An Improved Synthesis of Captopril

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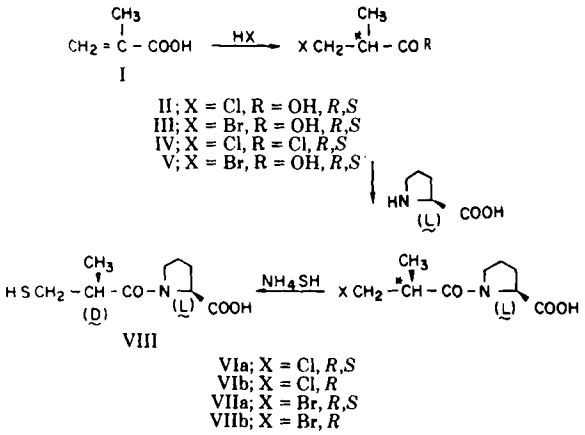
Abstract □ An improved synthesis of captopril using methacrylic acid as the starting material is described. Treatment of methacrylic acid (I) with a hydrogen halide gave the 3-halogeno-2-methylpropanoic acids II and III, which were treated with thionyl chloride to yield the corresponding 3-halogeno-2-methylpropanoyl chlorides IV and V. Treatment of IV or V with L-proline yielded the *N*-(*R,S*-3-halogeno-2-methylpropanoyl)-L-prolines VI and VII, which were separated into optically pure *R*- and *S*-diastereoisomers using dicyclohexylamine. Treatment of halides of VI or VII with methanolic ammonium hydrosulfide gave captopril in 28% yield.

Keyphrases □ Captopril—new synthetic method, antihypertensive, inhibitor of angiotensin-converting enzyme □ Antihypertensive—captopril, new synthetic method

Captopril[1], an orally active hypertensive agent, is a competitive inhibitor of angiotensin I-converting enzyme (1, 2). The synthesis of captopril was first reported by Cushman *et al.* (2) in an overall yield of 12%, starting with 3-acetylthio-2-methylpropanoic acid. More recently, a facile synthesis of captopril was reported (3). This synthesis is convenient and the yield is good (26%); however, the conversion of methacrylic acid to the optically active starting material, *R*-3-hydroxy-2-methylpropanoic acid, using a microbial oxidative transformation (4, 5) is poor. We have developed a more convenient synthesis of captopril using methacrylic acid as a starting material (Scheme I).



Scheme I

EXPERIMENTAL SECTION[2]

***R,S*-3-Halogeno-2-methylpropanoyl Chloride (IV, V)**—Methacrylic acid (I)[3] was treated with anhydrous hydrogen halide to give *R,S*-3-halogeno-2-methylpropanoic acid (II and III) according to the method of Groszkowski *et al.* (6); II (bp_{15} 106–107°C) and III (bp_{15} 106–108°C) were identical with the reported materials (6) by IR and NMR spectroscopy. Treatment of II and III with thionyl chloride to yield IV and V was also carried out by the procedure of Groszkowski *et al.* (6), except a small quantity of *N,N*-dimethylformamide (0.1 mol of II or III) was used as the catalyst (7). Compounds IV (bp_{45} 74–75°C) and V (bp_{30} 72–73°C) were identical with those previously reported by Horii *et al.* (8) by IR and NMR spectroscopy.

***N*-(*R*-3-Halogeno-2-methylpropanoyl)-L-proline (VI, VII)**—For the *N*-acylation of L-proline with IV or V, the procedure of Hongo *et al.* (9) was employed. L-Proline (13.8 g, 0.12 mol) was allowed to react with IV (14.1 g, 0.1 mol) or V (20.1 g, 0.1 mol) in the presence of 84 mL of 2 M NaOH at 0°C for 1 h and then at room temperature for 3 h. The mixture was acidified to pH 1.5 with concentrated hydrochloric acid, and extracted with 500 mL of ethyl acetate. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to yield the syrupy residue (VIa[4] or VIIa[4]). This material was dissolved in acetonitrile, and dicyclohexylamine (21.7 g, 0.12 mol) was slowly added in a dropwise manner with rapid stirring and cooling in an ice bath. The product was removed by filtration to give 36.1 g of the dicyclohexylammonium salt of VIa (90% yield), mp 179–183°C (dec.), or 37.8 g of the salt of VIIa (85% yield), mp 175–180°C (dec.). The crude dicyclohexylammonium salt was dissolved in refluxing acetonitrile–dichloromethane (1:1), and the saturated solution was cooled at room temperature. The dicyclohexylammonium salt of the *R,S*-diastereoisomer of the chloro compound was obtained in 43% yield (15.5 g, white crystals), mp 184–187°C (dec.), $[\alpha]_D^{20}$ −40° (*c*, 2.0, ethanol); the salt of the *R,S*-diastereoisomer of the bromo compound was obtained in 40% yield (15.2 g, white crystals)[5], *mp* 180–183°C (dec.), $[\alpha]_D^{20}$ −44° (*c*, 2.0, ethanol). The optically purified dicyclohexylammonium salt of *R,S*-diastereoisomers dissolved in 1 M $KHSO_4$ was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate–hexane (1:1) to recover 7.8 g of VIb[6] as white crystals (90% yield), mp 110–112°C, $[\alpha]_D^{20}$ −98.9° (*c*, 2.0, ethanol) [IR (KBr): 1710 (amide C=O) and 1590 cm^{-1} (amide C—N); ^{1}H-NMR ($CDCl_3$): δ 1.38 (d, 3, J = 3 Hz, —CH_3), 2.30 (m, 4, —CH_2— in proline), 3.11 (m, 1, —CH—), 3.79 (m, 4, Cl—CH_2—, N—CH_2—), 4.69 (t, 1, J = 2.3 Hz, N—CH—), and 11.30 ppm (s, 1, —COOH)] or 8.6 g of VIIb[6] as white crystals (95% yield), mp 113–115°C, $[\alpha]_D^{20}$ −103.2° (*c*, 2.0, ethanol) [IR (KBr): 1720 (amide C=O) and 1600 cm^{-1} (amide C—N); ^{1}H-NMR ($CDCl_3$): δ 1.50 (d, 3, J = 3 Hz, —CH_3), 2.33 (m, 4, —CH_2— in proline), 3.38 (m, 1, —CH—), 3.86 (m, 4, Br—CH_2—, N—CH_2—), 4.77 (t, 1, J = 2.5 Hz, N—CH—), and 11.40 ppm (s, 1, —COOH).

Anal.—Calc. for VIb ($C_9H_{14}ClNO_3$): C, 49.21; H, 6.42, N, 6.38. Found: C, 49.00; H, 6.69; N, 6.19. Calc. for VIIb ($C_9H_{14}BrNO_3$): C, 40.93; H, 5.34, N, 5.30. Found: C, 41.05; H, 5.43; N, 5.26.

***N*-(*R*-3-Mercapto-2-methylpropanoyl)-L-proline (VIII)**—To the solution of 100 mL of methanolic ammonium hydrosulfide[7], VIb (2.1 g, 0.01 mol) or VIIb (2.6 g, 0.01 mol) was added at room temperature. The resulting mixture was refluxed for 24 h with stirring under a nitrogen atmosphere. The mixture was concentrated to 20 mL under reduced pressure, acidified with 5 M HCl (pH 1), and then extracted with ethyl acetate. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was fractionated by column chromatography using Wakogel C200 by linear gradient of methanol in ethyl acetate (0 to 100%), and the fractions positive to sodium nitroprusside were combined. Recrystallization from ethyl acetate–hexane (1:1) gave 1.86 g of VIII as white crystals from VIb or 1.95 g of VIII from VIIb, mp 105–106°C [lit. (2) mp 104–105°C; lit. (3) mp 105–106°C; $[\alpha]_D^{20}$ −128.2° (*c*, 2.0, ethanol); lit. (2) $[\alpha]_D^{22}$ −131.0°; lit. (3) $[\alpha]_D^{25}$ −129.8°], which was identical by IR and NMR spectroscopy (3) with authentic captopril[8].

RESULTS AND DISCUSSION

To develop a more convenient synthesis of captopril from methacrylic acid, the addition of hydrogen halide to methacrylic acid was attempted using the

[1] *N*-(*R*-3-mercapto-2-methylpropanoyl)-L-proline (*S,S*), SQ 14,225.

[2] Melting points were determined by using a Thomas-Hoover capillary melting point apparatus. IR spectra with a Perkin-Elmer 735B grating IR spectrometer and NMR spectra with a Varian T-60A NMR spectrometer were recorded with each sample. An Autopol III automatic polarimeter (Rudolph Research, N.J.) for the determination of optical rotation, and a Perkin-Elmer 240 elemental analyzer for elemental analysis were also employed.

[3] Methacrylic acid stabilized with 200–300 ppm of *p*-methoxyphenol was obtained from Eastman Kodak Co., Rochester, N.Y.

[4] *N*-(*R,S*-3-halogeno-2-methylpropanoyl)-L-proline.

[5] Optical resolution was performed by the preferential crystallization technique of dicyclohexylammonium salts until its optical rotation was no more increased.

[6] *N*-(*R*-3-halogeno-2-methylpropanoyl)-L-proline.

[7] Prepared by dissolving hydrogen sulfide gas in 98 mL of methanol after addition of 2 mL of concentrated ammonium hydroxide.

[8] Supplied from Squibb Institute for Medical Research, Princeton, N.J.

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method of Groszkowski *et al.* (6). The carboxylic acids (II and III) were converted to their corresponding acyl halides (IV and V) in nearly 95% yield using *N*,*N*-dimethylformamide as a catalyst (7). To avoid protecting the carboxylic function of L-proline, the direct *N*-acylation of L-proline with IV or V was carried out in 90% yield using the procedure of Hongo *et al.* (9). *N*-(*R*,*S*-3-Halogeno-2-methylpropanoyl)-L-proline (VIa or VIIa) was successfully separated into optically pure diastereoisomers using dicyclohexylamine. Treatment of halides of VIb or VIIb with methanolic ammonium hydrosulfide afforded captopril in 28% overall yield. This synthetic method is an improvement over that reported by Cushman *et al.* (12%) (2) and is more convenient than the method reported by Shimazaki *et al.* (3), which involves a fermentation step.

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Phosphorous-Containing Analogues of Aspartame

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Abstract □ Four analogues of aspartame (aspartylphenylalanine methyl ester) were prepared in which one of the carboxylate groups was replaced by a phosphonate group. None of the peptides so obtained was sweet, in contrast with the parent compound which is over 100 times sweeter than sucrose. These results contrast with several published reports of phosphonate analogues of amino acids and peptides which are potent inhibitors of enzymes containing acceptor sites for the parent compound.

Keyphrases □ Aspartame—phosphonate analogues, sweetness

Since the discovery in 1969 that the synthetic dipeptide aspartame (*S*-aspartyl-*S*-phenylalanine methyl ester, I) was over 100 times sweeter than sucrose (1), many analogues have been prepared to ascertain which structural features are responsible for the sweetness. Quite early it was shown that alteration of the aspartyl moiety often result in loss of sweetness, but the phenylalanine moiety can be modified significantly with retention of sweetness (1, 2). More recent work (3) has shown that there are many exceptions to this simple rule, and that the structure-taste relationships are subtle and complicated.

One modification not yet reported is the replacement of one of the two carboxylate groups with a phosphonic acid function. There are several examples in the literature of amino acid and peptide analogues in which carboxylate groups have been replaced by phosphonate groups with retention of biological activity. For example, 1-amino-2-phenylethanephosphonic acid, the phosphonic acid analogue of phenylalanine, is a competitive inhibitor of phenylalanyl-tRNA synthetase (4), 1-amino-3-phosphonobutyric acid inhibits glutamine synthetase (5), and a series of peptides incorporating 1-aminoethanephosphonic acid as the C-terminal residue are shown to have antibacterial properties (6).

These results prompted us to synthesize the following aspartame analogues as diastereomeric mixtures (Scheme I): *R*,*S*-2-amino-3-phosphonopropionyl-*S*-phenylalanine methyl ester (IV); the free acid thereof (V); *S*-aspartyl-*R*,*S*-aminobenzylmethanephosphonate diethyl ester (VIII) and its free acid (IX).

RESULTS AND DISCUSSION

The peptide analogues were made by a standard coupling method (7) from the blocked amino acids. Although other coupling methods have been used to prepare dipeptides incorporating amino phosphonic acids (8), in our hands the mixed anhydride method employing ethyl chloroformate as coupling agent (7, 9) proved most successful. Compound IV was synthesized from *S*-phenylalanine methyl ester and the *N*-benzoxycarbonyl derivative of racemic 2-amino-3-dimethylphosphonopropionic acid (II). After coupling, the fully blocked peptide was partially deblocked to the methyl carboxylate (IV) by treatment with hydrogen bromide in acetic acid. The remaining methyl group was shown to reside on the carboxylate rather than the phosphonate group by recovery of starting material after attempted reesterification with thionyl chloride and methanol, a method which esterifies carboxylic acids but not phosphonic acids. This ester was converted to the fully deblocked peptide (V) by treatment with methanolic sodium hydroxide. Compound VIII was synthesized by coupling *S*-aspartic acid in the form of its *N*-benzoxycarbonyl-γ-benzyl ester derivative (10) with the diethyl ester of racemic aminobenzylmethanephosphonic acid (VI) (11), followed by hydrogenolysis. Deblocking with hydrogen bromide in acetic acid yielded the fully deblocked peptide analogue IX. Spectral data for the blocked aminophosphonic acid (II), blocked peptides (IV and VII), and deblocked peptides (V and IX) are presented in the *Experimental Section*. No attempt was made to separate the diastereomers in each product mixture since a significantly sweet isomer could have been detected by taste in the presence of a large amount of tasteless material.

Following the method previously used for testing sweetness in aspartame analogues (1), cotton swabs were soaked in water solutions of compounds to be tested, and the solutions were sucked off the swab. Usually compounds are not considered significantly sweet unless solutions of ≤2% concentrations evoke a sweet taste. However, even with 5% solutions, each peptide was found to be tasteless or slightly bitter by three different people. The lack of sweetness in IV and V is perhaps not surprising when one considers which modifications of the aspartyl residue of aspartame have previously been found to destroy sweetness. Replacement with an α-aminomalonyl moiety (*i.e.*, removing a methylene group from the aspartyl side chain) yields a compound even sweeter than aspartame (12), while replacing the aspartate by a glutamate moiety (thus adding an extra methylene group to the side chain) destroys sweetness (1). All other modifications of the aspartyl residue have led to nonsweet compounds. This suggests (3) that the N-terminal end of the molecule must incorporate a five- or six-membered zwitterionic ring in order to exhibit

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