The Rosenmund reduction[4] of the chloride of methyl hydrogen phthalate has not previously been described; in fact, there is a statement in the literature[5] to the effect that the acid chloride on warming decomposes into phthalic anhydride and methyl chloride. We have found that this decomposition can be prevented almost entirely by limiting the time of the reaction of thionyl chloride with methyl hydrogen phthalate. Under controlled conditions methyl phthalaldehydate is readily obtained from the phthalate ester in a reproducible yield of about 80%. It can be converted into phthalaldehydic acid in 90% yield by acid hydrolysis; the over-all yield of this acid from phthalic anhydride is 60%.

### Experimental[6]

**Preparation of Methyl Hydrogen Phthalate.**—Phthalic anhydride (74 g., 0.5 mole) and absolute methanol (50 ml.) were refluxed for two hours. The excess methanol was distilled and 25 ml. of dry benzene was added. Distillation was continued for ten minutes to ensure removal of unreacted methanol, whose presence impeded crystallization of the product. The residue was filtered hot through a cotton plug into a one-liter flask and diluted to about 300 ml. with benzene. Ligroin (b. p. 30–60°) was added to the solution until the volume approximated 600 ml., at which point crystallization commenced. After standing overnight in the refrigerator, the product was collected, washed twice with 50-ml. portions of ligroin and dried in air, giving 75 g. (83%) of pure methyl hydrogen phthalate, m. p. 82–82.5° (lit.[7] 82.4–82.7°).

**Conversion of Methyl Hydrogen Phthalate to the Acid Chloride.**—A mixture of 18 g. (0.1 mole) of methyl hydrogen phthalate and 50 ml. of thionyl chloride (Eastman Kodak Co. White Label grade) was refluxed exactly one hour on the water-bath. (Excessive prolongation of this heating period led to the production of considerable quantities of phthalic anhydride in the reduction product.[5] Reduction of the reflux time likewise diminished the final yield of aldehyde considerably.) The excess thionyl chloride was removed under reduced pressure. Dry benzene (three 25-ml. portions) was then added and distilled off the acid chloride *in vacuo* three times to complete the removal of unreacted thionyl chloride. The acid chloride thus prepared was used immediately in the following step.

**Methyl Phthalaldehydate.**—The Rosenmund procedure followed was essentially that described in "Organic Reactions."[4] Xylene (*ca.* 60 ml. for a 0.1-mole run) was employed as the solvent for the reduction. The quinoline-S poison[4] was used to the extent of 0.2 ml. per 0.1 mole run, along with 2 g. of palladium-barium sulfate catalyst.[4] The reduction started more rapidly when the catalyst was added *after* the flask containing the xylene-poison mixture had been heated to boiling for ten minutes with a slow stream of dry hydrogen passing through the solution. When the heating bath was at 175°, the acid chloride was added through the top of the condenser. Reduction proceeded best at 175–180° (bath temperature) and was complete in two to three hours as evidenced by the cessation of hydrogen chloride evolution. After removal of the catalyst by filtration and of the xylene by distillation under reduced pressure the residue was fractionated *in vacuo* through a six-inch Vigreux column. Methyl phthalaldehydate was collected at 136–138° (13 mm.) or 146–147° (17 mm.)[3] as a colorless liquid having a pleasant odor; yield, 13.1–13.8 g. (80–84%); $n^{20}D$ 1.5411. (Auwers and Heinze[3] have reported values ranging from 1.5410 to 1.5423.)

The semicarbazone of methyl phthalaldehydate crystallized from dilute methanol in clusters of white, elongated prisms melting sharply at 194.5°.

*Anal.* Calcd. for $C_{10}H_{11}O_3N_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.19; H, 4.74; N, 18.88.

**Hydrolysis of Methyl Phthalaldehydate.**—Methyl phthalaldehydate (5.0 g., 0.0305 mole) was refluxed for twelve hours with 25 ml. of 6 *N* hydrochloric acid. The solution was concentrated by removing the water and hydrochloric acid under reduced pressure. The residue crystallized on cooling. It was recrystallized from 20 ml. of water to yield 4.1 g. (90%) of phthalaldehydic acid melting at 93–96° (dried in a vacuum desiccator). A second recrystallization raised the melting point to 96–97°. The semicarbazone of the acid melted at 202° as reported in the literature.[8]

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[4] Mosettig and Mozingo in Adams, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 362 ff.

[5] H. Meyer, *Monatsh.*, **22**, 578 (1901).

[6] Melting and boiling points are uncorrected. Microanalysis by Micro-Tech Laboratories, Skokie, Ill.

[7] Goggans and Copenhaver, THIS JOURNAL, **61**, 2909 (1939).

[8] Liebermann, *Ber.*, **29**, 179 (1896).

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## Brominations with Tetramethylammonium Bromide–Bromine Mixtures

BY L. FARKAS AND O. SCHÄCHTER

Recently the use of pyridine hydrobromide perbromide was suggested for certain brominations.[1] This note has prompted us to report some of our experiments, in which bromine was added to double bonds with the aid of tetramethylammonium bromide–bromine mixtures.

Tetramethylammonium bromide and bromine form two addition compounds with bromine, *viz.*, $(CH_3)_4NBr_3$ and $(CH_3)_4NBr_9$ with congruent melting points at 118.5 and 56.7°.[2]

These two compounds form a eutectic at 15.8° of the stoichiometric composition $(CH_3)_4NBr_{5.6}$; at 25°, in the composition range $(CH_3)_4NBr_{5.1}$ to $(CH_3)_4NBr_{6.2}$ the system is liquid and can be used for brominations. Particularly in such reactions which call for mild conditions, these liquids offer a number of advantages as brominating agents. Diluents and intensive cooling can be omitted. Weighing and dosage of the bromine in this form is simplified, and operations may be performed without a hood, because their bromine pressure at room temperature is only about 10 mm.

As an example, the preparation of 2,3-dibromopropanol will be described. The brominating agent contained 72.2% free bromine by weight, and was prepared as follows: 154 g. (1 mole) tetramethylammonium is dissolved in 500 g. of water, and 400 g. of (2.5 moles) bromine is added during a period of fifteen minutes under stirring. The temperature is maintained between 20 and 30° by cooling. A dark-red liquid (density, 2.33) is formed, which is drawn off the aqueous solution in a separating funnel. The yield is over 90%. However, if the aqueous solution is used again for the preparation of subsequent batches, a theoretical yield is practically achieved. To 58 g. (1 mole) of allyl alcohol, 222 g. of the brominating agent is slowly (within forty minutes) added under stirring.

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[1] Djerassi and Scholz, THIS JOURNAL, **70**, 417 (1948).

[2] The phase diagram of the system tetramethylammonium bromide and bromine has been studied in this Laboratory and the results will be published shortly.

The temperature is kept at 40° by cooling. During the reaction tetramethylammonium bromide precipitates and is recovered practically *in toto* by filtration. The precipitated salt is washed with ether and the etheric solution is added to the filtrate from which the 2,3-dibromopropanol is obtained by fractionation *in vacuo*. The yield is 85%.

When dibromopropanol is prepared according to Kohler[3], or according to Read and Hurst,[4] low temperatures and diluents such as carbon disulfide or alcohol and water must be employed and the yield is substantially lower.

Mixtures of tetramethylammonium bromide-bromine are not suitable for brominations which are sluggish. In the case of benzene the reaction is slow and stops as soon as the composition $(CH_3)_4NBr_3$ is reached.

When the liquid mixtures mentioned are heated above 70° hydrobromic acid is gradually formed, apparently by bromine substitution of the hydrogen in the methyl groups.

Finally it should be mentioned that these liquids do not cause any injuries when in contact with the skin even for several minutes.

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(3) Kohler, *Am. Chem. J.*, **42**, 381 (1909).

(4) Read and Hurst, *J. Chem. Soc.*, **121**, 995 (1922).

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## Preparation of Some N-Substituted Amino Acid Analogs

BY EMERY M. GAL[1]

Friedman and Gutman,[2] while studying phenylalanine derivatives, reported excellent yields of the N-methylphenylalanine through cold condensation of phenyl-α-bromopropionic acid with methylamine and subsequent slow crystallization over a period of three weeks. This method with modifications proved to be very satisfactory, and led to yields of 60–80% as calculated from the alpha halo-acid. Crystallization set in within three days.

TABLE I

| Product | Formula | M. p., °C. | Point of sublimation, °C. | Composition, % Calculated Carbon | Calculated Hydrogen | Calculated Nitrogen | Found Carbon | Found Hydrogen | Found Nitrogen |
|---|---|---|---|---|---|---|---|---|---|
| N-Ethylvaline | $C_7H_{15}NO_2$ | ... | 250 | 57.92 | 10.31 | 9.65 | 57.60 | 10.00 | 9.48 |
| N-Propylvaline | $C_8H_{17}NO_2$ | ... | 250 | 60.32 | 10.64 | 8.80 | 59.97 | 10.60 | 9.24 |
| N-Isopropylvaline | $C_8H_{17}NO_2$ | ... | 250 | 60.32 | 10.64 | 8.80 | 59.71 | 10.25 | 9.16 |
| N-Phenylvaline | $C_{11}H_{15}NO_2$ | 125[a] | ... | 68.47 | 7.77 | 7.25 | 68.13 | 7.64 | 7.25 |
| N-Ethylleucine | $C_8H_{17}NO_2$ | ... | 250 | 60.32 | 10.64 | 8.80 | 59.58 | 10.58 | 8.80 |
| N-Propylleucine | $C_9H_{19}NO_2$ | ... | 230 | 62.75 | 10.99 | 8.09 | 62.45 | 10.84 | 8.12 |
| N-Isopropylleucine | $C_9H_{19}NO_2$ | ... | 260 | 62.75 | 10.99 | 8.09 | 62.88 | 10.10 | 8.19 |
| N-Phenylleucine | $C_{12}H_{17}NO_2$ | 158[b] | ... | 69.59 | 8.21 | 6.76 | 69.41 | 8.46 | 6.24 |
| N-Ethylphenylalanine | $C_{11}H_{15}NO_2$ | ... | 270 | 68.47 | 7.77 | 7.25 | 68.15 | 7.63 | 7.60 |
| N-Propylphenylalanine | $C_{12}H_{17}NO_2$ | ... | 290 | 69.54 | 8.21 | 6.76 | 69.49 | 8.44 | 6.79 |
| N-Isopropylphenylalanine | $C_{12}H_{17}NO_2$ | ... | 280 | 69.54 | 8.21 | 6.76 | 68.24 | 8.35 | 5.86 |
| N-Phenylphenylalanine | $C_{15}H_{15}NO_2$ | 165 | ... | 75.52 | 6.28 | 5.85 | 74.79 | 6.48 | 6.08 |
| N-Ethylnorvaline | $C_7H_{15}NO_2$ | ... | 265 | 57.92 | 10.31 | 9.65 | 57.84 | 10.43 | 9.60 |
| N-Phenylnorvaline | $C_{11}H_{15}NO_2$ | 115–120 | ... | 68.47 | 7.77 | 7.25 | 67.69 | 7.32 | 7.80 |
| N-Ethyl-α-amino-*n*-butyric acid | $C\ H_{13}NO_2$ | 282 d. | ... | 54.90 | 9.92 | 10.62 | 54.73 | 9.70 | 10.03 |

[a] Bischoff (*Ber.*, **30**, 898, 2470 (1897)) reports 135°. [b] Miller and Ploechl (*Ber.*, **25**, 2040 (1892)) report 168–170°.

These compounds are very poorly soluble in either cold or hot water. At *p*H 7.4 their solubility is 1.25–1.50 g./100 ml., with the exception of α-amino-*n*-butyric acid and the norvaline derivative, which are soluble to the extent of 4–6 g./100 ml. Their solubility in organic solvents is varying. The phenyl derivatives are soluble to the extent of 2.5 g./100 ml. of absolute alcohol, whereas the propyl and isopropyl derivatives only to the extent of 0.7–1 g./100 ml. in hot absolute alcohol, and are almost insoluble in ether, benzene and propylene glycol.

Table I presents the compounds prepared by the author with the aid of this method. All compounds are DL-amino acid derivatives. One example will demonstrate the mode and ease of preparation.

### Experimental

**N-Propyl-phenylalanine.**—22.9 g. (0.1 mole) of phenyl-α-bromopropionic acid, prepared according to the method of Fischer,[3] distilled at 120° (2 mm.) with slight decomposition and obtained in 70% yield, was cooled to 0°. To this compound 15 g. (0.127 mole) of propylamine (Eastman Kodak Co.) in 40 ml. of ice cold water was added dropwise and carefully shaken after each addition of the amine. (Too fast addition of the amine results in heating up of the mixture and in decrease of yield.) After the amine was added, the mixture was shaken for thirty minutes and left to stand overnight. Next morning, either crystals or a slight turbidity appeared. The mixture was then refluxed for ten minutes and left to crystallize. After a day or two, densely grown crystals of N-propylphenylalanine separated out. The crystals were collected on a Büchner funnel, washed several times with ice cold water to remove the amine hydrobromide salt, and finally washed with 30 ml. of ice cold 95% alcohol in three portions. The crude product was recrystallized from hot absolute alcohol to yield analytically pure samples of white crystals; yield 10 g. (73.9%).

A small sample of the crude product was recrystallized from twenty times its weight of hot water and dried in a desiccator over phosphorus pentoxide. The analytical results obtained with this sample were closely identical with those from alcohol recrystallization.

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[1] U. S. Public Health Special Fellow. This work was supported by a grant from the Cancer Research Grants Branch, U. S. Public Health Service, to D. M. Greenberg.

[2] Friedman and Gutman *Biochem. Z.*, **27**, 493 (1910).

[3] Fischer, *Ber.*, **37**, 3062 (1904).