Interaction of Pharmaceuticals with Schardinger Dextrins II

Interaction with Selected Compounds

By JOHN L. LACH and JACK COHEN†

Data for the interaction of the Schardinger dextrins with 19 pharmaceuticals in aqueous solution are presented. All the compounds interact with both alpha and beta cyclodextrin. Data are presented to show that the less soluble the drug is in water, the greater is its per cent increase in solubility as a function of cyclodextrin concentration. Comparison of the isothermal slopes of the interactions shows that the largest molecules show the smallest slopes and therefore the smallest degree of interaction with the cyclodextrins. Molecular structure is a very important factor in the interaction which is believed to be a combination of inclusion formation and other intermolecular attractive forces.

THE PHENOMENON of complexation has become a very active area of pharmaceutical research. Only during this past decade has its importance in pharmaceutical formulations been fully realized. Many varied types of molecules and macromolecules have been found to interact with drug molecules of widely differing structures. Beginning with the work of Higuchi and Zuck (1), pharmaceutical researchers have devoted a good deal of time to elucidation of the nature of these phenomena.

Solubility changes have been observed as a function of these interactions and substantial increases in drug stability have been reported (2–6). Of particular importance in pharmacy and medicine is the relationship of complexation to the absorption and distribution of a drug in the body and the way that complexation influences the onset and duration of drug action (7).

In Part I of this series (8) it was observed that the Schardinger dextrins form complexes with the hydroxybenzoic acids and the *p*-hydroxybenzoates. This work was an attempt to extend the study to a variety of pharmaceutical compounds to obtain additional information concerning this interaction.

EXPERIMENTAL

The apparatus and reagents used in this study were those reported in Part I of this series, except that the following drugs were tested for complexing activity; benzocaine, m.p. 87–88°; aspirin, m.p. 134–135°; tetracycline, m.p. 170–173°; *p*-aminobenzoic acid, m.p. 185–186°; sulfadiazine, m.p. 255–256°; morphine, m.p. 250°; vanillin, m.p. 78–81°; N-acetyl-*p*-aminophenol, m.p. 169–170°; *p*-aminosalicylic acid, m.p. 150–151°; ephedrine, m.p. 34°; and sorbic acid, m.p. 134–138°.

The Schardinger dextrins were prepared by accepted methods (9, 10) and the interactions studied by the solubility method of Higuchi and Lach (11). The drugs were analyzed spectrophotometrically at the following wavelengths: benzocaine, 285 mμ; aspirin, 275 mμ; tetracycline, 357 mμ; *p*-aminobenzoic acid, 278 mμ; sulfadiazine, 266 mμ; morphine, 285 mμ; vanillin, 279 mμ; N-acetyl-*p*-aminophenol, 244 mμ; *p*-aminosalicylic acid, 267 mμ; ephedrine, 257 mμ; and sorbic acid, 259 mμ.

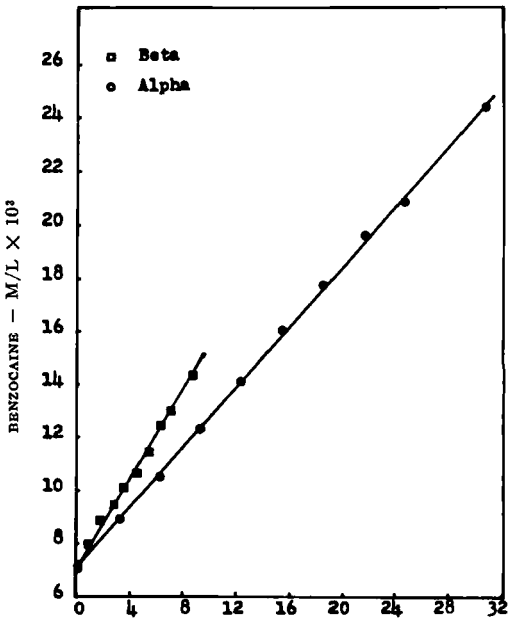

Fig. 1.—Interaction of benzocaine with the cyclodextrins at 30°.

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Aspirin was run in 10^{-3} *M* sulfuric acid to decrease its rate of hydrolysis.

RESULTS AND DISCUSSION

Figures 1–11 represent solubility isotherms of the interactions of 11 drugs with the alpha and beta cyclodextrins. The Schardinger dextrins interact with all compounds tested. Linear plots are obtained with most drugs and both cyclodextrins, demonstrating first order dependence of the inter-

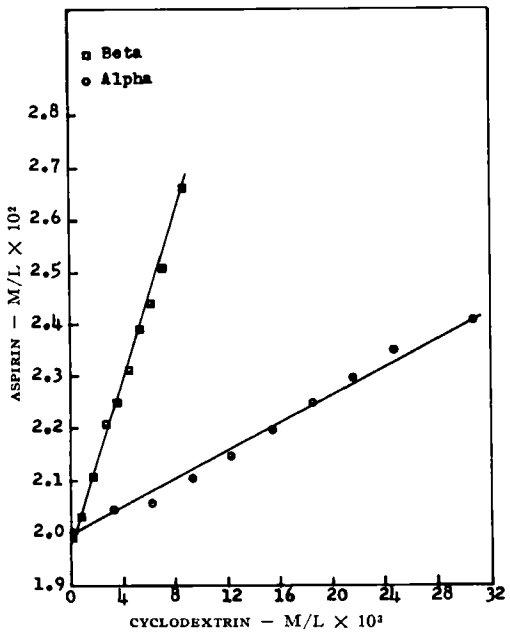

Fig. 2.—Interaction of aspirin with the cyclodextrins at 30°.

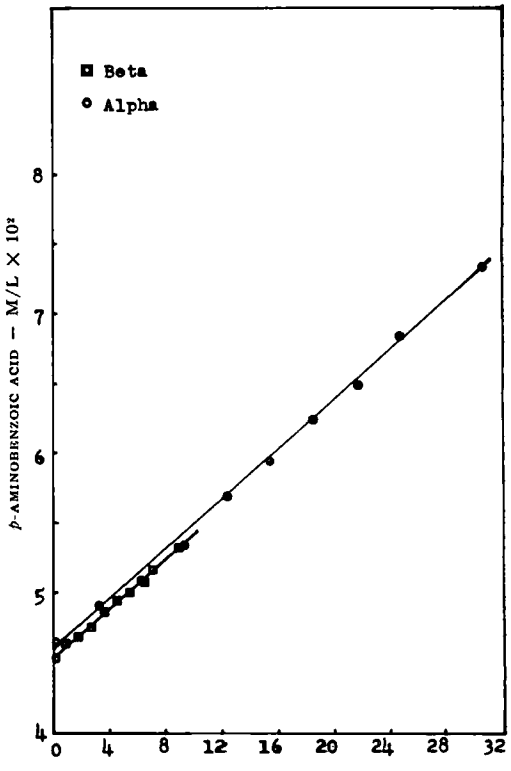

Fig. 4.—Interaction of *p*-aminobenzoic acid with the cyclodextrins at 30°.

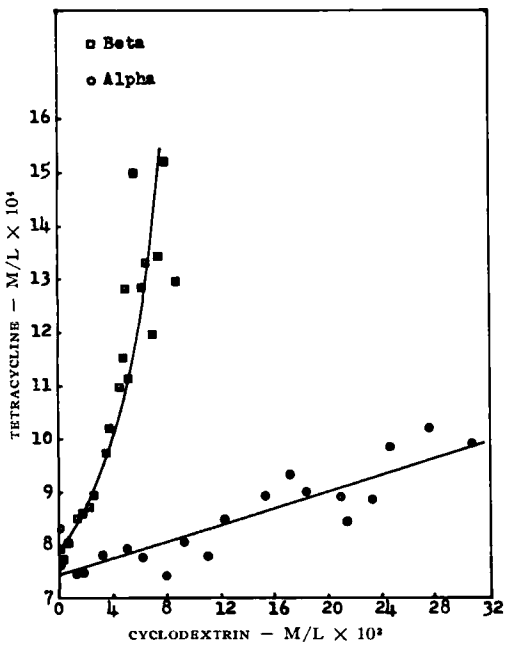

Fig. 3.—Interaction of tetracycline with the cyclodextrins at 30°.

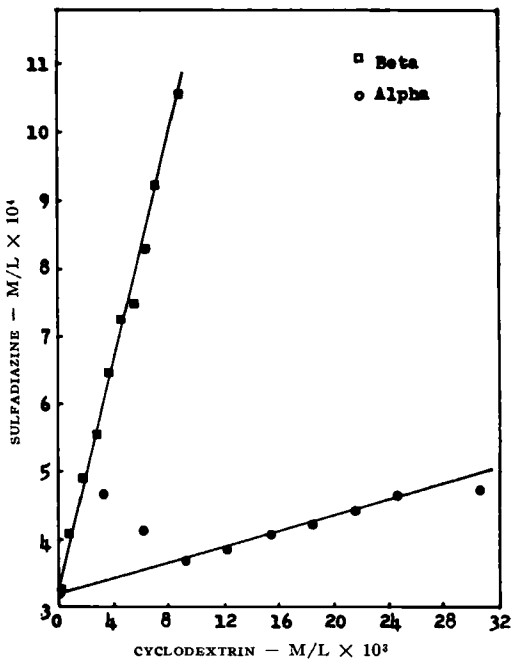

Fig. 5.—Interaction of sulfadiazine with the cyclodextrins at 30°.

action upon cyclodextrin concentration. The morphine-beta and tetracycline-beta plots show a curvature, probably due to the nature of the complex (which prevented complete filtration) or to unperceived complexities in the interaction. The tables and figures presented also include some data from Part I of this series (8), for comparative purposes.

All the compounds studied, except morphine, tetracycline, sulfadiazine, and sorbic acid, are substituted benzene rings. Benzene rings will fit into the voids of both alpha and beta cyclodextrins since the dextrin voids are 6 and 8 Å. in diameter, respectively, while the phenyl structure occupies a space measuring approximately 7 × 7 × 3.4 Å. (12, 13).

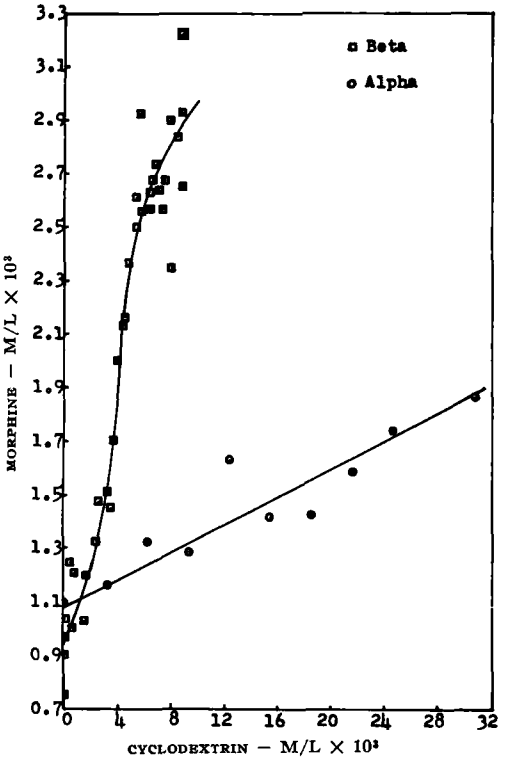

Fig. 6.—Interaction of morphine with the cyclodextrins at 30°.

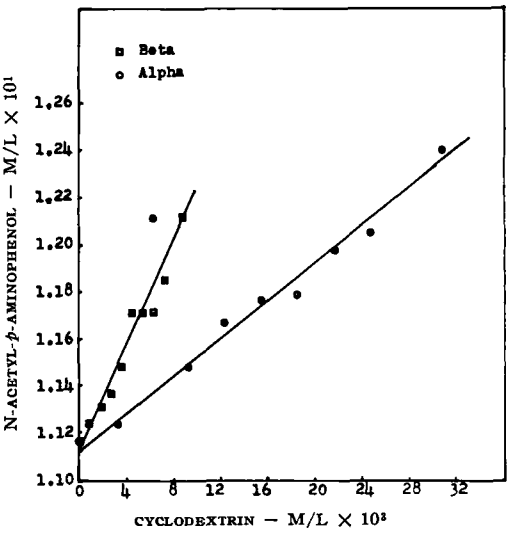

Fig. 8.—Interaction of *N*-acetyl-*p*-aminophenol with the cyclodextrins at 30°.

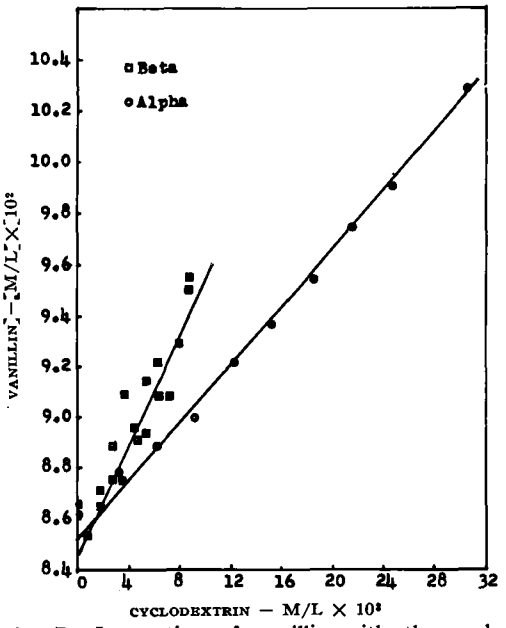

Fig. 7.—Interaction of vanillin with the cyclodextrins at 30°.

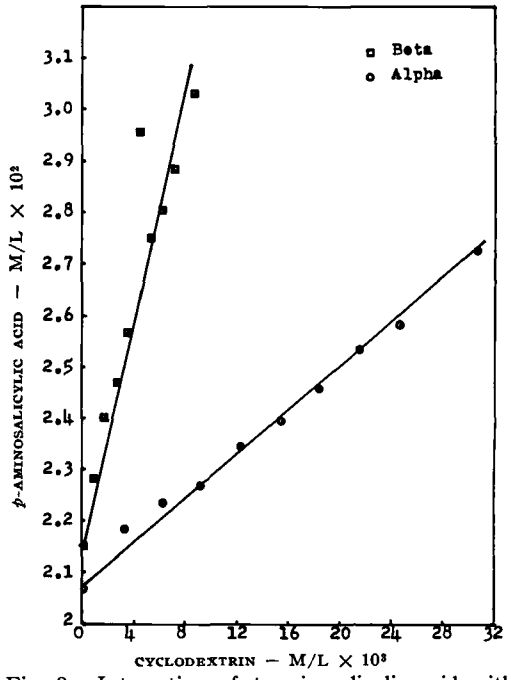

Fig. 9.—Interaction of *p*-aminosalicylic acid with the cyclodextrins at 30°.

Allowing for slight molecular structural changes caused by inclusion formation and other distorting forces, it is apparent that these molecules would be prone to inclusion by the alpha and beta cyclodextrins.

Morphine, tetracycline, and sulfadiazine, being polynuclear ring systems, are quite large compared to the phenyl group and fit into the voids with difficulty. If we assume that the others are complexed, in part, by inclusion formation, we can see that these three, being too large for inclusion, cannot interact in this way to any significant degree.

It is possible, however, that side chains and substituent groups may fit into the dextrin void and that the complexation is actually a matter of these groups being included in the void, thereby forming the inclusion complex. Since questions of this sort concern exact structural conformation of the complex, which can be determined only by X-ray diffraction, elucidation of this mechanism is postponed until further study.

Several methods have been used to compare relative complexing tendencies using data obtained from solubility studies. Comparison of the per cent increase in solubility has been used (14) as a comparison of relative complexing tendencies with the assumption being made that a higher per cent increase in solubility involves a greater degree of interaction. In this study it was felt that a truer picture of relative complexing tendencies could be obtained by comparing the slopes of the interaction isotherms.

In phase diagrams showing a plateau region, stoichiometries and formation constants can be calculated and overall complexing tendencies compared by interpretation of these constants. Since, in this study, no plateau regions were observed, slopes of the interaction isotherms are used as indications of relative complexing tendencies (Table I).

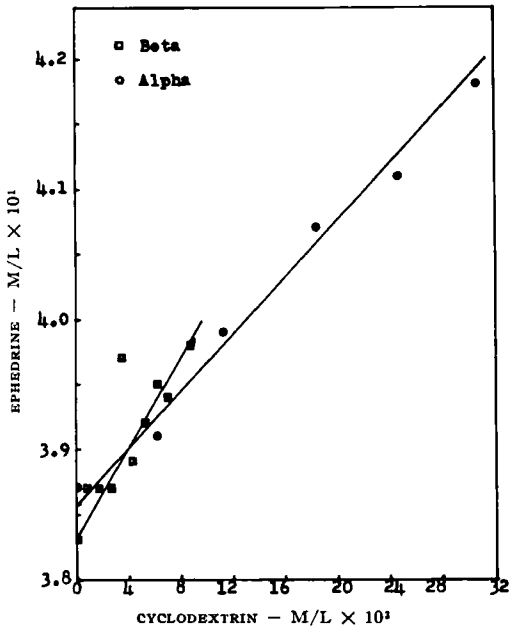

Fig. 10.—Interaction of ephedrine with the cyclodextrins at 30°.

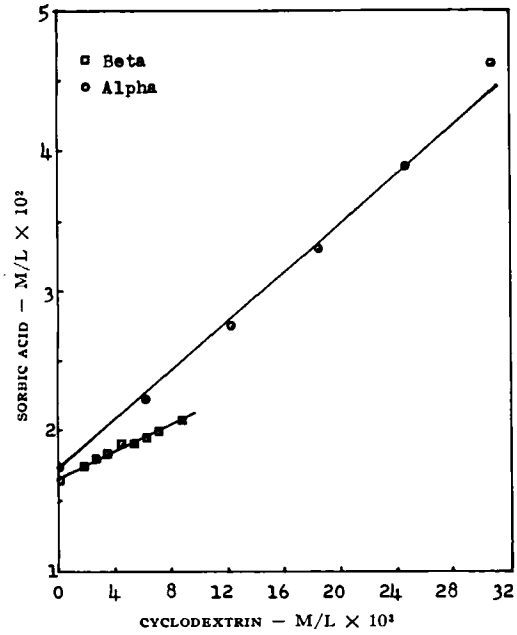

Fig. 11.—Interaction of sorbic acid with the cyclodextrins at 30°.

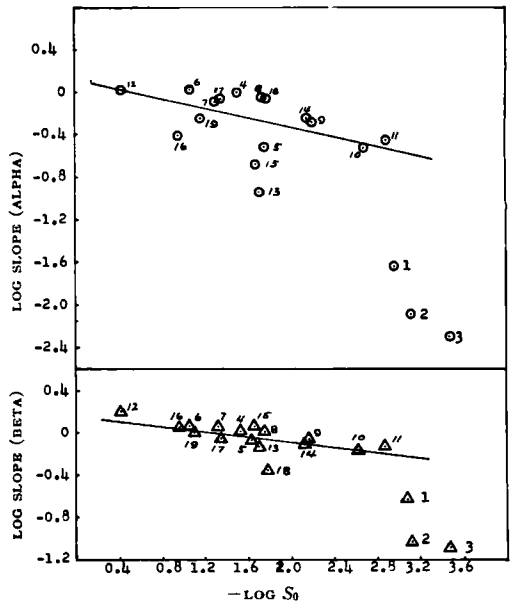

Fig. 12.—Relationship of slope of interaction isotherms of drugs with the cyclodextrins to initial solubility at 30°. Key: 1, morphine; 2, tetracycline; 3, sulfadiazine; 4, benzoic acid; 5, salicylic acid; 6, *m*-hydroxybenzoic acid; 7, *p*-hydroxybenzoic acid; 8, methylparaben; 9, ethylparaben; 10, propylparaben; 11, butylparaben; 12, ephedrine; 13, acetylsalicylic acid; 14, benzocaine; 15, *p*-aminosalicylic acid; 16, N-acetyl-*p*-aminophenol; 17, *p*-aminobenzoic acid; 18, sorbic acid; and 19, vanillin.

TABLE I.—SLOPES OF INTERACTION ISOTHERMS OF 19 COMPOUNDS WITH ALPHA AND BETA CYCLODEXTRIN

Alpha		Beta	
Drug	Slope	Slope	Drug
Sulfadiazine	0.00519	0.0845	Sulfadiazine
Tetracycline	0.0081	0.0937	Tetracycline
Morphine	0.025	0.237	Morphine
Aspirin	0.133	0.454	Sorbic acid
p-Aminosalicylic acid	0.211	0.687	Propylparaben
Propylparaben	0.295	0.747	Butylparaben
Salicylic acid	0.305	0.772	Aspirin
Butylparaben	0.357	0.795	Benzocaine
N-Acetyl-*p*-aminophenol	0.395	0.891	*p*-Aminobenzoic acid
Ethylparaben	0.510	0.885	Salicylic acid
Benzocaine	0.567	0.896	Ethylparaben
Vanillin	0.567	1.010	Vanillin
p-Hydroxybenzoic acid	0.813	1.044	Benzoic acid
p-Aminobenzoic acid	0.891	1.044	Methylparaben
Methylparaben	0.911	1.100	N-Acetyl-*p*-aminophenol
Sorbic acid	0.911	1.111	*p*-Aminosalicylic acid
Benzoic acid	1.004	1.135	*p*-Hydroxybenzoic acid
m-Hydroxybenzoic acid	1.085	1.192	*m*-Hydroxybenzoic acid
Ephedrine	1.101	1.588	Ephedrine

However, it must be realized that this comparison of slopes is an approximation. If complexes show the same stoichiometries, comparison of their slopes directly relates stability constants of the interactions. Since these stoichiometries are unknown, due to the nature of the phase diagram, comparison of slopes of interactions of different stoichiometries can lead to errors in interpretation. Thus, the correlation is accepted as an approximation and is used because of the lack of exact stoichiometric data.

Inspection of Table I shows that the largest molecules show the smallest slopes. Their solubilization by the cyclodextrins, relative to their initial solubilities, is great but the extent of complex formation with these compounds is small.

In general, the smallest and most soluble drugs show the highest slopes. Since compounds of lower molecular weight are usually more water soluble, one is a corollary of the other. A plot of log slope *vs.* log S_o (solubility in absence of dextrin), Fig. 12, shows fair regularity of this trend. In view of the part played by inclusion formation in this interaction, we feel that the smaller molecules show a greater inclusion tendency because of greater ease of fitting into the dextrin voids. Morphine, tetracycline, and sulfadiazine show deviation from this linearity, presumably caused by the decrease in inclusion formation tendency because of their large sizes. These large molecules show interaction with the cyclodextrins even though they are too large to be guests in the dextrin ring. Hydrogen bonding, due to the multiplicity of hydroxyl and carboxyl groups on the cyclodextrin ring, occurring in aqueous solution, is probably the chief interaction mechanism here and is responsible for solubilization of the larger molecules.

Most of the compounds tested show a greater slope for beta interaction than for alpha interaction with a few compounds showing the same slope for both. This greater interaction with beta is reasonable in that the beta void is larger than the alpha void and can include molecules to a greater degree. The compounds studied, being phenyl derivatives, fit more easily into the beta void than the alpha void since the alpha void is of approximately the same size as the diameter of the benzene ring.

Sorbic acid was the only straight chain compound studied. This is the only compound studied where the complexing activity with alpha is greater than that with beta. Here the chain molecule fits into the alpha void with ease, unlike compounds containing one benzene ring where some strain is necessarily involved by inclusion formation with alpha. It is also possible that the chain molecule is too small in diameter to form a stable complex with beta cyclodextrin since a minimum size of guest is necessary for stable inclusion formation. If a guest is too small, forces holding it within the void are too weak to form a stable complex. This reverse of previous observations by sorbic acid is logical evidence of the existence of strong inclusion formation by the compounds studied.

Most studies of inclusion formation have been carried out in nonaqueous media. It is felt that a study of this type conducted in nonaqueous media would yield additional information as to the mechanism of interaction and estimates of the relative contributions of molecular complexing and inclusion formation could be made. A study of this type is currently under way in our laboratories.

CONCLUSION

The data in this study indicate that the Schardinger dextrins form complexes with a variety of pharmaceutical compounds. It was observed that those drugs which are least soluble in water showed the greatest per cent increase in solubility as a function of quantity of cyclodextrin present. In general, the smallest drug molecules showed the greatest complexing activity with the cyclodextrins. Interaction with sorbic acid demonstrates the importance

of the structure of the guest molecule to the degree of interaction where inclusion formation is a major contributing mechanism.

Molecules which are too large to be included within the cyclodextrin voids interact with the cyclodextrins indicating an interaction mechanism other than inclusion formation. The literature dealing with inclusion formation by various host molecules usually considers only inclusion formation as a mechanism of interaction for these compounds. However, in this aqueous system, we believe that other intermolecular attractive forces, particularly hydrogen bonds, seem to play a part in the net observed interaction.

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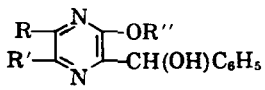
Synthesis of Several Derivatives of Phenyl(2-hydroxy-3-pyrazyl)carbinol

By VINCENT S. VENTURELLA†, J. A. BIANCULLI, and R. W. SAGER‡

Several derivatives of 2-hydroxypyrazine were prepared containing a phenylcarbinol moiety in the 3-position. A method was developed to prepare these compounds in order to test the efficacy of the basic cyclization reaction between a bifunctional α-amino amide and several 1,2-dicarbonyls. The synthetic method used necessitated some study of the chemistry of threo-β-phenylserine and its amide. After many unsuccessful experiments, it was found that the amide of this acid is best prepared through the use of the N-carbobenzoxy methyl ester.

THE PURPOSE of this investigation was to prepare several compounds of general structure, I, which might be useful as psychopharmacological agents.



	R	*R'*	*R''*
I	H	H	H
	H	H	CH_3
	H	CH_3	H
	H	CH_3	CH_3
	CH_3	CH_3	H
	CH_3	CH_3	CH_3
	C_6H_5	C_6H_5	H
	C_6H_5	C_6H_5	CH_3

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In the event that two nitrogen functions (as present in serotonin) and added hydroxyl functions (1) are necessary for antimetabolite activity, these compounds should exhibit some activity toward blocking or reversing the physiological activity of excess serotonin (2, 3).

DISCUSSION

Several methods have previously been used for the preparation of substituted hydroxypyrazines (4, 5), but none of these methods was applicable to the introduction of the phenylcarbinol group into the 3-position of the pyrazine ring.

The most promising methods available were those developed by Sharp and Spring (6) and by Jones (7). The Jones method was chosen for the synthesis of the cyclized product because the former method would require the use of the nitrile of β-phenylserine as an intermediate. The preparation of this compound, although possible, was expected to result in a great deal of difficulty because of the presence of the β-hydroxy group. The Jones method for the final step in the synthesis is represented in Eq. 1