substrates with a cardiac glycoside or malonate it has been demonstrated that both may act through the removal of a rate-limiting step in the conversion of glycogen or glucose to pyruvate and thus, at least in part, affect energy production or utilization (4, 5). Such an hypothesis does not account for the inhibition observed with high concentrations of malonate, but neither does it preclude the possibility of other concentration-related mechanisms. Malonate may owe a portion of its positive inotropic effect to removal of a rate-limiting step in the glycolytic pathway and possibly to its ability to function as a metabolite (9). Its inhibition of succinic dehydrogenase (10) could account for the initial decrement and that decrement observed with high concentrations. While the results of the ouabain-malonate interaction suggest neither the sites of action nor the mechanisms, they do indicate the individual actions to be different from one another. If these agents shared the same site or mechanism of action, the interaction would be either additive or antagonistic. The potentiative response indicates complementary activity.

REFERENCES

(1) Wollenberger, A., *Pharmacol. Rev.*, **1**, 311(1949).
(2) Hajdu, S., and Leonard, E., *ibid.*, **11**, 173(1959).
(3) Moran, N. C., and Cotten, M., "Structure and Function of Muscle," Vol. 3, Academic Press, New York, N. Y., 1960.
(4) Berman, D. A., Masuoka, D. T., and Saunders, P. R., *Science*, **126**, 746(1957).
(5) Covin, J. M., and Berman, D. A., *J. Pharmacol. Exptl. Therap.*, **117**, 443(1956).
(6) Wenzel, D. G., Siegel, I. A., and Nichols, R. E., THIS JOURNAL, **49**, 614(1960).
(7) Loewe, S., *Ergeb. Physiol. Biol. Chem. Exptl. Pharmakol.*, **27**, 47(1928).
(8) Masuoka, D. T., and Saunders, P. R., *Proc. Soc. Exptl. Biol. Med.*, **74**, 879(1950).
(9) Nakada, H. I., Wolfe, J. B., and Wick, A. N., *J. Biol. Chem.*, **226**, 145(1957).
(10) Quastel, J. H., and Wooldridge, W. R., *Biochem. J.*, **22**, 689(1928).

Stability of Vitamins A, B_1, and C in Selected Vehicle Matrices

By KEE-NENG WAI, H. GEORGE DEKAY, and GILBERT S. BANKER

The relative stability of vitamins A, B_1, and C in eight commonly used solid vehicle matrices was determined. Vitamin preparations, each containing one vitamin and one solid matrix, were first subjected to accelerated aging tests and were evaluated for their loss in vitamin contents. The results indicated that a diluent moisture content in excess of one per cent played an important role in determining the stability of these preparations. Mannitol and lactose were found to be superior solid diluents on the basis of the stability studies conducted. The influence of formulation (use of coated or U.S.P.-grade vitamins), method of combination, and manufacturing procedures were studied for their effect on vitamin stability in an uncoated tablet dosage form.

IN RECENT years many new, uncoated multivitamin tablets have appeared on the market. The majority of these products have been chewable, pediatric vitamin tablets, although conventional vitamin tablet formulations in uncoated, compression-coated, and film-coated form are also making their appearance. The advantages of uncoated vitamin tablets over vitamin liquids, capsules, and coated tablets are numerous, obvious, and of considerable economic significance. The development of commercially feasible uncoated vitamin tablet formulations is being made possible by at least three advances: (*a*) the application of new excipient materials to solid vitamin products; (*b*) the commercial availability of new, more stable chemical forms of vitamins, and coated, wax imbedded, and other modifications of vitamin materials, and (*c*) studies which accurately describe the stability, reaction kinetics, and incompatibilities of the various vitamins.

Received March 29, 1962, from Purdue University, School of Pharmacy, Lafayette, Ind.
Accepted for publication May 24, 1962.
Abstracted from a thesis submitted to the Graduate School of Purdue University, by K. N. Wai in partial fulfillment of the requirements for the Master of Science degree.
Presented to the Scientific Section, A.PH.A. Las Vegas meeting, March 1962.

The reports of McLaughlan, Clark, Campbell, and McLeod (1–3) have revealed that vitamins A, B_1, B_{12}, and pantothenic acid in many commercial multivitamin products are quite unstable. Ascorbic acid is known to be incompatible with riboflavin, vitamin B_{12}, and folic acid (4). Thiamine reacts with riboflavin (5) and folic acid (6). Extensive investigations of the interactions among thiamine, niacinamide, and vitamin B_{12} have also been carried out in the past few years (7–14).

Accelerated aging tests of vitamin products have been conducted by Garrett (15) and Yamamoto (16). These workers related the stability of various vitamins with storage time and temperature and found that the degradation of ascorbic acid, thiamine, vitamin B_{12}, and pantothenyl alcohol was a first-order reaction and the degradation rate of vitamin A was independent of concentration. They also showed that at 45° the degradation of vitamin A in 8 weeks and ascorbic acid in 6 weeks was approximately equivalent to their degradation at room temperature for 1 year. Taub and Katz (17) have indicated that thiamine decomposition in tablets and capsules, after storage at 45°

for 3 weeks, was comparable to a year of shelf life.

While a good deal has been learned about vitamin stability in recent years, no comprehensive report of the stability of the less stable vitamins in common, solid vehicles is in the literature. Such information could be of value in the development of uncoated tablets, whether designed to be chewed or swallowed, compression-coated tablets in which a portion of the vitamin formulation is in the coat or all the vitamin formulation is in the coat and the core is comprised of minerals, or film-coated tablets in which the film adds pharmaceutical elegance but affords incomplete protection to oxygen or water vapor transmission.

It was the objective of this research to study the stability of three selected, relatively unstable, vitamins in different solid vehicle matrices and to study various formulations and manufacturing procedures which might relate to the stability of solid multivitamin products.

EXPERIMENTAL

Materials.—The vitamins A and D[1] used in this study were in the form of a granulation containing gelatin, sugar, and starch with a labeled content of 500,000 U.S.P. units (150 mg.) of vitamin A acetate and 50,000 U.S.P. units of vitamin D_2 per gram of granulation. The other vitamins used were U.S.P.-grade chemicals or coated vitamins in the form of thiamine mononitrate Mercote,[2] niacinamide Mercote, riboflavin Mercote, and ascorbic acid coated with 5% ethylcellulose type N.[3]

The diluents used included mannitol, lactose, sucrose, aluminum hydroxide dried gel, kaolin, starch, calcium sulfate, and hydrous dextrose. All of these were U.S.P.- or N.F.-grade chemicals with the exception of the calcium sulfate which was in the form of $CaSO_4 \cdot 2H_2O$.[4] The lubricant in all of the preparations was magnesium stearate, U.S.P.

Equipment.—The equipment used to prepare the solid vitamin products included a kitchen-aid model Hobart mixer[5] for the mixing of powders and granulations; stainless steel wire screens for the reduction of particle size and mixing of powders (30 mesh) and for granulating and resizing (20 mesh); the Stokes oscillating granulator,[6] fitted with a 12-mesh screen, for dry granulating; and a Stokes B2 rotary tablet machine[6] equipped with $^3/_8$-inch standard concave punches and dies and $^5/_8$-inch flat-face punches and dies, for tableting and slugging, respectively.

The instruments used for the assays of the vitamins included a Beckman model DU spectrophotometer[7] for the measurement of absorbance of vitamin A solution and a Fisher nefluorophotometer[8] for the measurement of the fluorescence of thiochrome.

A constant-temperature electric oven, adjusted to 45° (±2°) was used to store the tablets for the accelerated aging tests. The other equipment used included the Monsanto hardness tester[9] and the Cenco moisture balance.[10]

Methods of Assay for Vitamins A, B_1, and C.—The official methods for the assay of these three vitamins as described in the monograph of decavitamin tablets U.S.P. were used throughout the course of this study. However, some modifications were made. In the assay of vitamin A, the saponification of vitamin A acetate was carried out in 7 ml. of glycerin, 25 ml. of alcohol, and 3 ml. of 50% potassium hydroxide solution. The glycerin was used because it had a greater softening effect than alcohol on the brand of commercial vitamin A granules used. All calculations for vitamin A content were based on the absorbance at 325 mμ instead of the three points prescribed by the U.S.P. In the assay of vitamin B_1, the concentration of the "Standard Preparation" was about 1.0 mcg. per ml. instead of 0.2 mcg. per ml. as suggested in the U.S.P. This change was made in order to permit the measurement of fluorescence at the optimum sensitivity range of the equipment employed in this work. The alcoholic extracts of the vitamin A and aqueous extracts of vitamin B_1 were transferred into 100-ml. volumetric flasks and brought to volume with dilute alcohol or water before filtration. Exactly 50 ml. of the filtrates was collected for the assays.

Study of the Stability of Vitamins A, B_1, and C in Solid Matrices.—Thirty-six samples, each containing one vitamin, one diluent, and 0.5% magnesium stearate, were separately prepared with the three vitamins and 12 commonly used solid matrices. The solid matrices included mannitol, sucrose, lactose, calcium sulfate, aluminum hydroxide dried gel, starch, kaolin, dextrose, and combinations of 80% mannitol with 20% each of starch, aluminum hydroxide dried gel, sucrose and dextrose. Each gram of sample contained 4 mg. of vitamin A in the form of dry vitamin A acetate with D, or 5 mg. of thiamine hydrochloride, U.S.P., or 300 mg. of ascorbic acid U.S.P. These combinations were compressed on a rotary-tablet machine into one-gram disks, $^5/_8$ inch in diameter. These disks were employed to individually study the stability of the vitamins in the various matrices in a compacted, simulated tablet condition. They were kept in six-ounce, brown, dry-square bottles and stored at 45° and at room temperature. The vitamins in these preparations were assayed as follows: (*a*) prior to storage, (*b*) after 1 month's storage at 45°, (*c*) after 3 months' storage at room temperature, and (*d*) after 3 months' storage at 45°.

Study of the Stability of Multivitamin Chewable Tablets.—Following the study of vitamin stability in various solid matrices, one of the tablet diluents was selected for subsequent research dealing with the stability of multivitamin chewable tablets. Utilizing mannitol as the selected diluent, six batches of tablets were prepared. These tablets differed

[1] Hoffmann-La Roche, Inc., Nutley, N. J.
[2] Merck & Co., Inc., Rahway, N. J.
[3] Hercules Powder Company, Wilmington, Del.
[4] Miles Laboratory, Inc., Elkhart, Ind.
[5] Hobart Manufacturing Co., Troy, Ohio.
[6] F. J. Stokes Corporation, Philadelphia, Pa.
[7] Beckman Instruments, Inc., Fullerton, Calif.
[8] Fisher Scientific Company, New York, N. Y.
[9] Monsanto Chemicals, St. Louis 4, Mo.
[10] Central Scientific Company, Chicago, Ill.

TABLE I.—A FORMULA FOR A MULTIVITAMIN CHEWABLE TABLET (TABLET NO. 1)

Ingredients	Quantity in Gm.	Labeled Content per Tablet	Overage, %
Granulation 1			
Vitamin A } granules	11.00	5000 Units	10
Vitamin D }		500 Units	10
Thiamine hydrochloride	1.65	1.5 mg.	10
Mannitol	94.70	...	...
Magnesium stearate	0.54	...	...
Granulation 2			
Ascorbic acid	66.00	60 mg.	10
Mannitol	189.50	...	...
Magnesium stearate	1.28	...	...
Granulation 3			
Niacinamide	10.50	10 mg.	5
Riboflavin	1.10	1 mg.	10
Cobalamin concentrate (1:1000)	2.20	2 mg.	10
Pyridoxine hydrochloride	2.20	2 mg.	10
Calcium pantothenate	4.50	3 mg.	50
Mannitol	94.70	...	...
Magnesium stearate	0.57	...	...
Running powder and flavors			
Magnesium stearate	2.60	...	...
Orange-dry flavor	5.00	...	...
Pineapple-dry flavor	5.00	...	...
Saccharin	7.50	...	...
To make 1000 tablets			

from one another in the forms of vitamins used, the methods of vitamin combination, and the method of manufacture. All of these formulas contained equal labeled quantities and overages of the vitamins. To prepare the tablets, the vitamins which were known to be mutually incompatible were granulated separately with a part of the mannitol and lubricated with magnesium stearate. One of the typical working formulas is given in Table I and the composition and methods of manufacture of the six batches of tablets are summarized in Table II.

These multivitamin chewable tablets were assayed immediately after manufacture and after storage for 1 month at 45°. Three commercial chewable tablets were studied simultaneously for the purpose of comparison. The hardness of these tablets and any changes in physical appearance with aging were also observed.

RESULTS AND DISCUSSION

The moisture contents of the solid vehicles used in this work are shown in Table III.

TABLE III.—MOISTURE CONTENT OF SOLID VEHICLES STUDIED

Vehicle	Moisture, %[a]
Mannitol	0.2
Sucrose	0.2
Lactose	1.0
Aluminum hydroxide	15.0
Starch	8.0
Calcium sulfate	2.7
Kaolin	1.0
Dextrose	8.0
Mannitol and sucrose	0.2
Mannitol and aluminum hydroxide	2.9
Mannitol and starch	1.8
Mannitol and dextrose	1.6

[a] Moisture contents were determined using the Cenco moisture balance at a pan temperature of 90°.

Tables IV, V, and VI show that vitamin A was most stable in manitol and lactose; thiamine was stable in mannitol, sucrose, lactose, and kaolin; and ascorbic acid appeared to have good stability in all of the diluents with the exception of aluminum hydroxide. Most of the ascorbic acid preparations, however, changed color during the storage period. The color change was not universally indicative of a loss of vitamin potency. Mannitol, sucrose, and lactose were the only three diluents in which no color change was observed with ascorbic acid under the conditions of storage.

Table IV also shows that the degradation of vitamin A at 45° for 1 month was usually slightly greater than its degradation after storage at room temperature for 3 months. Accordingly, it is expected that the degradation of vitamin A at 45° for 3 months might be approximately equal to its degradation at room temperature for a year.

Thiamine appears to be much more thermolabile than vitamin A. The accelerated aging test of the vitamin B_1 preparations after 1 month clearly indicated the role of the diluent on the stability of the vitamin.

The degradation of vitamins A, B_1, and C is accelerated by the presence of moisture in the solid vehicles. In mannitol, sucrose, lactose, and kaolin, which contained not more than 1% moisture, these vitamins were quite stable. In starch, aluminum hydroxide, and dextrose which contained 8, 15, and

TABLE II.—DESIGNATION OF TABLET COMPOSITION AND METHOD OF MANUFACTURING

Tablet Number	Form of Vitamins	Granulation Method	Granulation Agent	Vitamin-Granulation Combinations 1[b]	2	3
1	USP Powder	Dry	...	A, D, & B_1	C	Other B Vit.
2	Coated[a]	Dry	...	A, D, & B_1	C	Other B Vit.
3	Coated	Dry	...	A & D	B_1 & C	Other B Vit.
4	Coated	Wet	Alcohol	A & D	B_1 & C	Other B Vit.
5	Coated	Wet	Dil. Alc.	A & D	B_1 & C	Other B Vit.
6	Coated	Wet	Water	A & D	B_1 & C	Other B Vit.

[a] The coated vitamins included the Mercotes and the ethylcellulose coated ascorbic acid. The other B vitamins in the formula were uncoated U.S.P. grade. Since the coated vitamins contained less active ingredient than an equal weight of U.S.P.-grade vitamin, a correspondingly larger amount of coated vitamin was taken and the weight of the diluent in these formulations was reduced so that each tablet at the same theoretical weight would contain the same potency of each vitamin.
[b] The vitamins A and D in formulas 3 to 6 were not granulated with the diluent. The vitamin granules were added directly to granulations 2 and 3.

TABLE IV.—STABILITY OF VITAMIN A IN SOLID VEHICLE MATRICES

Vehicle	Initial Activity, mg./Gm.	Activity Retained after Storage: 30 Days at 45°C. mg./Gm.	%	90 Days at 45°C. mg./Gm.	%	90 Days at Room Temp. mg./Gm.	%	Color after Storage
Mannitol	4.16	3.75	90	3.06	74	...	...	white
Sucrose	3.97	3.18	80	2.65	67	...	...	white
Lactose	4.08	3.63	89	3.09	76	3.47	85	white
Calcium sulfate	3.67	2.75	75	2.43	66	2.92	80	white
Aluminum hydroxide	4.03	2.95	73	2.29	56	...	...	brown
Starch	3.99	2.37	59	2.00	50	3.37	85	yellow
Kaolin	3.60	2.71	75	2.42	67	...	...	brown
Dextrose	4.08	3.32	81	2.75	67	...	...	buff
Mannitol and sucrose	3.77	3.33	88	2.73	72	3.40	90	white
Mannitol and aluminum hydroxide	3.75	2.26	60	2.25	60	3.30	88	brown
Mannitol and starch	3.86	2.71	70	2.38	62	3.24	84	buff
Mannitol and dextrose	3.87	3.21	83	2.77	72	...	...	buff

TABLE V.—STABILITY OF VITAMIN B_1 (U.S.P. POWDER) IN SOLID VEHICLE MATRICES

Vehicle	Initial Activity, mg./Gm.	Activity after Storage: 30 Days at 45°C. mg./Gm.	%	90 Days at Room Temp. mg./Gm.	%	Color after Storage
Mannitol	5.43	5.42	100	5.30	98	white
Sucrose	5.16	5.21	100	5.12	99	white
Lactose	5.74	5.79	100	...	...	white
Calcium sulfate	5.61	4.94	88	5.58	99	white
Aluminum hydroxide	5.75	2.63	46	5.65	98	white
Starch	5.12	0.91	18	5.00	98	white
Kaolin	4.07	4.05	100	4.20	100	brown
Dextrose	4.85	0.63	13	4.24	87	white
Mannitol and sucrose	4.68	4.50	96	4.42	94	white
Mannitol and aluminum hydroxide	5.38	1.55	29	5.01	93	white
Mannitol and starch	5.46	1.73	32	4.98	91	white
Mannitol and dextrose	5.05	1.02	20	4.45	88	white
Mannitol (and coated vitamin B_1)	6.13	6.14	100	...	...	white

TABLE VI.—STABILITY OF VITAMIN C (U.S.P. GRANULAR) IN SOLID VEHICLE MATRICES

Vehicle	Initial Activity, mg./Gm.	Activity after Storage for 90 Days at 45° C. mg./Gm.	%	Color after Storage for 90 Days at 45°C.
Mannitol	289	290	100	white
Sucrose	282	279	99	white
	192	205	100	white
Lactose	307	298	97	white
	202	200	99	white
Aluminum	282	187	66	brown
hydroxide	212	156	74	brown
Starch	310	315	100	yellow
	207	204	99	yellow
Calcium	293	291	99	buff
sulfate	206	209	100	buff
Kaolin	285	287	100	brown
	191	181	95	brown
Dextrose	282	289	100	straw
	206	196	95	straw
Mannitol and sucrose	292	281	96	white
Mannitol and aluminum hydroxide	299	296	99	brown
Mannitol and starch	301	296	98	buff
Mannitol and dextrose	296	295	100	yellow

8% moisture, respectively, the vitamins were generally very unstable.

It is believed that kaolin adsorbed a part of the thiamine and caused the apparent low activity of thiamine in this combination. Also, in the assays of vitamin A in lactose and glucose, excessive caramelization of the sugars was observed. The light absorbance of the isopropanol extracts of these preparations measured at wavelengths of 310 mμ, 325 mμ, and 334 mμ indicated the presence of interference materials. However, no correction was made for this interference since all data were calculated by the same method according to the light absorbance of the sample at 325 mμ.

Table VII shows that maximum stability was achieved in Tablet No. 2 by using the dry granulation method and by granulating vitamins A and B_1 separately from the other vitamins. Tablets No. 3, 4, 5, and 6 each showed approximately the same degree of stability, but tablets No. 5 and 6, granulated with dilute alcohol and water, respectively, changed color quite rapidly. The tablets prepared by double compression had no apparent change in color after storage at 45° for a month and were generally softer than those prepared by the wet-granulation method. These results indicated that the use of water as the granulating agent or granulating agents containing water caused a more rapid change in the color of the solid multivitamin products than when no water was added. The findings

TABLE VII.—STABILITY OF VITAMINS A, B_1, AND C IN MULTIVITAMIN CHEWABLE TABLETS

Tablet[a] Number	Hardness, Kg.	Color Stability	Vitamins	Labeled Content, mg./Gm.	Initial Activity, mg./Gm.	Activity after Storage for 30 Days at 45°C. mg./Gm.	%
1	2.2	stable[c]	A	3.0	2.96	2.70	91.4
			B_1	3.0	3.43	3.38	98.5
			C	120	136.0	136.5	100
2	3.1	stable	A	3.0	2.96	2.81	95.1
			B_1	3.0	4.03	3.87	96.0
			C	120	132.6	135.2	100
3	3.3	stable	A	3.0	3.43	3.06	89.2
			B_1	3.0	3.99	3.92	98.2
			C	120	138.8	137.4	99.0
4	6.5	stable	A	3.0	3.58	3.16	88.3
			B_1	3.0	3.98	3.86	97.0
			C	120	135.8	136.5	100
5	8.1	darkened slowly	A	3.0	3.28	2.84	87.7
			B_1	3.0	3.95	3.85	97.2
			C	120	134.4	132.9	98.9
6	7.3	darkened	A	3.0	3.48	3.06	88.0
			B_1	3.0	3.89	3.89	100
			C	120	134.0	132.8	99.1
7	3.1	darkened slowly	A	2.75	3.61	2.97	93.9
			B_1	5.5	20.55	18.22	88.7
			C	92	104.7	99.5	95.0
8[b]	8.0	darkened slowly	A	3.20	3.46	4.04	92.7
			B_1	2.6	3.58	3.23	90.2
			C	123	146.9	148.6	100
9[b]	3.2	darkened slowly	A	4.35	4.82	4.26	88.5
			B_1	5.8	7.03	6.98	99.3
			C	172	187.4	184.0	98.2

[a] See Table II. [b] A commercial multivitamin chewable tablet. [c] "Stable" means no apparent change in color during the period of accelerated aging test.

of Table VII also showed that the manner in which the vitamins were combined was as important as the granulating method used (wet or dry) or the granulating agent used.

CONCLUSIONS

Of the eight commonly used diluents evaluated, mannitol appeared to be the best diluent with regard to the stability of the vitamin products studied with lactose being a close second. A diluent moisture content in excess of 1% played an important part in catalyzing the degradation of vitamins B_1 and C. Some chemical change in the tablets containing ascorbic acid is manifested by an intense discoloration of the products, although the actual assay values may not be significantly reduced. Hence, the choice of a nonhygroscopic solid vehicle is essential in formulating a stable, uncoated, multivitamin tablet.

The stability of uncoated multivitamin tablets was found to be improved by the following techniques:

1. Use of coated ascorbic acid, thiamine, riboflavin, and niacinamide. This process enhances the stability of the vitamins.

2. Preparation of the granulations of the incompatible vitamins separately with a portion of the inert matrices. The best stability results were obtained when the vitamins A, D, and B_1 were granulated with one-fourth of the matrix, the vitamin C with one-half of the matrix, and the remaining B vitamins with one-fourth of the matrix. These three granulations were blended together in the proper proportion before compression.

3. Avoiding use of water as a granulating agent. Vitamin tablets granulated with water or dilute alcohol discolored rather rapidly, however the assays of these tablets indicated no significant difference in stability from those granulated with alcohol or prepared by the dry-slugging method.

REFERENCES

(1) McLaughlan, J. M., Clark, J. A., and Campbell J. A., *Can. Pharm. J.*, **84**, 572(1951).
(2) Clark, J. A., McLaughlan, J. M., and Campbell, J. A., *ibid.*, **86**, 796(1953).
(3) Campbell, J. A., and McLeod, H. A., THIS JOURNAL, **44**, 263(1955).
(4) Gambier, A. S., and Rahn, E. P. G., *ibid.*, **46**, 134 (1957).
(5) Scheindlin, S., *Drug Cosmetic Ind.*, **83**, 46(1958).
(6) Biamonte, A. R., and Schneller, G. H., THIS JOURNAL **40**, 313(1951).
(7) Blitz, M., Eigen, E., and Gunsberg, E., *ibid.*, **43**, 651(1954).
(8) Macek, T. J., and Feller, B. A., *ibid.*, **44**, 254(1955).
(9) Feller, B. S., and Macek, T. J., *ibid.*, **44**, 662(1955).
(10) Dony, J., and Coter, J., *J. Pharm. Belg.*, **11**, 186 (1956).
(11) Blitz, M., Eigen, E., and Gunsberg, E., THIS JOURNAL, **45**, 803(1956).
(12) Ravin, L. J., and Doerge, R. F., *ibid.*, **48**, 425(1959).
(13) Mukherjee, S. L., and Sen, S. P., *J. Pharm. Pharmacol.*, **11**, 26(1959).
(14) Gambier, A. S., and Rahn, E. P. G., THIS JOURNAL, **47**, 356(1958).
(15) Garrett, E. R., *ibid.*, **45**, 171(1956).
(16) Yamamoto, E., *et al.*, *Annual Report of Shionogi Research Laboratory, No.* **7**(1), 55(1957).
(17) Taub, A., Katz, I., and Katz, M., THIS JOURNAL, **38**, 119(1949).