[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

# Dibasic Aminoacids Based on *p*-Chloromethylbenzoyl Chloride

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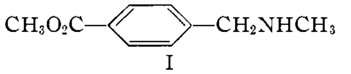
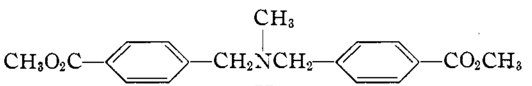
In previous papers we have described a number of esters[1] and dibasic acids[2] prepared from *p*-chloromethylbenzoyl chloride. This paper extends the series to include one dibasic acid containing a secondary amino group and three containing a tertiary amino group.

The primary and secondary amines in this series tended to polymerize when heated, so that they had to be isolated as their hydrochlorides. Therefore many of the yields were low.

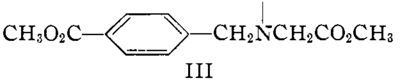
Methyl *p*-chloromethylbenzoate was prepared from *p*-chloromethylbenzoyl chloride and methanol as described previously[1] and then condensed with ammonia in methanol solution to give 49% of crude N-*p*-carbomethoxybenzylamine.[3] Treatment of this compound with additional methyl *p*-chloromethylbenzoate in methanol in the presence of sodium bicarbonate yielded 43% of N,N-bis-(*p*-carbomethoxybenzyl)-amine.[4]

Methyl *p*-chloromethylbenzoate reacted with methylamine in methanol to give 95% of crude N-methyl-*N*-*p*-carbomethoxybenzylamine (I). No attempt was made to purify this compound. It was condensed with additional methyl *p*-chloromethylbenzoate to give N-methyl-N,N-bis-(*p*-carbomethoxybenzyl)-amine (II) in 49% conversion and 53% yield.


I


II

Sodium *p*-chloromethylbenzoate, prepared as described previously,[1] reacted with sarcosine and with *p*-methylaminobenzoic acid in aqueous alkali to give in 66 and 68% yields, respectively, N-carboxymethyl-N-methyl-N-*p*-carboxybenzylamine, isolated as its methyl ester (III), and N-*p*-carboxyphenyl-N-methyl-N-*p*-carboxybenzylamine (IV).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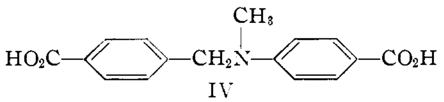
IV

The N-carbomethoxymethyl-N-methyl-N-*p*-carbomethoxybenzylamine was converted to the 2-ethylhexyl ester by prolonged heating with 2-ethylhexanol and sodium methylate.

Attempts to prepare the *p*-methylaminobenzoic acid employed above by the aminolysis of *p*-chlorobenzoic acid were unsuccessful. The maximum conversion under a variety of conditions was 2%.

## Experimental

**Starting Materials.**—Sodium *p*-chloromethylbenzoate was prepared as needed by the alkaline hydrolysis of *p*-chloromethylbenzoyl chloride.[1] Methyl *p*-chloromethylbenzoate was prepared as described previously.[1] The methylamine was obtained from the Mathieson Company and the sarcosine was Eastman Kodak Co. "Pure" grade.

***p*-Methylaminobenzoic Acid.**—A mixture of 180 g. of *p*-chlorobenzoic acid, 47 g. of sodium hydroxide, 500 cc. of water containing 105 g. of methylamine, 2.0 g. of copper powder, 2.0 g. of copper sulfate and 2.0 g. of potassium iodide was charged to a stainless steel autoclave and stirred at 150° for 21 hours. After the charge had been removed from the bomb, 300 cc. of water was distilled. The residue was filtered and made strongly acid with 6 *N* hydrochloric acid. The unreacted *p*-chlorobenzoic acid was separated by filtration, washed with water and dried. The recovery was 168.5 g. (93%). A sample was crystallized from ethanol–water, m.p. 235–237°[5] (243°).[6] The *p*H of the filtrate was adjusted to 4–5 with ammonium hydroxide and the *p*-methylaminobenzoic acid was separated by filtration. Recrystallization from water yielded 3.5 g. (2% conversion, 37% yield), m.p. 163–164° (168°).[7]

When the reaction was run at 200°, 34% of methylaniline was obtained and 51% of the *p*-chlorobenzoic acid was recovered. When methyl *p*-chloromethylbenzoate was treated with methylamine in methanol solution at 160° in the presence of copper, copper sulfate and potassium iodide, *p*-methylaminobenzoic acid was obtained in 2% conversion. Much of the unreacted *p*-chlorobenzoic acid was recovered as its methylamide.

**N,N-Bis-(*p*-Carbomethoxybenzyl)-amine Hydrochloride.**—To a solution of 64 g. of ammonia in 500 cc. of methanol was added 35.5 g. of methyl *p*-chloromethylbenzoate. After the mixture had stood for 5 days, 15 g. of sodium bicarbonate was added and the ammonia and methanol were distilled at reduced pressure. The residue was boiled with methanol and filtered free of inorganic salts. By continual evaporation of the filtrate followed by dilution with ether and hexane, there was isolated in four crops 19 g. (49%) of crude N-*p*-carbomethoxybenzylamine hydrochloride. This compound gave a copious precipitate with silver nitrate in warm methanol.

A mixture of 18 g. of this N-*p*-carbomethoxybenzylamine hydrochloride, 20.2 g. of methyl *p*-chloromethylbenzoate and 200 cc. of methanol was brought to boiling over a 1-hour period and then refluxed for 4 hours. After the first hour sufficient sodium bicarbonate was added at intervals to keep the mixture slightly alkaline. The slurry was filtered hot and the inorganic salts were washed with 15 cc. of hot methanol. By continual evaporation of the combined filtrate and washings followed by dilution with ether, there was isolated in five crops 13.5 g. (43%) of N,N-bis-(*p*-carbomethoxybenzyl)-amine hydrochloride. A sample of the first crop was crystallized from methanol, m.p. 265.0–265.5°. This compound gave a copious white precipitate with silver nitrate in warm methanol.

*Anal.*[8] Calcd. for $C_{18}H_{20}O_4NCl$: C, 61.8; H, 5.72. Found: C, 61.7; H, 5.52.

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(1) Emerson and Heimsch, THIS JOURNAL, **72**, 5152 (1950).

(2) Emerson and Heimsch, *ibid.*, **73**, 1297 (1951).

(3) Blicke and Lilienfeld, *ibid.*, **65**, 2281 (1943), aminated ethyl *p*-iodomethylbenzoate by means of hexamethylenetetramine in 40–64% yield.

(4) Rupe and Bernstein, *Helv. Chim. Acta*, **13**, 457 (1930), prepared the corresponding ethyl ester in 44% yield by the hydrogenation of ethyl *p*-cyanobenzoate.

(5) All of the melting points are uncorrected.

(6) Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1943, Vol. I, p. 440.

(7) Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1936, Vol. II, p. 613.

(8) All of the analyses are microanalyses by Mr. P. J. Adams and Mr. Donald Stoltz of this laboratory and the Micro-Tech Laboratories, 8000 Lincoln Avenue, Skokie, Illinois.

**N-Methyl-N-*p*-carbomethoxybenzylamine.**—To a solution of 88 g. of methylamine in 250 cc. of methanol was added 74 g. of methyl *p*-chloromethylbenzoate. After the mixture had stood for 9 days at room temperature, 16 g. of sodium hydroxide was added and the methanol and excess methylamine were distilled at reduced pressure. After 50 cc. of benzene had been added to the residue, a stream of nitrogen was passed through the mixture to remove the last traces of methylamine. The mixture was then diluted with another 50-cc. portion of benzene, filtered, and the precipitate was washed with benzene. Evaporation of the benzene from the combined washings and filtrate yielded 68 g. (95%) of crude N-methyl-N-*p*-carbomethoxybenzylamine. Since the amine polymerized when its crystallization was attempted, a small sample was dissolved in methanol and treated with hydrogen chloride. The N-methyl-N-*p*-carbomethoxybenzylamine hydrochloride was separated by filtration and crystallized from a mixture of methanol and benzene, m.p. 245–246°.

*Anal.* Calcd. for $C_{10}H_{14}O_2NCl$: C, 55.7; H, 6.50. Found: C, 55.8; H, 6.65.

**N-Methyl-N,N-bis-(*p*-carbomethoxybenzyl)-amine.**—A mixture of 13.5 g. of methyl *p*-chloromethylbenzoate, 15.7 g. of N-methyl-N-*p*-carbomethoxybenzylamine hydrochloride, 150 cc. of methanol and 3.0 g. of sodium hydroxide was stirred for 2 hours at 25° and then allowed to stand overnight. After the mixture had been refluxed for 2 hours, as much methanol as possible was distilled at reduced pressure. The residue was slurried with 75 cc. of 5% sodium carbonate and then extracted four times with benzene. The combined extracts were washed twice with water and dried over calcium chloride. After the benzene had been distilled at reduced pressure, 50 cc. of anhydrous ether was added to the residue. The resulting solution was filtered free of tar before hydrogen chloride was introduced. The crude N-methyl-N,N-bis-(*p*-carbomethoxybenzyl)-amine hydrochloride, which was separated by filtration and dried, weighed 13 g. (49% conversion and 53% yield). An analytical sample was crystallized twice from a mixture of benzene, methanol and hexane, m.p. 236.0–236.5°.

*Anal.* Calcd. for $C_{19}H_{22}O_4NCl$: C, 62.7; H, 6.05. Found: C, 63.0; H, 6.21.

N-Methyl-N,N-bis-(*p*-carbomethoxybenzyl)-amine was prepared by dissolving its hydrochloride in water and adding excess sodium bicarbonate. The crude amine thus obtained was crystallized three times from a mixture of benzene and hexane to obtain an analytical sample, m.p. 95.0–95.5°.

*Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.7; H, 6.42. Found: C, 69.8; H, 6.41.

**N-Carbomethoxymethyl-N-methyl-N-*p*-carbomethoxybenzylamine.**—After a mixture of 19 g. of *p*-chloromethylbenzoyl chloride, 4.0 g. of sodium hydroxide and 150 cc. of water had boiled for one-half hour, a solution of 12.5 g. of sarcosine hydrochloride and 12 g. of sodium hydroxide in 100 cc. of water was added. The resulting solution was boiled under reflux for 3 hours, filtered and then acidified with concd. hydrochloric acid. The resulting slurry was evaporated to dryness and the residual salt mixture extracted twice with 200-cc. portions of boiling methanol. Evaporation of the combined extracts yielded 26 g. of crude N-carboxymethyl-N-methyl-N-*p*-carboxybenzylamine hydrochloride.

This 26 g. was stirred under reflux for 17 hours with 260 cc. of methanol containing 13 cc. of concentrated hydrochloric acid. After 185 cc. of methanol had been distilled, the mixture was diluted with 200 cc. of water. It was made nearly neutral with sodium hydroxide and then slightly basic with sodium bicarbonate and extracted five times with benzene. The combined extracts were washed three times with water, dried over calcium chloride and distilled to give 16.5 g. (66%) of N-carbomethoxymethyl-N-methyl-N-*p*-carbomethoxybenzylamine, b.p. 140–165° (0.8 mm.). An analytical sample, obtained on redistillation, boiled at 145–155° (0.45 mm.), $n^{25}_{D}$ 1.5250, $d^{25}_{25}$ 1.152.

*Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.2; H, 6.77. Found: C, 62.3; H, 6.58.

**N-Carbo-2-ethylhexoxymethyl-N-methyl-N-*p*-carbo-2-ethylhexoxybenzylamine.**—A mixture of 37 g. of N-carbomethoxymethyl-N-methyl-N-*p*-carbomethoxybenzylamine, 65 g. of 2-ethylhexanol and 1.0 g. of sodium methylate was refluxed under a 24-inch Vigreux column under slight vacuum so that the pot temperature was 145–160°. Methanol was removed continuously over a 58-hour period. During this time 3.0 g. of sodium methylate was added at intervals in 0.5-g. quantities and 50 cc. of toluene was added after the first 6 hours. Upon cooling, the residue was washed with water, with 50 cc. of 5% acetic acid, with 25 cc. of 1% sodium bicarbonate and then three times with water. After 1 g. of Norit had been added to the organic portion, the toluene and 2-ethylhexanol were distilled. The residue was heated at 165° and 0.25 mm. pressure for 1.5 hours. Filtration through a sintered glass filter yielded 35 g. (57%) of N-carbo-2-ethylhexoxymethyl-N-methyl-N-*p*-carbo-2-ethylhexoxybenzylamine, $n^{25}_{D}$ 1.4925, $d^{25}_{25}$ 0.985.

*Anal.* Calcd. for $C_{27}H_{45}O_4N$: C, 72.5; H, 10.06. Found: C, 73.0; H, 9.72.

**N-*p*-Carbomethoxyphenyl-N-methyl-N-*p*-carbomethoxybenzylamine.**—A mixture of 4.4 g. of *p*-chloromethylbenzoyl chloride, 0.9 g. of sodium hydroxide and 25 cc. of water was refluxed for one-half hour. After a solution of 3.5 g. of *p*-methylaminobenzoic acid and 1.8 g. of sodium hydroxide in 25 cc. of water had been added, the boiling was continued for 4 hours. The solution was cooled, filtered and made strongly acid with concentrated hydrochloric acid. The crude N-*p*-carboxyphenyl-N-methyl-N-*p*-carboxybenzylamine hydrochloride (5 g., 68% yield) was separated by filtration, washed with water and dried.

This 5 g. was added to 150 cc. of methanol containing 15 cc. of concentrated hydrochloric acid and the mixture was stirred under reflux for 4.5 hours. After cooling, it was diluted with 150 cc. of water and made slightly alkaline with sodium bicarbonate. The precipitate was separated by filtration, washed with water and dried to yield 3.0 g. of crude N-*p*-carbomethoxyphenyl-N-methyl-N-*p*-carbomethoxybenzylamine. An analytical sample was crystallized twice from a mixture of methanol and hexane, with Norit treatment prior to the second crystallization, and then from methanol, m.p. 98.5–99.0°.

*Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 69.0; H, 6.07. Found: C, 69.1; H, 6.17.

When the original filtrate from the esterification was rendered essentially neutral, 1 g. of unreacted N-*p*-carboxyphenyl-N-methyl-N-*p*-carboxybenzylamine precipitated. The methyl ester therefore was obtained in 62% conversion and 77% yield.

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