[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OCCIDENTAL COLLEGE]

The Meerwein Reaction in Amino Acid Synthesis. I. α-Bromo-*o*-, *m*-, and *p*-Chlorohydrocinnamic Acids and the Corresponding Chlorophenylalanines; α-Bromo- and α-Chlorohydrocinnamamide

GEORGE H. CLELAND

Received January 23, 1961

The Meerwein reaction,[1] appropriately modified, yielded α-bromo-*o*-, *m*-, and *p*-chlorohydrocinnamic acids from acrylic acid and chlorobenzenediazonium bromides, and α-bromo- and chlorohydrocinnamamides from acrylamide and benzenediazonium bromide and benzenediazonium chloride, respectively. The bromo acids were ammonolyzed to the corresponding chlorophenylalanines. It is suggested that in some cases this synthesis of β-arylalanines would possess certain advantages over the methods customarily employed.

α-Alanines with β-aromatic substituents (I)

$$RCH_2CH(NH_2)COOH$$

I. R = an aromatic group

are usually made by variations of reactions involving halomethyl aromatic compounds and the sodio derivatives of malonic ester or of substituted malonic ester,[2] or by Erlenmeyer azlactone and related syntheses.[3] Each method presents complications in certain cases. Ammonolysis of α-halo acids has been used for the preparation of α-amino acids in many instances,[2] but the appropriate α-halo acids necessary for syntheses of I are seldom readily available. The Meerwein reaction seems to offer an attractive route to the synthesis of I *via* the corresponding α-halo acids or derivatives thereof, and the reaction has been used for this purpose in several instances.[4] The yields of amino acids, however, have been relatively poor[4a,c] or not reported.[4b] Certain of the results obtained by Kochi[5] in his investigations of the kinetics and mechanism of the Meerwein reaction stimulated an interest in this laboratory in further studies of the reaction as a route to preparation of α-amino acids (I). It has been found that, under reaction conditions which reflect a number of Kochi's observations on the Meerwein reaction,[6] *o*-, *m*-, and *p*-chlorobenzenediazonium bromides react with acrylic acid, with cuprous bromide as catalyst, to give α-bromo-*o*-, *m*-, and *p*-chlorohydrocinnamic acids in good yields. In those cases where parallel experiments were conducted, reaction media with *low water-contents* led to cleaner recoveries and much higher yields of Meerwein products than did those media which included the relatively high water-contents usually employed in Meerwein (and Sandmeyer) reactions. The α-bromo acids were ammonolyzed to the corresponding chlorophenylalanines. It was also found that, under similar reaction conditions, acrylamide can serve as the unsaturate,[7] as exemplified by syntheses of α-bromo- and α-chlorohydrocinnamamides in reasonable yields by reactions of benzenediazonium bromide and of benzenediazonium chloride with acrylamide, with cuprous bromide and cuprous chloride serving as respective catalysts. Preliminary studies have indicated that benzenediazonium bromides with either a strongly *meta*-directing group (nitro) or a strongly *ortho*, *para*-directing group (methoxy) present on the ring can be used successfully in place of the chlorobenzenediazonium bromides in the preparation of α-bromohydrocinnamic acids. These reactions are being studied in detail and the results will be the subject of a later article.

EXPERIMENTAL[8]

α-Bromo-o-chlorohydrocinnamic acid. Method A. *o*-Chloroaniline, 6.4 g. (0.05 mole), was treated with 15 ml. of 48% hydrobromic acid and the mixture was stirred while 50 ml. of acetone was added. Stirring was continued until a part of the amine hydrobromide was dissolved and the remainder was finely divided, and the mixture was then cooled to 8° and diazotized beneath the surface with 10.0 ml. of 5.0*M* sodium nitrite, the rapidly stirred solution being kept below 15° during the diazotization. Acrylic

(1)(a) H. Meerwein, E. Büchner and K. van Emster, *J. prakt. chem.*, **152**, 237 (1939). (b) The Meerwein reaction has been reviewed recently [C. S. Rondestvedt, Jr., *Org. Reactions*, **11**, 189 (1960)].

(2) For a review of several of these reactions see R. J. Block, *Chem. Revs.*, **38**, 501 (1946).

(3) For a review of azlactone chemistry and a list of amino acids prepared from azlactones through 1944, see H. E. Carter, *Org. Reactions*, **3**, 198 (1946).

(4)(a) R. Gaudry, *Laval med.*, **9**, 412 (1944); *Can. J. Research*, **23B**, 88 (1945). (b) E. Müller, *Angew. Chem.*, **61**, 179 (1949). (c) R. Filler and H. Novar, *Chem. & Ind. (London)*, 468 (1960).

(5) J. K. Kochi, *J. Am. Chem. Soc.*, **77**, 5090 (1955); **78**, 1228 (1956); **79**, 2942 (1957).

(6) Kochi's observations which were of particular interest in connection with the present investigation can be summarized as follows: Copper(I) rather than copper(II) appears to be the catalyst; acetone reduces copper(II) to copper(I); dissolved oxygen should be removed from the reaction media; the ratio of Meerwein to Sandmeyer product increases with increasing olefin concentration; buffering, traditionally used in Meerwein reactions, is not necessary for obtaining a good yield of Meerwein product.

(7) It has been reported[1b] that acrylamide gave 0% Meerwein product under other reaction conditions.

(8) Melting points were determined on a Fisher-Johns apparatus and are corrected.

acid,[9] 50 ml. (0.7 mole), was added to the mixture and the solution was swept with nitrogen for 15 min., the temperature being kept at 10–15°. The solution was cooled to 5°, 100 mg. of cuprous bromide added and stirred at 20–25° after an initial rise to 20°. It was necessary to employ an efficient cooling bath and to regulate the rate of stirring in order to control the temperature. Nitrogen was evolved almost immediately after the addition of the cuprous bromide, and the theoretical amount was obtained within five minutes. The dark solution was added to 600 ml. of water, and a red oil which separated soon began to crystallize. After 24 hr. the solid was filtered, washed three times with 50-ml. portions of water, air-dried, and freed in large part of a dark oily contaminant by pressing between filter papers. The crude product (9.8 g.) was crystallized from benzene after partial decolorization with carbon in benzene solution to give 8.8 g. (67%) of α-bromo-*o*-chlorohydrocinnamic acid, m.p. 116.5–117.5°. A sample was crystallized twice from benzene and twice from benzene–petroleum ether (b.p. 60–71°) for analysis, m.p. 117.5–118.5°.

Anal. Calcd. for $C_9H_8O_2BrCl$: C, 41.0; H, 3.1; total silver halide from a 10.98-mg. sample, 13.80 mg. Found: C, 41.2; H, 3.2; total silver halide, 13.98 mg. Neut. equiv. Calcd.: 263.5. Found: 266.

A sample of the acid (1.32 g., 0.005 mole) was refluxed with methanolic potassium hydroxide for 20 min., the alcohol was removed, an excess of 6*N* hydrochloric acid was added, and the solid which precipitated was filtered, washed with water, and crystallized from ethanol to give 0.85 g. (93%) of *o*-chlorocinnamic acid, m.p 210.5–211.5°, mixed melting point with *o*-chlorocinnamic acid prepared *via* a Perkin reaction, 210.5–211.5°.

Method B. o-Chloroaniline, 6.4 g. (0.05 mole), was treated with 15 ml. of 48% hydrobromic acid and then with 25 ml. of water and 25 ml. of acetone. The stirred mixture was cooled to 8° and diazotized beneath the surface with 10.0 ml. of 5.0*M* sodium nitrite, the rapidly stirred solution being kept below 15° during the diazotization. Acrylic acid, 50 ml. (0.7 mole), was added and the solution was swept with nitrogen for 15 min., the temperature being kept at 10–15°. The solution was cooled to 5°, 100 mg. of cuprous bromide added and stirred at 20–25° after an initial rise to 20°. Nitrogen was evolved shortly after the addition of the cuprous bromide, but the rate of formation was much slower than in the case of Method A. The theoretical amount of nitrogen was obtained in about 30 min. The solution was added to 600 ml. of water and a red oil separated. After 48 hr. the oil had partially crystallized. The mixture was filtered, the solid was washed three times with 50-ml. portions of water, air-dried, and pressed between filter papers to remove a dark oily contaminant. The crude product (6.0 g.) was crystallized from benzene after partial decolorization with carbon in benzene solution to give 4.8 g. (36%) of α-bromo-*o*-chlorohydrocinnamic acid, m.p. 116–117.5°, mixed melting point with the acid obtained by Method A, 116.5–117.5°.

α-Bromo-m-chlorohydrocinnamic acid. The synthesis of this acid was carried out in the same manner as that of the *o*-isomer as described above (Method A), using *m*-chloroaniline as the amine, and with all reactants in the same proportions as described for the synthesis of the *ortho*-isomer. The results were similar to those described above save that the red oil resulting from the addition of the reaction mixture to 600 ml. of water did not crystallize on standing. After numerous trials, crystalline α-bromo-*m*-chlorohydrocinnamic acid was obtained from the oil by the following operations: The supernatant was decanted, the oil was taken up in 200 ml. of benzene, washed three times with 100-ml. portions of water, and extracted with a slight excess of 1*M* sodium bicarbonate. The aqueous bicarbonate layer was extracted two times with 50-ml. portions of chloroform, stirred with carbon, filtered, and acidified with hydrobromic acid. An oil which separated was extracted with 200 ml. of benzene, the benzene solution was washed three times with 50-ml. portions of water, and dried (Drierite). The filtered solution was concentrated *in vacuo* to give 9.8 g. of a pale yellow oil (this oil may be used for the preparation of *m*-chlorophenylalanine with little decrease in yield as compared with the use of the crystalline bromo acid.) The oil crystallized on standing at 0° for some time. After 100 hr. the solid was pressed between filter papers to eliminate a small amount of light yellow oil and dissolved in benzene. Petroleum ether was added until the solution (at 27°) was slightly cloudy, stored at 0° for 24 hr. and decanted from a small amount of a pale yellow oil. The solvents were removed *in vacuo* to give a colorless oil which crystallized after it was layered with petroleum ether, seeded with a small crystal of the original solid and stirred, stored at 0° until a number of small crystal sites had developed, and then kept at 25–30°. The solid obtained was pressed free of a little colorless oil and this last crystallization process was repeated, giving 7.5 g. (57%) of α-bromo-*m*-chlorohydrocinnamic acid, m.p. 46.5–47.5°. A sample was crystallized twice from benzene and once from petroleum ether for analysis, m.p. 46.5–47.5°.

Anal. Calcd. for $C_9H_8O_2BrCl$: C, 41.0; H, 3.1; total silver halide from a 9.41 mg. sample, 11.82 mg. Found: C, 40.7; H, 3.3; total silver halide, 11.88 mg. Neut. equiv. Calcd.: 263.5. Found: 261.

A sample of the acid (1.32 g., 0.005 mole) was converted to *m*-chlorocinnamic acid in 81% yield by the same method as that used to make the o-isomer, m.p. 161–162°, mixed melting point with *m*-chlorocinnamic acid prepared *via* a Perkin reaction, 161–162°.

α-Bromo-p-chlorohydrocinnamic acid.[10] The synthesis of this acid was accomplished by a reaction similar in all respects to Method A described for the *ortho*-isomer, using *p*-chloroaniline as the amine. The crude product, after partial decolorization with carbon in benzene, was crystallized from benzene to give 9.5 g. (72%) of α-bromo-*p*-chlorohydrocinnamic acid, m.p. 102–103.5°. A sample was crystallized from ethanol and then from benzene for analysis, m.p. 102.5–103.5°; lit.[10] m.p. 99°.

Anal. Calcd. for $C_9H_8O_2BrCl$: C, 41.0; H, 3.1; total silver halide from a 9.78 mg. sample, 12.29 mg. Found: C, 41.2; H, 3.1; total silver halide, 12.30 mg. Neut. Equiv. Calcd.: 263.5. Found: 264.

Synthesis of α-bromo-*p*-chlorohydrocinnamic acid by Method B gave 3.6 g. (27%) after one crystallization from benzene.

A sample of the acid (1.32 g., 0.005 mole) was converted to *p*-chlorocinnamic acid in 91% yield by the same method as that used to make the *o*-isomer, m.p. 244.5–245.5°, mixed melting point with *p*-chlorocinnamic acid prepared *via* a Perkin reaction, 244.5–245.5°.

α-Bromohydrocinnamamide.[11] Aniline. 4.7 g. (0.05 mole), was treated with 15 ml. of 48% hydrobromic acid, and then with 50 ml. of acetone. The mixture was stirred and cooled to 0–1°, and diazotized beneath the surface with 10.0 ml. of cold 5.0*M* sodium nitrite, the temperature being kept below 15° during this operation. The solution was cooled to 0–1°, acrylamide, 14.2 g. (0.2 mole) added, the mixture swept with nitrogen for 15 min., 300 mg. of cuprous bromide added, and stirred at 20–25° after an initial rise to 20°, the temperature being controlled by employment of an ice-salt bath. The theoretical amount of nitrogen was evolved within thirty minutes. A small

(9) Acrylic acid (Eastman 3588) was used as received from the manufacturers in all of the experiments reported since no noticeable differences were observed when, in several trials, acrylic acid freshly distilled from the stabilizer (*p*-methoxyphenol) was used instead.

(10) J. v. Braun and J. Nelles, *Ber.*, **66B**, 1464 (1933).

(11)(a) K. Freudenberg, H. Fikentscher, and M. Harder, *Ann.*, **441**, 157 (1925); (b) W. Baker and A. Lapworth, *J. Chem. Soc.*, **125**, 2333 (1924).

amount of undissolved material was removed and the reaction mixture was added to 800 ml. of water, whereupon a mass of crystals plus a red oil separated. The mixture was stirred and filtered, the solid washed three times with 50-ml. portions of water, and air-dried. The crude product (5.2 g.) was decolorized with carbon in boiling aqueous methanol and crystallized from the same solvent to yield 4.3 g. (37%) of α-bromohydrocinnamamide, m.p. 126.5–128.5°. A sample was crystallized twice from benzene for analysis, m.p. 129–130°; lit. m.p.s: 127°,[11a] 128.5°.[11b]

Anal. Calcd. for $C_9H_{10}ONBr$: C, 47.4; H, 4.4; N, 6.1. Found: C, 47.1; H, 4.5; N, 5.8.

A sample of the amide was refluxed with methanolic potassium hydroxide until ammonia ceased to be evolved, methanol was removed, and the mixture was acidified with hydrochloric acid to give cinnamic acid, as shown by the melting point and a mixed melting point with authentic cinnamic acid (132–133° in each case).

α-Chlorohydrocinnamamide.[4a] Aniline, 4.7 g. (0.05 mole), was treated with 12 ml. of concd. hydrochloric acid and then with 100 ml. of acetone. The mixture was cooled to 0–1° and diazotized beneath the surface with 10.0 ml. of 5.0*M* sodium nitrite, the temperature being kept below 15° during the diazotization. Acrylamide, (14.2 g., 0.2 mole), was added, the mixture was cooled to 5°, and swept with nitrogen for 15 min. Cuprous chloride, 300 mg., was added and the mixture was stirred and kept at 20–25° by use of an ice-salt bath. The theoretical amount of nitrogen was evolved within 15 min. A small amount of undissolved material was removed, 400 ml. of water was added, and the mixture was allowed to stand for 72 hr., during which time a large part of the acetone evaporated. A solid which formed was filtered and the filtrate was extracted with three 50-ml. portions of chloroform. Removal of the chloroform left a red oil which on treatment with 50 ml. of water solidified in large part. The material was filtered, combined with the original solid, and the total solids air-dried to give 6.8 g. of a colored product. This material was decolorized with carbon in aqueous methanol and then crystallized from the same solvent to give 5.1 g. (55%) of α-chlorohydrocinnamamide, m.p. 87.5–89°. A sample was crystallized twice from water and then three times from benzene for analysis, m.p. 90–91°; lit.[4a] m.p. 95–96°.

Anal. Calcd. for $C_9H_{10}ONCl$: C, 58.9; H, 5.5; N, 7.6. Found: C, 59.1; H, 5.8; N, 7.8.

α-Chlorohydrocinnamamide was prepared by an independent method[4a] and, after three crystallizations from benzene, its melting point and mixed melting point with the amide described above were found to be 90–91°.

o-Chlorophenylalanine.[12] α-Bromo-*o*-chlorohydrocinnamic acid (3.2 g., 0.012 mole) was dissolved in 100 ml. of an ammonium carbonate-ammonium hydroxide mixture[13] and kept at 25–30° for 96 hr. The solution was concentrated to dryness *in vacuo*, the solid washed twice with cold 50-ml. portions of methanol, and crystallized twice from aqueous methanol to give 1.4 g. (58%) of *o*-chlorophenylalanine, m.p. 234–236° (dec.; softening and yellowing at 229°)[14]; lit. m.p.s.: 260–261°,[12] 241–242° dec.,[15] 226–228.°[16] A sample of authentic *o*-chlorophenylalanine showed the same melting behavior.

Anal. Calcd. for $C_9H_{10}O_2NCl$: N, 7.0. Found: N, 7.2. The amino acid gave positive ninhydrin and Dakin-West reactions.

A sample of the amino acid was benzoylated. The melting point of this benzoyl derivative, the melting point of *N*-benzoyl-*o*-chlorophenylalanine prepared from authentic *o*-chlorophenylalanine, and a mixed melting point of the two had the same value in each case (186.5–187.5°); lit.[17] m.p. 206°.

m-Chlorophenylalanine.[18] The amino acid was prepared by dissolving α-bromo-*m*-chlorohydrocinnamic acid, 5.0 g. (0.019 mole), in 100 ml. of ammonium carbonate-ammonium hydroxide mixture,[13] allowing the mixture to stand at 25–30° for 96 hr., and then working up the solution in the same manner as that described for the *ortho*-isomer; two crystallizations from aqueous methanol gave 2.0 g. (53%) of *m*-chlorophenylalanine, m.p. 215–216° (dec.; softening and yellowing at 209°)[14]; lit. m.p.s.: 234° dec.,[18] 239–241° (dec.).[15] A sample of authentic *m*-chlorophenylalanine showed the same melting behavior.

Anal. Calcd. for $C_9H_{10}O_2NCl$: N, 7.0. Found: N, 7.3. The amino acid gave positive ninhydrin and Dakin-West reactions.

A sample of the amino acid was benzoylated. The melting point of this benzoyl derivative, the melting point of *N*-benzoyl-*m*-chlorophenylalanine prepared from authentic *m*-chlorophenylalanine, and a mixed melting point of the two had the same value in each case (178–179°); lit.[18] m.p. 174°.

p-Chlorophenylalanine.[19] The amino acid was prepared from α-bromo-*p*-chlorohydrocinnamic acid, 5.0 g. (0.019 mole), and an ammonium carbonate-ammonium hydroxide mixture,[13] 100 ml., and purified by the same procedure as that used for the *ortho*-isomer; yield of *p*-chlorophenylalanine, 2.3 g. (60%), m.p. 238–240° (dec.; softening and yellowing at 223°)[14]; lit. m.p.s.: 243–244° (dec.),[19] 253° (dec.),[20] 258–259° (dec.),[15] 236–241°.[16] A sample of authentic *p*-chlorophenylalanine showed the same melting behavior.

Anal. Calcd. for $C_9H_{10}O_2NCl$: N, 7.0. Found: N, 7.3. The amino acid gave positive ninhydrin and Dakin-West reactions.

A sample of the amino acid was benzoylated. The melting point of this benzoyl derivative, the melting point of *N*-benzoyl-*p*-chlorophenylalanine prepared from authentic *p*-chlorophenylalanine, and a mixed melting point of the two had the same value in each case (175.5–176.5°); lit.[19] m.p., 171–172°.

Acknowledgment. The author wishes to express his sincere thanks to Research Corporation for financial support of this work and to Dr. Carl Niemann of the California Institute of Technology for a generous gift of samples of chlorophenylalanines.

LOS ANGELES 41, CALIF.

(12) H. R. Henze, W. B. Whitney, and M. A. Eppright, *J. Am. Chem. Soc.*, **62**, 565 (1940).

(13) N. D. Cheronis and K. H. Spitzmueller, *J. Org. Chem.*, **6**, 349 (1941).

(14) Melting points of the amino acids were determined by introducing the samples on the stage at 200° and controlling the heating rate at 5°/min.

(15) J. C. Nevenzel, W. E. Shelberg and C. Niemann, *J. Am. Chem. Soc.*, **71**, 3024 (1949).

(16) J. H. Burckhalter and V. C. Stephens, *J. Am. Chem. Soc.*, **73**, 56 (1951).

(17) H. Blaschko and J. Stiven, *Biochem. J.*, **46**, 88 (1950).

(18) L. Flatow, *Z. physiol. Chem.*, **64**, 367 (1910).

(19) E. Friedmann and C. Maase, *Biochem. Z.*, **27**, 97 (1910).

(20) A. H. Cook, G. Harris, J. R. A. Pollock, and J. M. Swan, *J. Chem. Soc.*, 1947 (1950).