respectively, while r_{SN} in thioacetamide is 2.66 Å and approximately 2.8 Å in the benzisothiazole (**2**). Perhaps there is a separate antisecretory mechanism related to r_{SN} in the compounds above which acts jointly with the principally proposed distance criterion, but to a somewhat lesser degree.

The gastric antisecretory activity of several 3-amino-4-chromanone hydrochlorides[27] provides a partial check on the validity of our model. The two most potent of these compounds (**20** and **21**) clearly contain the elements of our model, with the distance between the ether oxygen and amino nitrogen estimated to be about 3.8 Å.



20, X = $NH_2 \cdot HCl$
21, X = $NHCOCH_3$

Conformational considerations for the flexible molecules have been introduced primarily to establish that the required structural feature is presented to the receptor in a low energy rotational form. The reasoning behind the choice of a low energy form may best be described in the context of elementary collision theory,[28] where the rate constant for reacting molecules A and B is given by eq 1.

$$K = PZ \exp(-E/RT) \quad (1)$$

In this equation, E represents the minimum energy required for A and B to react, Z represents the collision frequency of the two species, and P is a steric or probability factor, which roughly represents the fraction of collisions in which A and B are in the proper orientation for reaction.

Conformational arguments refer to the value of the factor P, since pharmacologically active molecules are usually considered to conform specifically to their target receptors. P may roughly be set equal to a Boltzmann factor $\exp(-\Delta E/RT)$, in which ΔE is the potential energy difference in the drug between its preferred conformation and the conformation (not necessarily associated with a local energy minimum) which is complimentary to the receptor. Thus, if the complimentarity of the drug to the receptor is met only in a high energy conformation of the drug, the binding event (formation of drug–receptor complex) will take place with lower probability. Reduction of the rate of receptor binding by several orders of magnitude in the P term may thereby make rates of metabolism, excretion, *etc.*, favored pathways over target receptor stimulation. The underlying assumption that has been made throughout is that E remains relatively constant for a given receptor type, while P alone is affected by variations in agonist structure and conformation.

When drug–receptor complex formation takes place nonspecifically, conformational characteristics are irrelevant. Once a molecule is bound nonspecifically to the receptor, there is ample time for the molecule to undergo conformational rearrangement (conformational half-life is $\leq 10^{-5}$ sec for barriers of 10 kcal/mole or less), since drug–receptor complexes have measured half-lives of several seconds.[29-31] (These observed half-lives represent upper limits, since an underlying assumption is that translation of receptor occupancy to tissue response is a relatively fast step.)

In summary, the arguments advanced with respect to conformation suggest that a molecule does not necessarily act

on a receptor in its preferred conformation, but rather that molecular complimentarity to the receptor must be sufficiently probable conformationally for a molecule to form a complex with the receptor. It is with this in mind that the preceding conformational and structural model of peptic ulcer therapy has been presented.

Appendix A

The basic computational results upon which the conformational analysis of 2-phenyl-2-(2-pyridyl)thioacetamide has been based are included in Tables III–VI. The angle definitions and initial positions of the $CS(NH_2)$, pyridyl, and phenyl groups are defined by structure **10** and the accompanying discussion. The minima at $\theta_2 = 103$ and 277° were estimated from the results in Table III by parabolic interpolation and the more refined calculations were based on these values. The tabular energies are related to the EHT calculated energies by $E = E(\text{calcd}) + 33{,}400$ kcal/mole in order to make the energy variation more obvious.

Appendix B

The computational results upon which the conformational analysis of phenylalanine amide has been based are summarized in Tables VII–IX. The angle θ_1 and its initial position at 255° are defined by **15**, and θ_2 and its initial position at 0° are defined by **16**. The variation of E *vs.* θ_1 at $\theta_2 = 110°$ (the estimated local minimum for this variable) has not been performed as thoroughly as that appearing in Tables VIII and IX. However, this rotamer would contribute minimally to the population since $E = 1.4$ kcal/mole at $\theta_1 = 255°$, while from Tables VIII and IX, the corresponding minima are −2.5 kcal/mole and −1.8 kcal/mole, respectively. The E above and in the tables is related to the calculated EHT energies by $E = E(\text{calcd}) + 26{,}900$ kcal/mole.

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Semisynthetic β-Lactam Antibiotics. 1. Acylation of 6-Aminopenicillanic Acid with Activated Derivatives of α-Sulfophenylacetic Acid[1]

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α-Sulfobenzylpenicillin is a new semisynthetic penicillin with a wide-spectrum activity against Gram-positive and Gram-negative bacteria and peculiar in possessing a potent inhibitory effect against *Pseudomonas aeruginosa*. Acylation of 6-aminopenicillanic acid (6-APA, VI) by using a new activated derivative of α-sulfophenylacetic acid, *i.e.*, α-sulfophenylacetyl chloride(III), yielded α-sulfobenzylpenicillin (I). In contrast, the reaction of 6-APA with α-chlorosulfonyl-α-phenylacetic acid (V) gave another penicillin corresponding to the isomer of I, namely, 6-(α-carboxy-α-toluenesulfonamido)penicillanic acid (VII), which showed poor results as expected from the same kind of penicillin having a SO_2NH side chain at the 6 position.

In the course of a study on semisynthetic penicillins, we became interested in the preparation of a new penicillin derived from α-sulfophenylacetic acid and in examining whether the α-sulfoacyl side chain would confer physicochemical and biological properties on the penicillin molecule different from those conferred by the α-carboxyacyl side chain. As compared to the α-carboxyl group of carbenicillin, the sulfo group of α-sulfobenzylpenicillin (I) is stronger in acidity and larger in size, consisting of highly polar hetero atoms, sulfur and oxygen. A difference, dependent on the