The Reaction of *o*-Phenylenediamine With 3-Methylglutaric Anhydride

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The combination of *o*-phenylenediamine and 3-methylglutaric anhydride in xylene as solvent produces a complex mixture of products. Isolation and characterization of four products from this reaction has shed some light on the mechanism by which 4-(2-benzimidazolyl)-3-methylbutyric acid (**1**) is formed under these reaction conditions.

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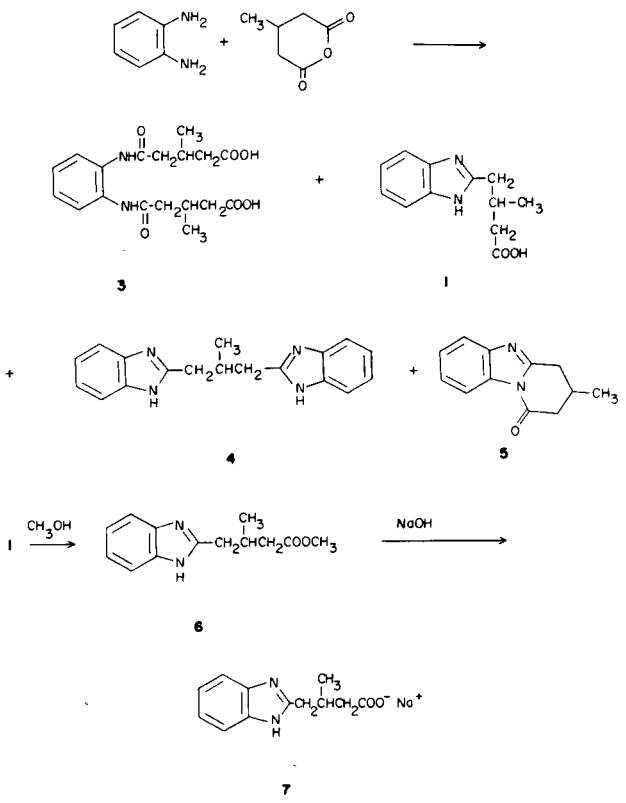
In connection with another project, we required some 4-(2-benzimidazolyl)-3-methylbutyric acid (**1**). Vinot (1), in an earlier report using essentially the method of Chatterjee (2), described the preparation of the related acid, 4-(2-benzimidazolyl)butyric acid (**2**) by combining *o*-phenylenediamine and two equivalents of glutaric anhydride in reluxing xylene. When we applied the literature reaction conditions to the preparation of **1**, the desired acid **1**, unlike the previously reported (1) acid **2**, failed to

1, R = CH_3
2, R = H

crystallize from the cooled xylene solution. After a more careful study of the reaction, several products were isolated and identified. In the course of this work a useful procedure for preparing compound **1** was developed.

Combination of *o*-phenylenediamine and two equivalents of 3-methylglutaric anhydride in hot xylene solution produced a complex mixture of products. The principal product from this reaction is the bis-adduct **3**. Although not mentioned by Vinot (1) or Chatterjee (2), who employed mineral acid in the work up of their reactions, treatment of compounds such as **3** with hot aqueous mineral acid causes cyclization to the respective benzimidazole butyric acids (**1** and **2**). The bis-benzimidazole **4** was also isolated in low yield; this compound evidently arises from reaction of two equivalents of *o*-phenylenediamine with one equivalent of the anhydride followed by cyclodehydration to produce **4**. A small amount of the cyclodehydrated product **5** was also isolated from the reaction in xylene solution. This latter compound very likely arises from cyclodehydration of **1** under the forcing reaction conditions. These results suggest that compound **3** is the principal product from this reaction and that **1** forms mainly from **3** upon subsequent treatment with acid.

The best yield (80%) of the desired carboxylic acid **1**, as a viscous oil, was obtained by first isolating the bis-adduct **3** and then cyclizing **3** in aqueous hydrochloric acid. Compound **1** was further characterized by conversion to the crystalline sodium salt **7**, *via* the solid ester **6**, both of which were identified by spectral data and combustion analysis.



EXPERIMENTAL

4-(2-Benzimidazolyl)-3-methylbutyric Acid (**1**).

A suspension of *N,N'*-bis-(4-carboxy-3-methylbutyryl)-*o*-phenylenediamine (**3**) (6 g, 0.016 mole) in 4*N* hydrochloric acid (25 ml) was heated to reflux for 2 hours. The resulting solution was cooled and evaporated *in vacuo* to a tan gum. This residue was triturated twice with ethyl acetate (20 ml) to give 2.9 g (80%) of **1** as a semi-solid. Attempts to crystallize this viscous oil failed, however mass spectral and tlc evidence indicated this pure, new material to be the desired compound **1** which was further characterized as the crystalline sodium salt **7** and solid methyl ester **6**; ms m/e 218 (M^+), 159 (M^+- CH_2COOH), 131 (M^+-CCH_3CH_2COOH). (See below).

N,N'-bis-(4-Carboxy-3-methylbutyryl)-*o*-phenylenediamine (**3**).

Under conditions described below for compound **5**, *o*-phenylenediamino and 3-methylglutaric anhydride were combined in xylene and the mixture refluxed for 2 hours. Separation and evaporation of the xylene

layer gave a residue which was dissolved in warm 6*N* hydrochloric acid (30 ml). The cooled solution was washed with methylene chloride (50 ml). An insoluble oil, 6.5 g (39%), which separated from the two phases, was shown to be compound **3** by tlc. This oil was crystallized from ethanol (20 ml) to give 350 mg (2%) of **3** as white solid, mp 168°-170°. On evaporation of the ethanol filtrate an additional 6 g (35%) of **3** was obtained; ir (potassium bromide): λ max cm^{-1} 3411-2444 (H_2O, COOH), 1700, 1658, 1537; pmr: 8.95-1.2 (6H, m, $(-CCH_3-)_2$, 2.15-2.7 (10 H, m, $(-CH_2CHCH_2-)_2$, 7.05-7.75 (4H, m, aromatic).

Anal. Calcd. for $C_{18}H_{24}N_2O_6 \cdot \frac{1}{4}H_2O$: C, 58.60; H, 6.71; N, 7.59. Found: C, 58.62; H, 6.46; N, 7.60.

1,3-bis-(Benzimidazolyl)-2-methylpropane (**4**).

To a suspension of *o*-phenylenediamine (5 g, 0.046 mole) in xylene (40 ml) was added 3-methylglutaric acid (11.8 g, 0.08 mole) and the suspension heated to reflux at which time two phases were formed. After two hours of heating, the mixture was cooled and the xylene decanted. The residue was combined with 4*N* hydrochloric acid (30 ml) and warmed on a steam bath until a solution was formed. The solution was cooled and washed with chloroform (50 ml). The *p*H of the separated aqueous layer was adjusted to 10 with saturated sodium carbonate. The solid that precipitated was filtered and then dissolved in isopropanol (15 ml) and reprecipitated by the addition of acetone. Filtration gave 1 g (15%) of **4**. An analytically pure sample was prepared from ethyl acetate-2-propanol, mp 245-246°; ir (potassium bromide): λ max cm^{-1} 3209-2525 (H_2O, NH) 1456, 1435, 1274, 738; ms: m/e 290 (M^+), 159, 131: pmr: δ 0.85-1.1 (3H, m, CH_3), 2.65-3.1 (5H, m, $-CH_2CHCH_2-$), 6.95-7.65 (8H, m, aromatic).

Anal. Calcd. for $C_{18}H_{18}N_4 \cdot \frac{1}{4}H_2O$: C, 73.3l; H, 6.30; N, 19.00. Found: C, 73.44; H, 6.23; N, 18.81.

Compound **4** was also detected by tlc in the reaction used to prepare compound **1**.

2-Methyl-4-oxo-piperidino[1,2-*a*]benzimidazole (**5**).

A suspension of *o*-phenylenediamine (47.9 g, 0.44 mole) and 3-methylglutaric anhydride (Aldrich Chemical Co., 113.6, 0.88 mole) in 300 ml of xylene was heated to reflux at which time two phases were formed. After two hours of heating, the mixture was cooled, the xylene layer decanted away from a viscous oil and all the xylene evaporated to give 9.5 g (10%) of **5** as a yellow solid, mp 131-133°; ir (potassium bromide): λ max cm^{-1} 1715, 1330, 1142, 750; ms: m/e 200 (M^+), 185 (M^+-CH_3), 157.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.03; N, 13.98. Found: C, 71.78; H, 5.98; N, 13.87.

4-(2-Benzimidazolyl)-3-methylbutyric Acid, Methyl Ester (**6**).

Dry hydrochloric acid gas was added to a cold solution of 4-(2-benzimidazolyl)-3-methylbutyric acid (**1**) (87 g, 0.398 mole) in methanol (300 ml) for 15 minutes. The solution was stirred at 0-5° for 3 hours, and then evaporated *in vacuo* to a tan semi-solid. This residue was dissolved in methylene chloride (200 ml) and washed with a solution of sodium bicarbonate (200 ml). The organic layer was dried (magnesium sulfate) and evaporated *in vacuo* to yield a red residue. Chromatographic purification of this residue on silica gel, eluting with ethyl acetate, produced a yellow solid which was slurried with ether (300 ml) to give 50.2 g (54%) of **6** as a white solid, mp 81-84°; ir (potassium bromide): λ max cm^{-1} 1738, 1429, 1268, 747.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.05. Found: C, 67.08; H, 6.90; N, 11.76.

Sodium 4-(2-Benzimidazolyl)-3-methylbutyrate (**7**).

To a solution of 4-(2-benzimidazolyl)-3-methylbutyric acid, methyl ester (**6**) (0.4 g 1.7 mmoles) in 1:1 methanol-water (20 ml) was added sodium hydroxide (0.0689 g, 1.7 mmoles) and the solution allowed to stir for 48 hours at room temperature. On evaporation *in vacuo* a white gum remained which was dissolved in methanol (3 ml). Addition of ethyl acetate (6 ml) caused a white gum to separate. All solvent was decanted and the residue slurried with ether (10 ml). Filtration gave 266 mg (65%) of **7** as a white solid, mp 105-108°C; ir (potassium bromide): λ max cm^{-1} 3380-2830 (H_2O, NH), 1568, 1413, 1274, 740.

Anal. Calcd. for $C_{12}H_{13}O_2Na \cdot \frac{3}{4}H_2O$: C, 56.80; H, 5.51; N, 11.03. Found: C, 56.57; H, 5.87; N, 10.67.

REFERENCES AND NOTES

(1) N. Vinot, *Bull. Soc. Chim. France*, 522 (1963).
(2) B. Chatterjee, *J. Chem. Soc.*, 2965 (1929).