mercury[3] (3.52 g., 0.01 mole) mixed with 3.52 g. of Celite was suspended in 300 ml. of toluene by vigorous stirring and dried azeotropically by distilling 100 ml. of the toluene. 3,5-Di-O-(*p*-chlorobenzoyl)-2-deoxy-D-ribosyl chloride[15] (8.60 g., 0.02 mole) was then added in one portion and the mixture refluxed 8 min. After chilling to room temperature, the mixture was filtered through a small plug of glass wool and 1.5 l. of petroleum ether (b.p. 35–60°) was added. The clear supernate was decanted from the precipitated gum and discarded. The gum was dissolved in chloroform, washed with 30% potassium iodide solution, then water, and dried over magnesium sulfate. After filtration, the chloroform was evaporated and the resulting sirup heated at 100° *in vacuo* to leave the crude product as a tan glass, 4.37 g. (80%).

Isolation of the β-Anomer III.—The glass (4.2 g.) resulting from a condensation reaction was dissolved in methylene chloride and concentrated to a volume of 10 ml. A white powdery precipitate was removed (0.17 g.) which was identified as *p*-chlorobenzoic acid. After the solvent was removed *in vacuo* the sirup was dissolved in hot absolute ethanol, and on cooling an oil separated. After freezing in Dry Ice, the mixture was set aside for 16 hr. at room temperature. A fine white crystalline precipitate was separated from gummy material. This weighed 0.44 g. (8%), m.p. 145–152°. After recrystallization from 50 ml. of hot absolute ethanol, it melted at 153–155° (0.33 g.). An additional crystallization gave the analytical sample in white needles, m.p. 154–155°.

Anal. Calcd. for $C_{26}H_{22}Cl_2N_2O_7$: C, 57.26; H, 4.07; N, 5.14. Found: C, 57.09; H, 4.14; N, 4.77.

Although the crystallizations described above were not always successful it was the only technique found which permitted the isolation of a pure anomeric blocked nucleoside. During one series of experiments, 1.51 g. of crystalline material consisting mostly of the β-anomer III was collected and used in the following experiment.

Isolation of the β-Anomer V, 5-Allyl-2′-deoxyuridine.—The "purified" β-anomer III (1.51 g., 2.77 mmoles) was placed in a tube containing 60 ml. of absolute ethanol previously saturated with ammonia at 0°. The tube was sealed and heated overnight at 100°. After cooling, the tube was opened and the ethanol and ammonia were evaporated to leave a crystalline mass. Water (75 ml.) and chloroform were added and the aqueous layer extracted at least 5 times with 50-ml. portions of chloroform. Evaporation of the aqueous layer gave a tan gum (0.74 g., 100%) which could not be crystallized.

The gum (0.74 g.) was subjected to partition column chromatography on a Celite® 545 column using an ethyl acetate–water system according to a previously described procedure.[3] On the column used (45 × 2.7 cm.), materials which were colored and absorbed ultraviolet light were eluted with the first 15 ml. of eluent and discarded. The next 170 ml. of eluent contained nothing. Material absorbing ultraviolet light at 267 mμ was eluted during the passage of an additional 150 ml. of organic phase. Evaporation of the solvent gave 0.65 g. (87%) of pale yellow sirup. This was dissolved in 10 ml. of hot ethyl acetate and on cooling an oil separated which crystallized on standing during 16 hr. The tiny white crystals weighed 0.45 g. (61%), m.p. 116–118°. An additional crystallization gave the analytical sample, m.p. 116–118°.

N.m.r. spectra demonstrated that this was the β-anomer of 5-allyl-2′-deoxyuridine, $[\alpha]^{25}D$ +11.9° (*c* 0.44, water); $\lambda_{max}^{pH\ 7}$ 268 mμ (ε 9450); $\lambda_{min}^{pH\ 7}$ 236 mμ (ε 2440); $\lambda_{max}^{pH\ 13\ (0.1\ N\ NaOH)}$ 267 mμ (ε 6920); $\lambda_{min}^{pH\ 13\ (0.1\ N\ NaOH)}$ 246 mμ (ε 4390); $\lambda_{max}^{pH\ 14\ (1\ N\ NaOH)}$ 267 mμ (ε 7260); $\lambda_{min}^{pH\ 14\ (1\ N\ NaOH)}$ 246 mμ (ε 4440).

Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.29; H, 6.01; N, 10.36.

Alumina Column Chromatography of Anomers III and IV.—The crude blocked nucleosides from three condensation reactions were combined (13.1 g. total) and dissolved in benzene. The solution was applied to a column containing 400 g. of alumina[16] in benzene. Additional benzene (14.5 l.) was passed through the column until the eluent was free from solids or substances which absorbed ultraviolet light. From the benzene fractions there was obtained 6.9 g. (54% of the material applied to the column) of sirup that contained no nucleosides and this was discarded.

It had been observed that the passage of graded mixtures of benzene–methylene chloride eluted anomers III and IV but failed to effect a separation. Other combinations of solvents gave similar results. After anomers III and IV were eluted, solvents with higher eluting power did not remove additional material.

Therefore, on the column described here, benzene was replaced by ethyl acetate as eluent and the anomers III and IV were eluted and recovered as a tan glass (2.9 g., 21% of the sample applied to the column). The remaining 3.3 g. (25%) of the sample could not be recovered.

Curiously, this purified mixture of anomers III and IV could not be fractionally crystallized in a satisfactory manner.

Isolation of the α-Anomer VI.—The mixture of anomers III and IV obtained in the preceeding experiment (2.90 g.) was deacylated with ethanolic ammonia by the procedure used for the preparation of the β-anomer. The crude nucleosides weighed 1.44 g. (101%). The mixture was chromatographed on a Celite column by the usual procedure, and evaporation of the solvent gave a white crystalline mass which was recrystallized from 100 ml. of hot ethyl acetate. Clusters of white needles (0.65 g.) separated; m.p. 161–165°. An additional crystallization from 90 ml. of ethyl acetate gave 0.42 g. of analytically pure material, m.p. 164–167°; $[\alpha]^{25}D$ +20.5° (*c* 0.56, water); $\lambda_{max}^{pH\ 7}$ 268 mμ (ε 9900); $\lambda_{min}^{pH\ 7}$ 236 mμ (ε 2290); $\lambda_{max}^{pH\ 13\ (0.1\ N\ NaOH)}$ 267 mμ (ε 7350); $\lambda_{min}^{pH\ 13\ (0.1\ N\ NaOH)}$ 245 mμ (ε 4380) $\lambda_{max}^{pH\ 14\ (1\ N\ NaOH)}$ 267 mμ (ε 7660); $\lambda_{min}^{pH\ 14\ (1\ N\ NaOH)}$ 245 mμ (ε 4530).

Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found: C, 53.45; H, 5.94; N, 10.33.

Thin Layer Chromatography.—Glass plates were coated with silica gel G, dried at 110° for 0.5 hr., then cooled and exposed to the atmosphere for 2 hr. or more. Maximum separation was achieved using ethyl methyl ketone as solvent, which gave R_f values of 0.45 (α-anomer) and 0.57 (β-anomer). Detection was by means of a 2% aqueous potassium permanganate spray The compounds appeared instantly as cream-colored spots on purple background. The color fades after 5–10 min.

Acknowledgment.—We thank Dr. James G. Colson of the Buffalo Medical Group for assistance in the determination of the n.m.r. spectra.

(15) J. J. Fox, N. Yung, I. Wempen, and M. Hoffer, *J. Am. Chem. Soc.*, **83**, 4066 (1961). It is important that pure halogenose be used in the condensation reaction. Approximately 45 g. of crude halogenose can be dissolved in 500 ml. of hot carbon tetrachloride. A dark insoluble oily impurity is removed by several filtrations. Because of the instability of the halogenose, the recrystallization should be carried out as rapidly as possible.

(16) Woelm® alumina was purchased from Alupharm Chemicals, P. O. Box 755, New Orleans, La. Neutral alumina of activity grade IV (contains 10% water) was used. Directions for the preparation are supplied with the product.

Preparation of D- and L-Octopamine[1]

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The natural occurrence of octopamine (norsympatol, norsynephrine, α-(aminomethyl)-4-hydroxybenzyl alcohol) was first reported by Erspamer[2] who identified it as a constituent of extracts of salivary glands of the octopus. He showed that natural octopamine has the same configuration as natural D-(−)-norepinephrine (*l*-noradrenaline). The pharmacological responses given by purified octopamine were qualitatively the same as those of racemic octopamine, while quantitatively it appeared to be about twice as active as the synthetic compound. The recent demonstration that octopamine occurs in tissues of mammals[3] made it desirable to separate synthetic material into its optical isomers so that their physical properties might be de-

(1) This work was supported in part by Research Grant MH-02278 from the National Institute of Mental Health, U. S. Public Health Service.

(2) V. Erspamer, *Nature*, **169**, 375 (1952).

(3) Y. Kakimoto and M. D. Armstrong, *J. Biol. Chem.*, **237**, 422 (1962).

TABLE I

SALTS OF OCTOPAMINE ISOMERS WITH *d*-TARTARIC ACID

Octopamine isomer	Ratio, amine:acid, mmoles	Salt formed Amine isomer-acid	Yield, %	M.p., °C	$[\alpha]^{25}D$ (c 1, water)	Analysis of salt, % N calcd.	N found
DL	1:1	DL-*d*-tartrate	67	190–195 dec.		6.14	5.92
DL	2:1	DL-*d*-tartrate	96	195–200 dec.	+14.5°	6.14	5.94
D-(−)	1:1	D-(−)-*d*-tartrate	87	179–181 dec.	+24.4°	6.14	5.99
L-(+)	1:1	L-(+)-*d*-bitartrate	85	169–170 dec.	+44.6°	4.62	4.96
L-(+)	1:2	L-(+)-*d*-bitartrate	83	168–169 dec.	+43.9°	4.62	4.58
L-(+)	1.3:0.5	L-(+)-*d*-tartrate	100	194–195 dec.	+51.9°	6.14	6.14

termined and their pharmacological properties might be compared. Because of the much greater proportionate increase in the amount of octopamine than other amines in tissues of animals given monoamine oxidase inhibitors[3] the possibility might be considered that the increase in octopamine might be responsible for some of the clinical changes in patients who have been given monoamine oxidase inhibitors.[4]

Resolution of DL-octopamine was attempted by fractional crystallization of its salts with several optically active acids. These included mandelic, malic, quinic, *d*-tartaric, and *d*-10-camphorsulfonic acid. Crystalline salts could be obtained readily with all these acids, but there appeared to be a significant enrichment in one of the optical isomers only with *d*-10-camphorsulfonic acid. The behavior with *d*-tartaric acid was particularly disappointing, since DL-norepinephrine is readily resolved by fractional recrystallization of the *d*-bitartrates.[5] The behavior of DL-octopamine and of its optically active forms with *d*-tartaric acid was reinvestigated when pure D- and L-octopamine were available. The ineffectiveness of *d*-tartaric acid as a resolving agent is readily understood with the aid of the data listed in Table I. D-, L-, and DL-octopamine all form *d*-tartrates readily rather than *d*-bitartrates, so that two molecules of amine are associated with one molecule of tartaric acid. The physical properties of the DL-salt, in comparison with those of the pure D- and L-salts indicate that DL-octopamine *d*-tartrate crystallizes more readily than a mixture of D-octopamine *d*-tartrate and L-octopamine *d*-tartrate so that preferential crystallization of one of the latter salts cannot occur. It was possible to prepare a *d*-bitartrate from pure L-octopamine, but the salt is so much more soluble than the tartrates that it cannot be crystallized to effect a resolution of octopamine.

Several recrystallizations of the less soluble D-octopamine *d*-10-camphorsulfonate provided a good initial purification of the D-isomer. Pure D-salt could not be obtained by further recrystallization, however, probably because some racemization occurred when solutions were heated. The slightly impure D-octopamine regenerated from the salt was readily purified by recrystallization of the free base.

Octopamine enriched in the L-(+)-isomer was regenerated from the mother liquors which remained after separation of the less soluble D-camphorsulfonate and advantage was taken of the insolubility of the DL-octopamine *d*-tartrate to remove most of the remaining D-isomer. L-Octopamine sufficiently pure for recrystallization to yield pure material was obtained in this manner.

(4) "Amine Oxidase Inhibitors," *Ann. N. Y. Acad. Sci.*, **80**, 551 (1959).
(5) B. F. Tullar, *J. Am. Chem. Soc.*, **70**, 2067 (1948).

Experimental[6]

D-(−)-Octopamine.—To a solution of 50 g. of DL-octopamine (0.326 mole) and 76 g. of *d*-10-camphorsulfonic acid (0.326 mole) in 160 ml. of hot absolute ethanol was added 160 ml. of warm ethyl acetate and the resulting mixture was allowed to cool slowly and to stand at room temperature overnight; 61.0 g. (48%) of crystals was collected, m.p. 165–168° dec., $[\alpha]^{25}D$ +4.8° (*c* 1, water). Six further recrystallizations from the minimum amount of absolute ethanol in the same manner yielded 14.8 g. of camphorsulfonate, $[\alpha]^{25}D$ −8.0° (*c* 1, water). Further recrystallizations effected little further purification. The salt was dissolved in water and the solution was passed through a 2 × 12-cm. column of Amberlite CG-120 (H^+ form) (100–200 mesh). The resin was washed with water and the octopamine was eluted with 4 *N* ammonium hydroxide. The first 120 ml. of ammoniacal eluate was collected and concentrated *in vacuo* under nitrogen to a volume of 20 ml.; 5.4 g. of crystals was collected, $[\alpha]^{25}D$ −54.1° (*c* 1, 0.1 *N* hydrochloric acid). Recrystallization of this crop from hot water yielded 4.0 g. of D-(−)-octopamine, $[\alpha]^{25}D$ −56.0° (*c* 1, 0.1 *N* hydrochloric acid), −37.4° (*c* 1, water). Further recrystallization did not change these properties. Both D- and L-octopamine change at about 160° to a higher melting compound which melts above 250° dec.[7]

Anal. Calcd. for $C_8H_{11}NO_2$: N, 9.15. Found: N, 9.12.

D-(−)-Octopamine *d*-10-Camphorsulfonate.—Equimolar amounts of D-(−)-octopamine and *d*-10-camphorsulfonic acid were dissolved in the minimum amount of hot absolute ethanol, the solution was allowed to cool, and the salt was collected, m.p. 173–175° dec., $[\alpha]^{25}D$ −9.4° (*c* 1, water).

Anal. Calcd. for $C_{18}H_{27}NO_6S$: N, 3.64. Found: N, 3.77.

L-(+)-Octopamine.—All the mother liquors of the *d*-10-camphorsulfonic acid salt from the separation of D-(−)-octopamine were combined and evaporated to dryness. The residue was dissolved in 150 ml. of hot absolute ethanol and 150 ml. of ethyl acetate was added. After the solution had stood overnight at room temperature, 33 g. of camphorsulfonate was collected, $[\alpha]^{25}D$ +7.6° (*c* 1, water). The mother liquor was concentrated to dryness and the oily residue was dissolved in 200 ml. of water. This solution was cleaned with charcoal and octopamine was absorbed onto a 4 × 6-cm. column of Amberlite CG-120 resin and eluted as described above, 15.1-g. yield, $[\alpha]^{25}D$ +30.4° (*c* 1, 0.1 *N* hydrochloric acid). A mixture of 14.4 g. (0.094 mole) of this material and 14.1 g. of *d*-tartaric acid (0.094 mole) was dissolved in 40 ml. of hot water, 60 ml. of 95% ethanol was added, and the mixture was allowed to stand at room temperature for 24 hr., 7.3-g. yield of tartrate, $[\alpha]^{25}D$ +18.3° (*c* 1, water). The mother liquor was concentrated to complete dryness. The yellow residue was digested with 30 ml. of absolute ethanol to yield 15.5 g. of a pure white compound, $[\alpha]^{25}D$ +41.5° (*c* 1, water). Free octopamine was obtained from this salt by absorption onto a resin and elution as described above, yield 5.9 g.; $[\alpha]^{25}D$ +54.6° (*c* 1, 0.1 *N* hydrochloric acid). Recrystallization of this material from water yielded 4.8 g. of pure L-(+)-octopamine; $[\alpha]^{25}D$ +56.1° (*c* 1, 0.1 *N* hydrochloric acid), +37.2° (*c* 1, water).

Optically active octopamine may be stored as the free base or *d*-tartrate. The free base undergoes racemization slowly when it is heated above room temperature, while its solutions in mineral acid undergo racemization upon even gentle heating. This behavior is similar to that observed with optically active norepinephrine.[5] Aqueous solutions of the free base slowly darken when stored at room temperature in the light.

Salts of Octopamine Isomers with *d*-Tartaric Acid. The

(6) All melting points were made in open capillary tubes and are corrected.
(7) T. Kappe and M. D. Armstrong, *J. Org. Chem.*, **28**, 3551 (1963).

octopamine was dissolved in a minimum amount of hot absolute ethanol (3–5 ml.) and added to a solution of *d*-tartaric acid in sufficient hot ethanol to make a total volume of 6 ml. The resulting solution was allowed to stand in a refrigerator for 2 hr. and the salts were collected, washed with a small volume of absolute ethanol, and dried. The yields are based on the amount of octopamine used, with the exception of the single instance in which there was an excess of octopamine; in this case the yield is based upon the *d*-tartaric acid.

Pharmacological Studies with Octapamine Isomers.—The cardiovascular effects of the pure isomers were examined by Korol and Soffer.[8] They found that both isomers produced adrenergic cardiovascular responses in anesthetized dogs and cats as shown in Table II. The D-(−)-form was 3 times more potent

TABLE II[a]

AMOUNTS OF D-(−)- AND L-(+)-OCTOPAMINE AND *l*-NOREPINEPHRINE REQUIRED TO PRODUCE EQUIVALENT RESPONSES

Test	Animal	Octopamine isomer— D-(−)	L-(+)	*l*-Norepinephrine
Coronary flow	Dog	10–30 γ	30 γ	1 γ
Aortic flow (cardiac output)	Dog	100 γ	300 γ	4 γ
Blood pressure	Cat and dog	30 γ/kg.	100 γ/kg.	3 γ/kg.
Nictitating membrane	Cat	30 γ	100 γ	5 γ

[a] B. Korol and L. Soffer, personal communication.

than the L-(+)-form, but both isomers were markedly less potent than *l*-norepinephrine. They concluded that the responses were produced by a direct action of the octopamines on the cardiovascular system and were not dependent upon the release of adrenergic amines from the adrenal medulla or sympathetic nerve endings.

Acknowledgment.—Mrs. Kerin N. Yates carried out the nitrogen analyses reported here.

(8) B. Korol and L. Soffer, *The Pharmacologist*, **5**, 247 (1963).

4,4′-Dihydroxytriphenylacetic Acid

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Our interest in derivatives of hydroxytriphenylmethanes stems from the fact that several such compounds, such as phenolphthalein and *o*-(dihydroxybenzhydryl)benzyl alcohols, are good laxatives.[1]

Homolka[2] claims to have obtained some benzaurin from phenylglyoxylic acid and phenol at 120° in the presence of concentrated sulfuric acid. It was found in this laboratory that phenylglyoxylic acid reacted with phenol only in the presence of a condensing agent such as $ZnCl_2$, $SnCl_4$, or sulfuric acid. Best results were obtained at room temperature and in a solvent such as acetic acid. Without a solvent and at higher temperatures, the reaction was too violent, and only uncrystallizable tars were formed. The compound obtained in 83–96% yield was 4,4′-dihydroxytriphenylacetic acid (I). Its dimethyl ether, on decarboxylation, gave 4,4′-dimethoxytriphenylmethane in 86% yield.

When tested on the Rhesus monkey,[1] I showed no laxative activity. It was not tested for any other pharmacological activity.

(1) M. H. Hubacher, S. Doernberg, and A. Horner, *J. Am. Pharm. Assoc.*, **42**, 28 (1953); M. H. Hubacher, *J. Org. Chem.*, **23**, 1400 (1958).

(2) B. Homolka, *Ber.*, **18**, 988 (1885).

Experimental[3]

4,4′-Dihydroxytriphenylacetic Acid (I).—Concentrated sulfuric acid (2 ml.) was added to a solution, cooled to 20°, of 6.0 g. (0.04 mole) of phenylglyoxylic acid[4] (m.p. 65–66°) and 8.0 g. (0.085 mole) of phenol in 20 ml. of acetic acid. The mixture heated a few degrees and, within 12 hr., crystals formed. After keeping the mixture for 12 to 36 days at room temperature, a slurry with water was made, the crystals were filtered, washed free of SO_4^{-2}, and finally dried at 50° under reduced pressure. The acid (I), a light reddish powder, weighed 10.7–12.2 g. (83–95%) and melted at 251–254° dec.

I contained 0.5 mole of water when recrystallized from 41% ethanol or from 50% acetic acid, or by adding 20 ml. of benzene to a solution of 1 g. in 5 ml. of acetone.

Anal. Calcd. for $C_{20}H_{16}O_4 \cdot 0.5H_2O$: C, 72.95; H, 5.17. Found: C, 73.0 ± 0.6; H, 5.3 ± 0.2.

The acid slowly lost 3% in weight ($C_{20}H_{16}O_4 \cdot 0.5H_2O$, 2.7% H_2O) when dried to constant weight at 90° under high vacuum. It then was analyzed.

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 75.00; H, 5.00; mol. wt., 320. Found: C, 74.76; H, 4.97; neut. equiv., 327.

Anhydrous I melted at 257.8–259.4° decomposing to a red melt. The colorless acid turned orange on exposure to light. On heating I to 260°, water and CO_2 were evolved. After treating the dark residue with acetic anhydride, a small quantity of crystals, melting at 108–109°, was isolated. These were identified as 4,4′-diacetoxytriphenylmethane.

***d*-3-Methoxy-N-methylmorphinan Salt of I.**—A warm solution of 283 mg. of *d*-3-methoxy-N-methylmorphinan (m.p. 107–108°) in 3 ml. of 2-propanol was added to a warm solution of 320 mg. of I in 5 ml. of warm 2-propanol. The crystals which formed were filtered, washed with 2-propanol, and dried at 100° *in vacuo*. They weighed 570 mg., m.p. 258–259° dec.

Anal. Calcd. for $C_{38}H_{41}NO_5$: C, 77.15; H, 6.93; N, 2.36. Found: C, 76.63; H, 7.11; N, 2.01.

Diacetyl Derivative of I.—This compound was prepared from I, acetic anhydride, and sodium acetate and crystallized from 2-propanol. It melted at 250.4–252.3°.

Anal. Calcd. for $C_{24}H_{20}O_6$: C, 71.28; H, 4.95. Found: C, 71.37; H, 5.35.

The methyl ester of I was prepared by adding an ethereal solution of diazomethane to a solution of I in acetone. The compound was obtained as an oil, which slowly solidified. After crystallization from 1,2-dichloroethane or from xylene, the ester melted at 220.9–222.0°.

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.45; H, 5.39. Found: C, 75.21; H, 5.27.

Methylation of I.—Dimethyl sulfate (15 ml.) was added slowly to a stirred solution of 10 g. of I in 40 ml. of 5 *N* sodium hydroxide. The compound, which was insoluble in the aqueous sodium hydroxide, weighed 3.5 to 4.9 g. After crystallizations from ethanol, methyl 4,4′-dimethoxytriphenylacetate melted at 135.8–136.4°.

Anal. Calcd. for $C_{23}H_{22}O_4$: C, 76.24; H, 6.08. Found: C, 76.10; H, 6.21.

The precipitate, obtained by acidifying the alkaline filtrate, was recrystallized from 41% ethanol and yielded 5.1 to 7.0 g. of 4,4′-dimethoxytriphenylacetic acid (III), m.p. 194.3–196.7°.

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.86; H, 5.75. Found: C, 75.54; H, 5.88.

On heating 3.48 g. of III and 0.05 g. of basic cupric carbonate in 10 ml. of quinoline to 220°,[5] 0.422 g. of CO_2 was evolved, accounting for 96% of the carboxyl group, and 2.63 g. (86%) of 4,4′-dimethoxytriphenylmethane, m.p. 100.3–100.6°, was obtained.

Acknowledgment.—The author is indebted to Mr. Sidney Doernberg for the animal experiments.

(3) All melting points are corrected.

(4) Sold by S. B. Penick & Co. under the name of benzoylformic acid.

(5) M. H. Hubacher, *Ind. Eng. Chem. Anal. Ed.*, **21**, 945 (1949).