[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY, TRACERLAB, INC.]

THE PREPARATION OF DIAMINO ACIDS VIA THE SCHMIDT REACTION[1]

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The reaction of hydrazoic acid with malonic acid derivatives under the conditions of the Schmidt reaction affords a novel synthesis of α-amino acids (1, 2, 3). Although α-amino acids are apparently inert to further reaction with hydrazoic acid, diamines are obtained from dicarboxylic acids of the formula $HOOC(CH_2)_nCOOH$, where $n > 1$, and from amino acids other than *alpha* on treatment with hydrazoic acid.

We have prepared DL-α,γ-diaminobutyric acid, DL-ornithine, and DL-lysine by treating the tricarboxylic acids, $HOOC(CH_2)_nCH(COOH)_2$, $n = 2, 3, 4$, with hydrazoic acid and 100% sulfuric acid in chloroform solution. Adamson (2) has reported the preparation of DL-lysine, DL-ornithine, and D-α,γ-diaminobutyric acid from the corresponding α-aminodicarboxylic acids in yields of 74, 75, and 42%, respectively. Although the Schmidt reaction is usually performed at 40–45°, Adamson observed that the yield of glycine from malonic acid was increased from 29 to 46% by raising the temperature of the reaction from 40 to 50°. Our results, summarized in Table I, suggest that somewhat higher temperatures may be advantageous. Substitution of nitromethane (4) for chloroform as the solvent in one run with 1,1,4-tricarboxybutane led to a decrease in yield of diaminobutyric acid.

TABLE I

EFFECT OF TEMPERATURE ON THE YIELD OF DIAMINO ACID[a]

AMINO ACID	40°	50°	60°
DL-α,γ-Diaminobutyric acid			39
DL-Ornithine	35		42, 34[b]
DL-Lysine	30	36	44

[a] Isolated as the dipicrate. [b] This reaction performed in nitromethane solution.

The identities of the diamino acids were verified by the preparation of the monohydrochlorides from the dipicrates, *via* the dihydrochlorides. In the case of lysine dihydrochloride, an attempt to obtain pure material by repeated crystallization from aqueous ethanol-ether gave increasing amounts of pure lysine monohydrochloride, which was easily separated from the dihydrochloride because of the widely differing solubility properties of the two salts. This behavior was verified with authentic lysine dihydrochloride.

EXPERIMENTAL[2]

1,1,5-Tricarboxypentane. Prepared as described by Karrer and co-workers (5) from ethyl 5-bromovalerate and malonic ester, the triacid melted at 90–91°; reported 88–89°.

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[2] Microanalyses by Dr. C. K. Fitz.

1,1,3-Tricarboxypropane. Prepared by the above method from ethyl β-chloropropionate and malonic ester, the triacid melted at 122–124° after recrystallization from ether-petroleum ether; reported (6) m.p. about 125°.

Neut. equiv. Calc'd: 58.7. Found: 59.0.

1,1,4-Tricarboxybutane. Reaction of ethyl 4-bromobutyrate and malonic ester by the method of Karrer afforded 1,1,4-tricarboxybutane, m.p. 143–144° in 61% yield; the analytical sample, m.p. 145.5–146.0° dec., was obtained after several crystallizations from benzene-acetone, reported (7) m.p. 139–140°.

Anal. Calc'd for $C_7H_{10}O_6$: C, 44.21; H, 5.30; Neut. equiv., 63.4.
Found: C, 44.4; H, 5.0; Neut. equiv., 63.1.

The Schmidt reaction. The reactions were performed in a 100-ml. 3-neck flask equipped with a pressure-equalizing dropping-funnel, a mercury-sealed stirrer, and a condenser connected to a sulfuric acid bubbler. A 1.20 *N* solution of hydrazoic acid in chloroform (5.00 ml.) was added slowly to a vigorously stirred mixture of 2 mmoles of the triacid, 2 ml. of 100% sulfuric acid, and 10 ml. of chloroform maintained at the appropriate temperature. Gas evolution ceased after about two hours at 60°; in experiments at lower temperatures gas evolution continued for four to six hours. In some runs sulfuric acid was added dropwise to the chloroform solution of triacid and hydrazoic acid with no significant difference in the results.

The reaction mixture was poured into 15 ml. of water. The aqueous phase was separated and carefully neutralized by the addition of a hot concentrated solution of barium hydroxide. A hot aqueous solution containing 1.1 g. of picric acid was added to the filtrate after barium sulfate had been removed and the solution was allowed to stand at 0° for 24–48 hours to permit the complete separation of the dipicrate. The product was filtered and dried *in vacuo* at 100°. Concentration of the mother liquor invariably afforded picric acid, m.p. 121° or better, as the only remaining component in the solution.

DL-*α,γ-Diaminobutyric acid dipicrate*, m.p. 187–188° (dec.) was converted to the dihydrochloride by reaction with hydrochloric acid. Treatment of this salt with pyridine afforded the monohydrochloride, m.p. *in vacuo* 234–235° (dec.).

Anal. Calc'd for $C_4H_{11}ClN_2O_2$: C, 31.07; H, 7.17.
Found: C, 30.8; H, 7.2.

DL-*Ornithine* was identified as its dipicrate, m.p. 195–196° (dec.), reported (8) 195.5–196.5°; and its monohydrochloride, m.p. *in vacuo* 215.5–216.5° (dec.), reported 225° (8), 218° (9).

DL-*Lysine dipicrate*, m.p. 184–186° (dec.), reported (2) 188–190°, was converted to the dihydrochloride which after several crystallizations from aqueous ethanol-ether was largely converted to the monohydrochloride, insoluble in aqueous ethanol, m.p. *in vacuo* 260–261°, reported (10) 263–264°.

Anal. Calc'd for $C_6H_{15}ClN_2O_2$: C, 39.45; H, 8.28.
Found: 39.4; H, 8.4.

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