

REFERENCES

- (1) L. F. Tice and M. Barr, *J. Soc. Cosmetic Chemists*, **9**, 171 (1958).
- (2) H. B. Kostenbauder, in "Developments in Industrial Microbiology," vol. 3, Plenum Press, New York, N. Y., 1962, p. 286.
- (3) E. O. Bennett, *ibid.*, p. 273.
- (4) M. G. deNavarre, "The Chemistry and Manufacture of Cosmetics," vol. 1, D. Van Nostrand, Princeton, N. J., 1962, p. 257.
- (5) D. L. Wedderburn, in "Advances in Pharmaceutical Sciences", vol. 1, H. S. Bean, A. H. Beckett, and J. E. Carless, Eds., Academic, New York, N. Y., 1964, p. 195.
- (6) W. B. Hugo and E. G. Beveridge, *J. Appl. Bacteriol.*, **25**, 72(1962).
- (7) G. E. Myers and G. A. Leslie, *Can. J. Pharm. Sci.*, **4**, 64(1969).
- (8) J. B. Davis, "Petroleum Microbiology," Elsevier, New York, N. Y., 1967, p. 519.
- (9) M. Barr and L. F. Tice, *J. Amer. Pharm. Ass., Sci. Ed.*, **46**, 442(1957).
- (10) W. T. Sokolski, C. G. Chidester, and G. E. Honeywell, in "Developments in Industrial Microbiology," vol. 3, Plenum Press, New York, N. Y., 1962, p. 179.
- (11) M. Aoki, A. Kamata, I. Yoshioka, and T. Matsuzaki, *J. Pharm. Soc. Japan*, **76**, 939(1956).
- (12) N. K. Patel and H. B. Kostenbauder, *J. Amer. Pharm. Ass., Sci. Ed.*, **47**, 289(1958).
- (13) F. D. Pisano and H. B. Kostenbauder, *ibid.*, **48**, 310(1959).
- (14) S. M. Blaug and S. S. Ahsan, *J. Pharm. Sci.*, **50**, 441(1961).
- (15) N. K. Patel, *Can. J. Pharm. Sci.*, **2**, 77(1967).
- (16) *Ibid.*, **2**, 95(1967).
- (17) M. G. deNavarre and H. E. Bailey, *J. Soc. Cosmetic Chemists*, **7**, 427(1956).
- (18) M. G. deNavarre, *ibid.*, **8**, 68(1957).
- (19) L. M. Spalton, "Pharmaceutical Emulsions and Emulsifying Agents," 2nd ed., The Chemist and Druggist, London, England, 1956, p. 100.
- (20) H. S. Bean, S. M. Heman-Ackah, and J. Thomas, *J. Soc. Cosmetic Chemists*, **16**, 15(1965).
- (21) R. A. Anderson and C. E. Chow, *ibid.*, **18**, 207(1967).
- (22) F. Atkins, *Mfg. Chemist*, **21**, 51(1950).
- (23) N. K. Patel and J. M. Romanowski, *Can. J. Pharm. Sci.*, **4**, 66(1969).
- (24) N. K. Patel and N. E. Foss, *J. Pharm. Sci.*, **54**, 1495(1965).
- (25) N. K. Patel, P. C. Sheen, and K. E. Taylor, *ibid.*, **57**, 1370(1968).
- (26) Atlas Chemical Industries, Inc., "The Atlas HLB System," Wilmington, Del., 1962, p. 7.
- (27) W. P. Schorr and A. H. Mahajerin, *Arch. Dermatol.*, **93**, 721(1966).
- (28) N. K. Patel, unpublished data.
- (29) S. Riegelman, "The Pharmaceutical Sciences," Second Annual Visiting Lecturer Series, University of Texas, Austin, Tex., 1959, p. 135; through *Ref. 2*.

ACKNOWLEDGMENTS AND ADDRESSES

Received August 18, 1969, from the *Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton 7, Alberta, Canada.*

Accepted for publication October 8, 1969.

Presented in part at the XVth Canadian Conference on Pharmaceutical Research, Regina, Canada, August 1968.

This work was supported by research grant GR-766 from the University of Alberta General Research Fund.

The authors wish to thank Miss Marilynne S. Bergos for technical assistance during the initial phase of the work and Dr. Gordon E. Myers, Professor (Pharmaceutical Microbiology), for helpful suggestions.

* Present address: Frank W. Horner Limited, Research Laboratories, Montreal 307, P.Q., Canada.

Kinetics of Hydrus Aluminum Oxide Conversion in Mixtures of Amorphous Alumina Gels of Various Acid Reactivities

STANLEY L. HEM*, EMANUEL J. RUSSO, RICHARD J. HARWOOD†, BEHRAM H. TEJANI, SURENDRA M. BAHAL, and RALPH S. LEVI

Abstract □ Mixtures of two amorphous alumina gels of different acid reactivity change physically and chemically upon aging until a constant state is reached. The gels, when individually aged, retain their initial properties. The end-point appearance, viscosity, X-ray diffraction pattern, DTA thermogram, acid-insoluble fraction, and acid reactivity of the mixture are identical to those of the gel having the lower acid reactivity. The change in properties appears to be due to the conversion of the gel having the higher reactivity into the less reactive form. The rate of conversion is first-order, temperature-dependent, and directly dependent on the initial concentration of the less reactive gel.

Keyphrases □ Hydrus aluminum oxide conversion—kinetics □ Alumina gels, amorphous, effect— Al_2O_3 conversion □ X-ray diffraction—identity □ Calorimetry—analysis, gels

The physical and chemical properties of hydrus aluminum oxide depend on the nature of the reactants used in its formation (1, 2), the pH and temperature of

its precipitation (3–5), and the conditions under which it is aged (6, 7). The effects of mixing alumina gels of different physical and chemical properties have not been reported. Preliminary experiments in the authors' laboratories have indicated that when amorphous alumina gels of various acid reactivities are mixed, there are changes in the physical and chemical properties of the mixtures during aging. The purpose of the present study was to examine these changes in greater depth.

EXPERIMENTAL

Source of Gels—One alumina gel was prepared by the reaction of aluminum chloride with sodium carbonate and sodium bicarbonate at 25° and pH 5.8, according to the procedure of Papée *et al.* (8), and washed with deionized water until the concentration of chloride ion in the filtrate, as determined by the Volhard method (9), was less than 0.1%. This gel (I) possessed the full theoretical acid reactivity in terms of its Al_2O_3 content. Gels with reactivity less

Table I—Initial Properties of Alumina Gels I and II and Their 1:1 Mixture

Property	Alumina Gel I	Alumina Gel II	1:1 Mixture of Alumina Gels I and II
Physical appearance of 4% suspension	White, dense suspension	Opaque semisolid	White, dense suspension
Form	Amorphous	Amorphous	Amorphous
Percentage of theoretical acid-consuming capacity	100	25	62.5
Appearance after acid-consuming capacity test	Clear solution	Insoluble residue	Slight insoluble residue
Viscosity at 25° (c.p.s.)	140	3700	800
Endotherms by DTA ^a	140°	140°, 320°	140°, 320°

^a Differential thermal analysis.

Table II—Acid Reactivity, Both Initially and after Storage at Elevated Temperatures, of Mixtures Containing Various Initial Ratios of Alumina Gels I and II

Initial Concentration of II in Mixture %	Initial Acid Reactivity ^a , %	End-Point Acid Reactivity ^a when Aged at		
		35°	45°	60°
10	92.5	25%	25%	25%
20	85	25%	25%	25%
40	70	25%	25%	25%
50	62.5	25%	25%	25%

^a Expressed as percent of theoretical acid-consuming capacity.

than theory were prepared by the addition of strong ammonia solution NF to aluminum chloride solutions at 25° and controlled pH. Gels reacting at 25% of theory (II) and 70% of theory (III) were obtained by precipitating at pH 7.7 and 4.9, respectively; washing as in (I); and aging until the end-point reactivity was reached (10). Aluminum hydroxide compressed gel (F-5000)¹ (IV) was obtained through normal commercial channels. This gel possesses 10% of theoretical acid reactivity. Aluminum hydroxide compressed gel (F-500)¹ (V) and aluminum hydroxide gel² (VI) were likewise obtained from commercial sources and were found to react stoichiometrically with 0.1 N HCl.

Gel Mixtures—Binary mixtures containing 4% w/w Al₂O₃ were prepared from the gels so as to contain various concentrations of the less acid-reactive components. Appropriate weights of I, II, and III were used, depending on the Al₂O₃ content. Gels IV, V, and VI

were diluted with distilled water to form 4% w/w suspensions prior to the preparation of the mixtures.

The mixtures were aged in sealed, screw-capped glass bottles at 60, 45, and 35°. The sample bottles were tared and the weight checked at every assay. No weight losses were noted.

Tests—The acid reactivity of each gel was described by its percentage of the theoretical acid-consuming capacity, based on the stoichiometric reaction of the Al₂O₃ with 0.1 N HCl. The precision of the USP acid-consuming capacity test (11) was improved by titrating to pH 3.5 rather than by using bromophenol blue T.S.

The X-ray diffraction pattern of each gel was obtained in the colloidal state by irradiating a sample in dialyzer tubing.

The insoluble gel fraction which remained after the acid-consuming capacity test was collected by filtration on a tared 0.45-μ Millipore filter.³ Two filters were used so that one could serve as a control. The control filter and the filter with the residue were dried to constant weight at 90° in a vacuum desiccator. The results were reported as the residue obtained from 1 g. of alumina gel.

The viscosity of the alumina gels was determined at 25° using the Haake Rotovisco,⁴ system mv. II, head 500, speed 162.

Thermograms of each alumina gel were obtained using a DuPont model 900 differential thermal analyzer.⁵ The gels were dried at 25° in a vacuum desiccator. A 2- to 3-mg. sample was introduced into a microcell and heated at a rate of 20° per min. to obtain the DTA thermograms.

RESULTS AND DISCUSSION

Mixtures of I and II—Initial Properties—Gels I and II differed physically and chemically in several significant aspects, as seen in Table I. X-ray diffractometer scans indicate that the solid material in the gels is noncrystalline. The broad diffuse band is typical of

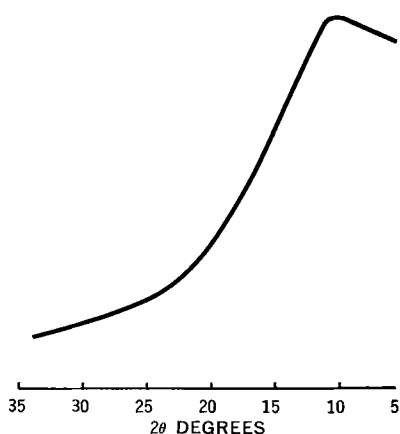


Figure 1—Initial X-ray diffraction pattern of Alumina Gel I.

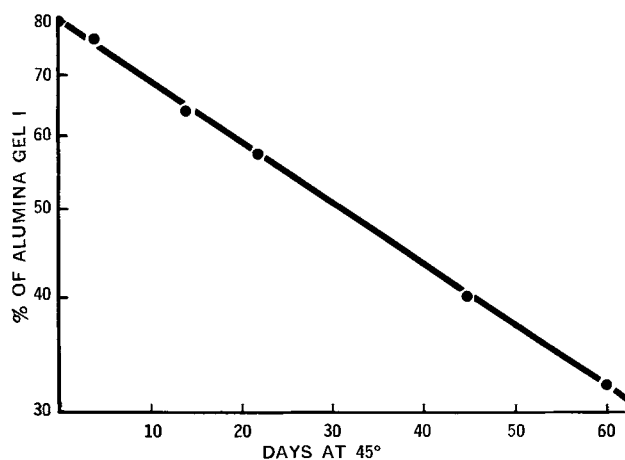


Figure 2—Change in concentration of Alumina Gel I during aging of a mixture of 80% I and 20% II at 45°.

¹ Reheis Chemical Co., Division of Armour Pharmaceutical Co., Chicago, Ill.

² Merlum No. 8031, Merck Chemical Division, Merck & Co., Inc., Rahway, N. J.

³ Millipore Filter Corp., Bedford, Mass.

⁴ Brinkmann Instruments, Inc., Great Neck, N. Y.

⁵ DuPont Instrument Products Division, Wilmington, Del.

Table III—Comparison of the Properties of an Aged 1:1 Mixture of Alumina Gels I and II with Those of II

Property	1:1 Mixture		Alumina Gel II
	Initial	Aged at 45° to End-Point Properties	
Physical appearance of 4% suspension	White, dense suspension	Opaque semisolid	Opaque semisolid
Form	Amorphous	Amorphous	Amorphous
Percentage of theoretical acid-consuming capacity	62.5	25	25
Appearance after acid-consuming capacity test	Slight insoluble residue	Insoluble residue	Insoluble residue
Viscosity at 25° (c.p.s.)	800	3700	3700
Endotherms by DTA	140°, 320°	140°, 320°	140°, 320°

scattering by amorphous material (Fig. 1). Figure 1 is typical of the scans obtained for both individual gels and mixtures throughout this study. These properties of the individual gels did not change upon aging, even at elevated temperatures. The 1:1 mixture of I and II had properties equivalent to the sum of those of the individual gels. Subsequent examinations of this mixture were conducted to determine the changes which occurred during aging.

Changes in Acid Reactivity upon Aging—At 45°, all mixtures lost acid reactivity until a minimum (end-point) level was reached. For the 1:1 mixture of Gels I and II, this end-point level was 25% of theory and was observed after aging for 12 days at 45°. For mixtures of Gels I and II containing 10, 20, 40, or 50% of Gel II, prepared and aged at 35, 45, and 60° (Table II), the end-point reactivities were also 25% of theory. Since the end-point reactivity was independent of the temperature or the ratio of I to II, but was always identical to the acid reactivity of II, it is assumed that I converts to II during the aging of the mixtures.

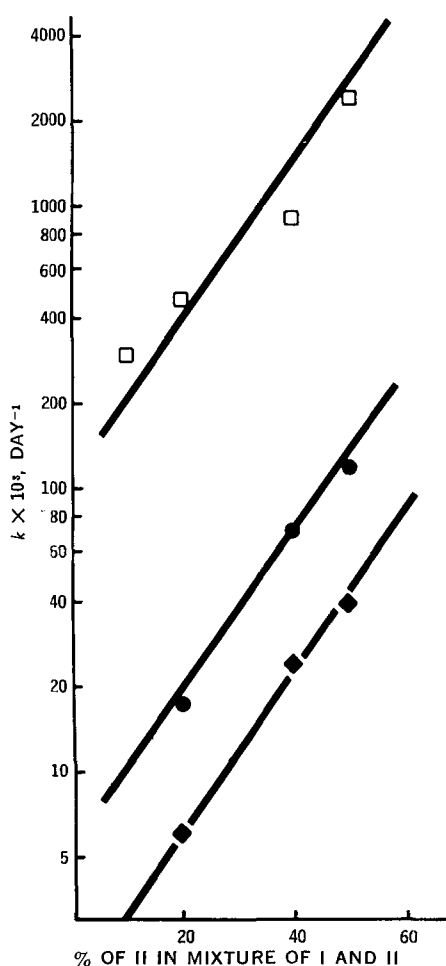


Figure 3—Effect of percentage of II on the rate of change of I in a mixture of Alumina Gels I and II. Key: □, 60°; ●, 45°; and ■, 35°.

Under this assumption, the reactivity of mixtures of Gels I and II would be related to the amount of each present at time t by the following equation:

$$R_t = \frac{100I_t + 25 [II_{init.} + (I_{init.} - I_t)]}{100}$$

where R_t = percent of theoretical acid-consuming capacity of the mixture at time t ; I_t = percent of I unchanged at time t ; $II_{init.}$ = percent of II in the initial mixture; $I_{init.}$ = percent of I in the initial mixture.

By rearranging the above equation, the amount of I present at any time in a mixture of I and II can be calculated and plotted. Such a plot shows that in a mixture initially containing 80% of I and 20% of II, I converts to II according to apparent first-order kinetics (Fig. 2).

Rate constants for the conversion of I to II in mixtures with various initial concentrations of II were calculated for mixtures aged at 35, 45, and 60°. The rate of conversion of I to II increased at all temperatures and was directly related to the initial concentration of II (Fig. 3).

The heat of activation for the conversion of I to II in a 1:1 mixture was calculated from Fig. 4 to be 26.2 kcal. mole⁻¹.

The effect of a change in temperature at which the acid reactivity test was conducted for the end-point mixture of I and II and for Gel II further indicates a conversion of I to II during aging. For example, the reactivity of II, which is 25% of theory at a test temperature of 37°, increased to 29.3% of theory when tested at 60°. The reactivity

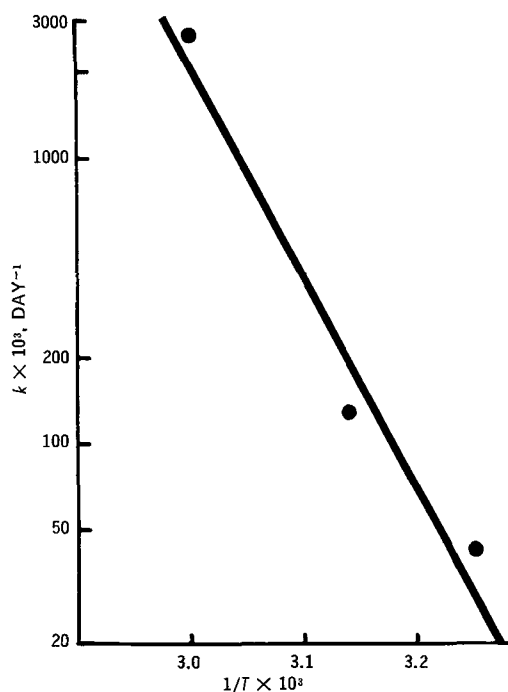


Figure 4—Effect of temperature on the rate of change of I in a 1:1 mixture of Alumina Gels I and II.

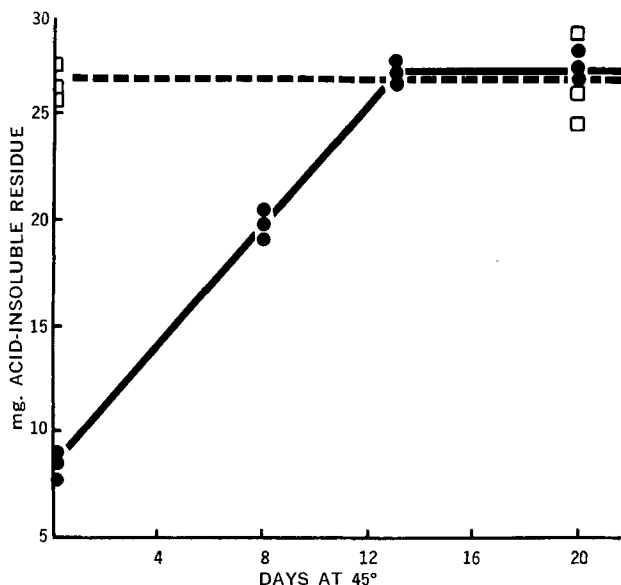


Figure 5—Effect of aging of alumina gels on the weight of the acid-insoluble residues. Key: ●, 2:1 mixture of Alumina Gels I and II; and □, II.

of the end-point mixture of I and II also increased from 25 to 29.3% of theory when the test temperature was increased from 37 to 60°.

Effect of Aging on Other Physical and Chemical Properties—Table III shows that the physical and chemical properties of the 1:1 mixture of Gels I and II changed during aging at 45° until they reached the indicated end-point values. The end-point physical appearance, acid reactivity, residue remaining after the acid-consuming capacity test, and viscosity of the mixture were identical to those of Gel II. The same changes occurred in the 1:1 mixture of Gels I and II aged at 35 and 60° and in various other mixtures of I and II aged at various temperatures. The only effect of temperature or ratio of gels was to change the rate of conversion of I to II. In each instance, identical end-point properties were observed.

Acid-Insoluble Fraction after Aging—All gels having less than the theoretical acid-consuming capacity left an acid-insoluble residue at the completion of the acid-consuming capacity test. This residue was believed to consist of completely acid-refractory aluminum oxide. Its weight was determined during the aging at 45° of a 2:1 mixture of Gels I and II and of Gel II. The values obtained from triplicate assays, and the lines determined by least-squares analyses which best fit these points, are given in Fig. 5.

As shown in the figure, 8.6 mg. of acid-insoluble residue was recovered from 1 g. of a freshly prepared 2:1 mixture of Gels I and II containing 4% w/w Al_2O_3 . This agrees well with the expected result of 10 mg., which assumes that I leaves no residue and that II is 75% acid-insoluble. The weight of acid-insoluble residue increased as the mixture aged at 45° until a constant value of 27 mg. was reached, beginning at 13 days, which is approximately the same time that the acid reactivity of the mixture reached its end-point reactivity of 25% of theory. From this point on, the quantity of acid-insoluble residue recovered from the mixture was virtually identical to the weight of residue recovered from a 4% w/w suspension of II. For II, the acid-insoluble residue remained constant during aging. These data again indicate a conversion of I to II in the 1:1 mixture of Gels I and II.

Properties of Mixtures of Other Alumina Gels—To test the general hypothesis that in mixtures of amorphous alumina gels of various acid reactivities, the more reactive gel is converted into the less reactive, a series of mixtures were prepared and aged at 60° (Table IV). In all cases when two alumina gels of different acid reactivities were mixed, the mixture lost reactivity until it reached a constant end-point reactivity equal to that of the less reactive gel.

Clearly, in an aged mixture, the more acid-reactive gel is converted into the less reactive form. Since these gels are amorphous, the conversion does not involve a change in form but instead may be analogous to the polymorphic transformations which occur as a system converts to its more stable form upon aging. It can be assumed that a completely acid-refractory form is thermodynamically

Table IV—End-Point Acid Reactivity of Aged 1:1 Alumina Gel Mixtures^a

Alumina Gels in Mixture, together with % of Theoretical Acid-Consuming Capacity of Each Gel (in Parentheses)	% Theoretical Acid-Consuming Capacity after Mixture Aged at 60° for	
	2 Weeks	3 Weeks
I(100):II(25)	25	25
I(100):III(70)	68	69
III(70):II(25)	30	25
I(100):IV(10)	14	12
V(100):IV(10)	8	8
VI(100):IV(10)	8	8

^a All gels and the aged mixtures in this table were amorphous.

ally the most stable, and that acid reactivity and related properties are inversely proportional to the thermodynamic stability. Thus the observed conversion of the system reflects its attainment of the most stable state.

CONCLUSIONS

Mixtures composed of two individually stable amorphous alumina gels of different acid reactivities change physically and chemically upon aging until they reach a constant state. At this point, their properties are identical to those of the less acid-reactive gel. The same constant state is obtained independent of temperature, but the rate of change depends on temperature and on the initial concentration of the less reactive gel. It is hypothesized that the more acid-reactive gel converts to the less reactive gel according to apparent first-order kinetics. Since no changes in form are observed, the change may be thought of as analogous to the polymorphic transformations which occur as a system converts to its most stable state.

REFERENCES

- (1) P. H. Hsu and T. F. Bates, *Mineral. Mag.*, **33**, 749(1964).
- (2) L. Erdey and F. Paulik, *Acta Chim. Acad. Sci. Hung.*, **7**, 45(1955).
- (3) H. Ginsberg, W. Hüttig, and H. Stiehl, *Z. Anorg. Allgem. Chem.*, **318**, 238(1962).
- (4) K. Pohl, D. Meissner, and W. Steinert, *ibid.*, **343**, 39(1966).
- (5) G. C. Bye and J. G. Robinson, *Kolloid-Z.*, **198**, 53(1964).
- (6) R. C. MacKenzie, R. Meldau, and J. A. Gard, *Mineral. Mag.*, **33**, 145(1962).
- (7) P. Souza Santos, A. Vallejo-Freire, and H. L. Souza Santos, *Kolloid-Z.*, **133**, 101(1953).
- (8) D. Papée, R. Tertian, and R. Biaï, *Bull. Soc. Chim. France*, **1958**, 1301.
- (9) H. A. Laitinen, "Chemical Analysis," McGraw-Hill, New York, N. Y., 1960, pp. 214–216.
- (10) S. L. Hem, E. J. Russo, S. M. Bahal, and R. S. Levi, to be published.
- (11) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, p. 26.

ACKNOWLEDGMENTS AND ADDRESSES

Received June 4, 1969, from the *Research and Development Department, Wyeth Laboratories Inc., Philadelphia, PA 19101*

Accepted for publication October 13, 1969.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Montreal meeting, May 1969.

The authors wish to thank Mr. J. A. Lash, Wyeth Laboratories, Inc., for chemical analyses and Mr. N. J. DeAngelis, Wyeth Laboratories, Inc., for thermal analyses. They also acknowledge the participation of Dr. T. H. Doyne, Department of Chemistry, Villanova University, Villanova, PA 19085, in analyzing the X-ray diffraction patterns.

* Present address: School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, IN 47907

† Present address: Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104