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.

REFERENCES

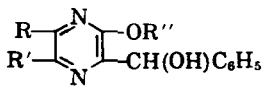
(1) Higuchi, T., and Zuck, D., THIS JOURNAL, 41, 10 (1952).
(2) Riegelman, S., *ibid.*, 49, 339(1960).
(3) Higuchi, T., and Lachman, L., *ibid.*, 44, 521(1955).
(4) Lachman, L., Ravin, L. J., and Higuchi, T., *ibid.*, 45, 290(1956).
(5) Lachman, L., and Higuchi, T., *ibid.*, 46, 32(1957).
(6) Lachman, L., Guttman, D., and Higuchi, T., *ibid.*, 46, 36(1957).
(7) Martin, A. N., "Physical Pharmacy," Lea & Febiger, Philadelphia, 1960, p. 425.
(8) Cohen, J., and Lach, J. L., THIS JOURNAL, 52, 132 (1963).
(9) French, D., Lavine, M. L., Pazur, J. H., and Norberg, E., *J. Am. Chem. Soc.*, 71, 353(1949).
(10) Tilden, E. B., and Hudson, C. S., *J. Bacteriol.*, 43, 527(1942).
(11) Higuchi, T., and Lach, J. L., THIS JOURNAL, 43, 349 (1954).
(12) Pauling, L., "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1960.
(13) "Tables of Interatomic Distances and Configuration in Molecules and Ions," Special Pub. No. 11, The Chemical Society, London, 1958.
(14) Poole, J. W., and Higuchi, T., THIS JOURNAL, 48 592(1959).

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

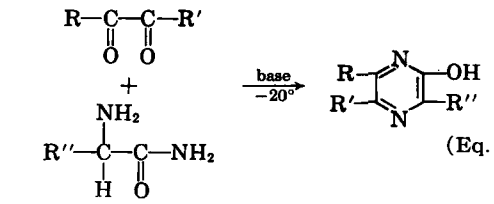
Received April 12, 1962, from the University of Pittsburgh School of Pharmacy, Pittsburgh 13, Pa.
Accepted for publication May 10, 1962.
Abstracted from a thesis submitted to the Graduate Faculty of the University of Pittsburgh, School of Pharmacy, by V. S. Venturella in partial fulfillment of the requirements for the Ph.D. degree.
† Present address: Fordham University, College of Pharmacy, New York 58, N. Y.
‡ Present address: Oregon State University, College of Pharmacy, Corvallis.

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



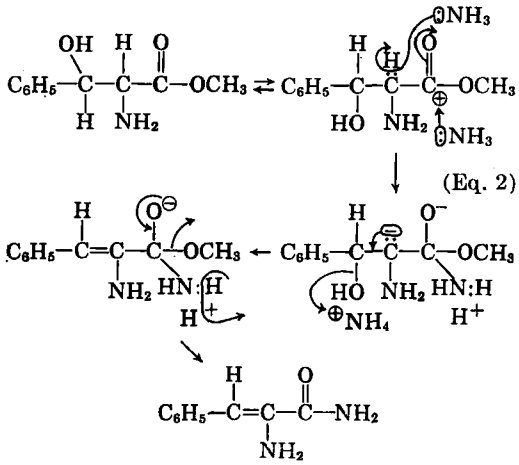
(Eq. 1)

The use of this method for the final step therefore required the use of one of the isomers of phenylserine due to R″ = $C_6H_5CH(OH)$—. The threo isomer was used throughout the experiments due to the possible steric interference that might result from the use of the erythro compound in the Jones sequence.

The isomerically pure acid was prepared by a modification of the procedure of Shaw and Fox (8) and its isomeric purity ascertained chromatographically (9) by comparison with authentic samples of the acids.[1]

The lower esters of the acid resisted ammonolysis using standard procedures, and treatment of the ethyl ester hydrochloride with liquid ammonia yielded only the erythro amide which gave an R_f value of 0.82 when chromatographed in a manner similar to the acid. The stereochemistry of this compound was demonstrated by infrared analysis which showed an absorption in the 11.9 to 12.1 μ range, which is indicative of the erythro isomers of this general series of compounds (10, 11). The absence of bands at 6.2 and 11 μ precludes the possibility that this compound was recovered β-phenylserine, which was suggested by the proximity of melting points.

When the ammonolysis of the methyl ester was attempted under pressure with continuous agitation over extended periods of time, a compound was isolated which was shown to be α-aminocinnamamide. The formation of this compound may be explained by the sequence of reactions in Eq. 2



(Eq. 2)

The infrared spectrum of this compound showed strong bands in the $—NH_2$ and $—CONH_2$ regions, presence of monophenyl substitution, absence of —CH(OH)—, and a conjugated carbonyl system, as evidenced by the shift in the carbonyl absorption followed by a doublet (12, 13).

Since previous attempts to prepare the threo amide were unsuccessful or resulted in isomerization, the electromeric carbobenzoxy group (14) was used to reverse the inductive effect of the amino group. This reversal permitted an easier discharge of the $—OCH_3$ group due to activation of the ester group followed by an unhindered attack of $:NH_3$, according to the inductomeric mechanism (15). The carbobenzoxy group prevents neighboring group neutralization of the carbonyl carbon as well as providing activation of the ester group.

The relationship of stability of isomers to favored formation of amide can be related to configuration versus reaction specificity. The erythro form is less stable, but its formation is favored due to the possibility of hydrogen bonding between the α-amino and the β-hydroxy groups. The relatively more stable threo isomer is made to form by the presence of the bulky carbobenzoxy group which sterically removes the possibility of inversion and electronically removes the possibility for hydrogen bonding.

Condensation Reactions.—Threo-β-phenylserine amide was reacted with the 1,2-dicarbonyls studied using a modification of the Jones procedure for the reaction of tyrosine amide (7). An excess of the dicarbonyl was used in the reaction in all cases except pyruvic aldehyde condensation. With this compound it was found that using an excess of the amide resulted in greater yield, purer product, and easier isolation of product.

Derivative Formation.—It has been shown (16) that compounds of this type exist in tautomeric equilibrium with the corresponding pyrazone structures. This phenomenon was further demonstrated during this study by the strong infrared absorption bands in the carbonyl region of the prepared compounds. The presence of this group along with the coexistence of the functional nuclear hydroxyl group and the side chain hydroxyl group suggested the possibility of hydroxylic and ketonic derivatives.

However, it was found that steric crowding prevented the formation of hydroxylic derivatives, phenylhydrazide and semicarbazide. In contrast to this, the compounds reacted in low yield in aqueous dimethylsulfate to form the corresponding methyl ethers of the nuclear hydroxyl groups.

EXPERIMENTAL[2]

Threo-β-phenylserine Monohydrate.—The procedure of Shaw and Fox (8) was followed for the preparation of this compound, with minor variations. Twenty-five Gm. (0.33 mole) of glycine in 100 ml. of 6 *N* sodium hydroxide was cooled to 10° and stirred vigorously while 70 Gm. (0.66 mole) of benzaldehyde was added slowly. When the resultant slurry thickened, 20 ml. of water was added and the thick edges were broken up. At this point the benzaldehyde addition was stopped and the slurry was stirred very vigorously until it was homogeneous. The benzaldehyde addition was then completed. The mixture was stirred for a half hour at 10°, and finally at room temperature until pasty. After standing at room temperature for 22 hours, the resultant condensation cake was fragmented and acidified with 49 ml. of concentrated hydrochloric acid, added slowly. The resultant yellow suspension was refrigerated at 5° for 40 hours.

[1] Kindly supplied by Dr. James M. Sprague, Merck Sharp & Dohme, Rahway, N. J.

[2] All melting points were taken on a Fisher-Johns apparatus and are uncorrected.

Filtration, followed by washing with three 250-ml. portions of boiling ethanol gave 46.2 Gm. (76.6%) of microcrystals, m.p. 197–200° [Erlenmeyer (17) reported 192–193°, Shaw and Fox (8) reported 185–200°].

Calcd. for neut. equiv. (formol): 199. Found: 203.

Anhydrous Threo-β-phenylserine (9).—Forty-five grams of the monohydrate in 300 ml. of boiling water recrystallized as layered plates after dilution with 300 ml. of boiling methanol and refrigeration overnight. The plates were suction dried and placed in a vacuum desiccator at 50–60° and dried over calcium chloride for 3 hours. The product melted at 196–196.5° [lit. (17) m.p. 195–196°]. Calcd. for neut. equiv. (formol): 181. Found: 182, 183. R_f, 0.47, 0.46 [lit. (9) 0.43].

Preparation of Threo-β-phenylserine Methyl Ester Hydrochloride (18, 19).—Fifteen grams (0.085 mole) of the anhydrous threo acid was suspended in 150 ml. of absolute methanol in a 500-ml. three-neck flask equipped with a water condenser and drying tube, and the mixture was stirred magnetically. A steady stream of dry hydrogen chloride was passed into the suspension at a rate sufficient to promote gentle refluxing. The solid dissolved immediately, and after 2.5 hours the yellow solution had cooled to room temperature. The solution was filtered after standing overnight to remove any erythro isomer formed and evaporated to dryness to give a light yellow solid. The solid was dissolved in a minimum amount of hot methanol and crystallized by the addition of 6 volumes of anhydrous ether. Recrystallization was effected from methanol-ether (1:6) at −15° as glistening white flakes, m.p. 162–163.5° (decompn.), 13.4 Gm., (70.5%). Shaw and Fox (8) reported 160° (decompn.), Bergmann, *et al.* (18), 161° (decompn.), Carrara and Weibnauer (19), 156° (decompn.).

Erythro-β-phenylserine Amide.—Seven grams (0.036 mole) of the threo methyl ester was dissolved in 300 ml. of absolute ethanolic ammonia at 0° contained in a 1-L. thick-walled round-bottom flask. The flask was stoppered and wired shut in a cage while at 0° and allowed to stand at room temperature for 72 hours.

After standing, the flask was cooled to 0° and reopened. Evaporation of the solution under reduced pressure gave a yellow solid which was taken up in absolute ethanol, and the evaporation was repeated. This procedure was repeated twice more to remove all traces of ammonia. The yellow solid was recrystallized from hot absolute methanol yielding 2.2 Gm. (36%) of white fluffy needles, m.p. 191–193°.

Anal.—Calcd. for $C_9H_{12}N_2O_2$: N, 15.55. Found: N, 15.25, 15.27, 15.05.

Isolation of α-Aminocinnamamide from Ammonolysis Experiment.—A 15-Gm. quantity (0.08 mole) of the methyl ester was dissolved in 300 ml. of absolute methanolic ammonia at 0° and the flask was sealed as previously described. The solution was shaken continuously for 60 hours at room temperature. The flask was then cooled to 0° and opened. The excess ammonia and methanol were removed at reduced pressure to yield a yellow residue which dissolved in 75 ml. of hot methanol. Refrigeration of the solution at 5° for 3 hours gave 2.2 Gm. of a tan powder, m.p. 186–190°. Evaporation of the filtrate under reduced pressure to dryness gave a red solid which partially dissolved in 100 ml. of hot benzene. Refrigeration of the filtrate at 5° for 12 hours gave 1.5 Gm. of yellowish-white needles, m.p. 122-123°. An additional 1.5 Gm. of product was obtained by concentration of the filtrate and refrigeration.

Anal.—Calcd. for $C_9H_{10}N_2O$: N, 17.28. Found: N, 17.27, 17.36, 17.56.

N - Carbobenzoxy - threo - β - phenylserine Methyl Ester.—Five grams (0.022 moles) of the threo methyl ester hydrochloride was treated with an excess of potassium bicarbonate solution. The solution was extracted, portionwise, with 300 ml. of ethyl acetate. The ethyl acetate layers were dried over sodium sulfate and placed in a 1-L. 3-neck flask equipped with a stirrer and a drying tube. The solution was cooled in an ice-salt bath and treated with 5 Gm. of solid potassium bicarbonate. To the vigorously stirred solution, 3.0 Gm. of carbobenzoxy chloride was added in two portions. The cloudy mixture was stirred in the cold for 4 hours, at which time no more carbon dioxide was evolved. Fifteen milliliters of dry pyridine was added. The resulting mixture was alternately washed with 100-ml. portions of water, dilute hydrochloric acid, and water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure to one-half the original volume. Refrigeration overnight gave a white slurry which yielded 2.0 Gm. of amorphous material when suction filtered and dried. Concentration of the filtrate and similar treatment gave an additional 2.5 Gm. Total yield was 73.5%. Crystallization from hot ethyl acetate gave white fluffy plates, m.p. 91.5–93°.

Anal.—Calcd. for $C_{18}H_{19}NO_3$: N, 4.26. Found: N, 4.64.

N - Carbobenzoxy - threo - β - Phenylserine Amide.—A 2.5-Gm. quantity (0.0076 mole) of the carbobenzoxy methyl ester was dissolved in 100 ml. of absolute methanolic ammonia according to previous procedures and allowed to stand at room temperature for 40 hours. Processing gave a white solid, weighing 2.1 Gm., m.p. 152–153° (88%). Recrystallization from methanol-water and vacuum drying gave fine white needles, m.p. 159–160°.

Anal.—Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.73; N, 8.91. Found: C, 64.35; H, 5.84; N 8.55.

Preparation of the Threo-amide.—Two grams (0.0063 moles) of the carbobenzoxyamide was dissolved in 100 ml. of methanol in a 300-ml. long-neck round-bottom flask, palladium catalyst was added, and the flask was fitted with a gas delivery adapter. The mixture was then shaken continuously while being flushed with a stream of dry nitrogen for 10 minutes. The amide was then reduced with a constant stream of hydrogen until the exit gases failed to precipitate barium carbonate in a saturated solution of barium hydroxide. The flask was again flushed with dry nitrogen for 10 minutes. The catalyst was removed by filtration through a Celite mat, washed with three small portions of methanol, and the filtrate was evaporated under reduced pressure to a semisolid mass. Drying in a vacuum desiccator over calcium chloride gave 1.1 Gm. of solid material (90.5%). The solid was washed with 10 ml. of ice-cold ether and recrystallized from methanol-petroleum benzin (cold). The final product was a white microcrystalline solid, m.p. 144–145°.

Anal.—Calcd. for $C_9H_{12}N_2O_2$: C, 60.00; H,

6.66; N, 15.55. *Found:* C, 60.54; H, 6.46; N, 15.34.

Phenyl(2 - hydroxy - 3 - pyrazyl)carbinol Hydrochloride.—Five grams (0.028 mole) of the threo amide was placed in a 100-ml. 3-neck flask equipped with a stirrer and dropping funnel and suspended in 50 ml. of absolute methanol. The flask was immersed in a dry ice bath and the contents stirred until the internal temperature reached −20°. Seven grams (0.035 moles) of 30% glyoxal was added all at once and 6 ml. (0.07 mole) of sodium hydroxide (12 *N* solution) was added dropwise over 15 minutes.

The tan suspension was stirred for 3 hours at −20°, 2 hours at room temprature, then acidified with 7 ml. of concentrated hydrochloric acid at 15°. A tan material precipitated which redissolved upon the addition of 10 ml. of water. Refrigeration at −20° for 40 hours gave 2.2 Gm. of a tan powder (39.4%), m.p. 199–203° (decompn.). Washing with ice-cold ether and crystallization from warm ether gave a tan microcrystalline powder, m.p. 199–201° (decompn.). Recrystallization from ethanol (charcoal)-ether (cold) gave fluffy plates, m.p. 203–204.5° (decompn.).

Anal.—Calcd. for $C_{11}H_{11}ClN_2O_2$: C, 55.50; H, 4.63; N, 11.79. Found: C, 56.35; H, 5.06; N, 12.34.

Phenyl(2 - hydroxy - 5 - methyl - 3 - pyrazyl)carbinol.—Six grams (0.034 moles) of the threo amide was suspended in 35 ml. of absolute methanol in a manner similar to above and treated with 7.0 Gm. (0.032 mole) of pyruvic aldehyde added in three portions over a 5-minute period. An equimolar amount (amide) of 12 *N* sodium hydroxide was added in 10 minutes over a 15-minute period. The suspension was stirred at −20 to −30° for 4 hours then at room temperature for 1 hour. The solution was acidified with concentrated hydrochloric acid to pH 6.8, treated with a small amount of solid sodium bicarbonate, and stirred for 10 minutes. Suction filtration gave 5.5 Gm. of a tan residue. The residue was washed with three 50-ml. portions of ice water and crystallized from hot acetone to give 3.2 Gm. (46.5%) of fluffy white needles, m.p. 174–176° (decompn.).

Anal.—Calcd. for $C_{12}H_{12}N_2O_2$: C, 65.60; H, 5.56; N, 12.95. Found: C, 64.99; H, 5.99; N, 12.91.

Phenyl(2 - hydroxy - 5,6 - dimethyl - 3 - pyrazyl)carbinol.—A suspension of 3.6 Gm. (0.02 mole) of the threo amide in 40 ml. of absolute methanol was treated with 2.58 Gm. (0.03 mole) of butanedione at −20°. While stirring, 4.5 ml. of 12 *N* sodium hydroxide was added over 20 minutes. The mixture was stirred for 4 hours and then for 1 hour at 0°. The dark brown solution was then acidified with concentrated hydrochloric acid to pH 7, diluted with 5 ml. of water, and allowed to come to room temperature. Tarry material present was precipitated by the addition of 15 ml. of water and the filtrate refrigerated to yield a tan granular material. Crystallization from 20% aqueous methanol gave 1.3 Gm. (33%) of light tan flakes, m.p. 181.5–183° (decompn.).

Anal.—Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.82; H, 6.09; N, 12.17. Found: C, 67.20; H, 6.05; N, 11.80.

Phenyl(2 - hydroxy - 5,6 - diphenyl - 3 - pyrazyl)carbinol.—To 5 Gm. (0.028 mole) of the threo amide, suspended in 50 ml. of absolute methanol contained in a 3-neck flask equipped with a stirrer, water condenser, and dropping funnel, was added 5.9 Gm. (0.028 mole) of benzil. The mixture was stirred and heated to reflux, after which 4.85 ml. of 12 *N* sodium hydroxide was added slowly. The solution was refluxed for 30 minutes, cooled to room temperature, and then acidified with concentrated hydrochloric acid, dropwise. One gram of solid potassium bicarbonate was added during a 10-minute stirring period. The suspension was cooled to 0° and filtered. The yellow residue was washed twice with 500 ml. of water. Air drying overnight gave 6.5 Gm. (65.8%) of yellow powder which recrystallized from hot butanol in yellow flakes, m.p. 213–216° (decompn.).

Anal.—Calcd. for $C_{23}H_{18}N_2O_2$: C, 77.96; H, 5.07. Found: C, 77.78; H, 5.41.

Methyl Ether of the Prepared Compounds.—The methyl ethers of the hydroxypyrazines were formed by treatment with dimethylsulfate (equimolar) in dilute aqueous base. Isolation procedures and analytical data for the compounds follow. All reactants were mixed at 0°, followed by reflux for at least 1 hour.

Phenyl(2-methoxy-3-pyrazyl)carbinol.—The reaction filtrate was cooled to room temperature and filtered to remove a crop of tan microcrystals. Refrigeration at 5° overnight gave an additional crop of crystals. From 0.5 Gm. of pyrazyl compound, 0.185 Gm. (34%) was obtained. Recrystallization from hot water gave fluffy tan microcrystals, m.p. 140–142°.

Anal.—Calcd. for $C_{12}H_{12}N_2O_2$: N, 12.96. Found: N, 12.53.

Phenyl(2 - methoxy - 5 - methyl - 3 - pyrazyl)carbinol.—Refrigeration of the reaction filtrate for 30 hours gave a precipitate of yellowish-white rods. Filtration and recrystallization from hot water gave 0.115 Gm. of white rhombs, m.p. 134.5–136.5°, from 2.0 Gm. of starting material.

Anal.—Calcd. for $C_{13}H_{14}N_2O_2$: N, 12.17. Found: N, 11.85.

Phenyl(2 - methoxy - 5,6 - dimethyl - 3 - pyrazyl)carbinol.—The reaction mixture from 0.4 Gm. of reactant was cooled to room temperature and filtered to give a soft gummy residue which was air-dried. The residue was dissolved in a minimum amount of hot acetone and cooled to 5° for 30 hours, giving 0.048 Gm. of tan flakes which were recrystallized from ether-petroleum benzin, m.p. 110–111.5°.

Anal.—Calcd. for $C_{14}H_{16}N_2O_2$: N, 11.47. Found: N, 11.08.

Phenyl(2 - methoxy - 5,6 - diphenyl - 3 - pyrazyl)carbinol.—When the reaction mixture from 2.0 Gm. of reactant was cooled to room temperature, a small amount of insoluble gum was filtered off. After 2 hours at room temperature, the cloudy solution was treated with methanol until clear, an equal volume of water was added, and the mixture was refrigerated at 5° for 10 hours. A greenish-yellow solid precipitated. Recrystallization from cold aqueous methanol gave 0.035 Gm. of a yellow amorphous solid, m.p. 94.5–96° (decompn.).

Anal.—Calcd. for $C_{24}H_{20}N_2O_2$: N, 7.60. Found: N, 7.48.

SUMMARY

1. A series of hydroxypyrazines, with a phenylcarbinol moiety in the 3-position, was prepared. The prepared compounds were unobtainable by any other existing method.

2. A study of β-phenylserine indicated that the amide of this acid is more stable in the threo form than in the erythro form. The erythro form is preferentially obtained by reaction mechanism due to the excess pressure required in the reaction. The inversion during the formation of the amide from the ester is minimized by the use of the bulky carbobenzoxy group.

3. It was shown, by infrared analysis and low yield of methoxy compound from reaction with dimethylsulfate, that the compounds exist in predominantly the keto or pyrazone form. In addition, it was shown that sufficient crowding of the 2-position is present to prevent normal hydroxylic and ketonic reactions due to preventing sterically the formation of the necessary transition states required for these compounds.

4. The steric crowding has little effect on the formation of the methyl ethers because of the size and the linearity of the entering group.

REFERENCES

(1) Woolley, D. W., "A Study of Antimetabolites," John Wiley & Sons, Inc., New York, N. Y., 1952.
(2) Woolley, D. W., and Shaw, E., *Proc. Natl. Acad. Sci.*, **40**, 288(1954).
(3) Shaw, E., and Woolley, D. W., *J. Biol. Chem.*, **203**, 979(1953).
(4) Weijlard, J., Tischler, M., and Erickson, A. E., *J. Am. Chem. Soc.*, **67**, 802(1945).
(5) Shreve, R. N., and Berg, L., *ibid.*, **69**, 2116(1947).
(6) Sharp, W., and Spring, F. S., *J. Chem. Soc.*, **1951**, 932.
(7) Jones, R. G., *J. Am. Chem. Soc.*, **71**, 78(1949).
(8) Shaw, K. N. F., and Fox, S. W., *ibid.*, **75**, 3417(1953).
(9) *Ibid.*, **75**, 3421(1953).
(10) Bolhofer, W. A., *ibid.*, **76**, 1322(1954).
(11) Drell, W., *ibid.*, **77**, 5429(1955).
(12) Bellamy, L. J., "Infrared-Red Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1958, pp. 216–219, 245.
(13) Shriner, R. L., Fuson, R. C., and Curtin, D. Y., "The Separation and Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1956, pp. 170, 175.
(14) Bergman, M., and Zervas, L., *Ber.*, **65**, 1192(1932).
(15) Ingold, C. K., "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 465–467.
(16) Pratt, Y. T., "Pyrazine and Piperazine, Heterocyclic Compounds," Vol. 6, John Wiley & Sons, Inc., New York, N. Y., 1957, pp. 405, 406.
(17) Erlenmeyer, E., Jr., *Ber.*, **25**, 3445(1892).
(18) Bergmann, E. D., Bendas, H., and Taub, W., *J. Chem. Soc.*, **1951**, 2673.
(19) Carrara, G., and Weibnauer, G., *Gazz. Chim. Ital.* **79**, 856(1949).

Influence of Excipients on the Analysis of Tablets and Capsules by Nonaqueous Titrimetry

By L. G. CHATTEN and C. A. MAINVILLE

Investigation of the effect of twenty-seven tablet and capsule excipients on the titration of medicinal organic acids and bases has shown that a careful choice of solvents can limit interference to a very small percentage of the excipients. Certain of these excipients which are titratable when dissolved alone in common nonaqueous solvents do not always consume titrant when combined with strong organic acids and bases. Polyvinylpyrrolidone and stearic acids cause the most difficulty in the titration of medicinal organic bases and acids, respectively.

ALTHOUGH the scientific literature of the past decade is filled with reports on the application of nonaqueous titrimetry to the analysis of drugs and chemicals, only a relatively few workers, by comparison, have adapted this technique to the analysis of pharmaceuticals. This situation can be attributed in part to the extensive use made of glacial acetic acid as a solvent, both by numerous investigators in the field as well as by such authoritative compendia as the British and United States pharmacopoeias (1, 2). While the wide solubilizing properties of glacial acetic acid enhance its utility, it is this very factor that limits its application in the analyses of pharmaceuticals. A second contributing cause to the reluctance of some workers in the field to accept nonaqueous titrations as a practical means of assaying pharmaceuticals has been the lack of investigations into the effect of excipients on the quantitative determination of active components of pharmaceutical forms.

The purpose of this report is to assess the influence of a number of excipients and to investigate means of obviating interference by altering the solvent system. The effect of the presence of drugs on interfering excipients is also within the scope of this work.

Received February 12, 1962, from the University of Alberta Faculty of Pharmacy, Edmonton.
Accepted for publication August 2, 1962.