bands at 3550(s), 1650(s), 1550(vs), 1465(s), 1400(w), 1300(w), 1220(w), 1178(m), 1080(m), 984(s), 950(s), 895(w), 820(s), 785(w), and 730(w) cm.$^{-1}$.

β-Chloropropionyl Chloride, Vinyl Acetate, and Aluminum Chloride. Method 6.—This reaction was run using 2 moles of β-chloropropionyl chloride.[13] In addition to a large amount of a chloroform-soluble, ether-insoluble red polymer there was obtained 3.3 g. of an orange liquid, b.p. 48°/0.25 mm., n^{25}D 1.4948. This material gave a positive enol test with ferric chloride and had two poorly resolved bands in its infrared spectrum between 1600 and 1700 cm.$^{-1}$ that might be indicative of the β-diketone structure.[3] Because of the low yield no further work was done on this reaction.

Acknowledgment.—The author is indebted to Professor C. S. Marvel for a postdoctoral research associateship and for his support and encouragement and to Dr. P. D. Gardner for helpful and stimulating conversations.

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Synthesis of Two Optically Active N-Acetyl Dipeptides by the *p*-Nitrophenyl Ester Method

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The desire recently arose in this laboratory to utilize the *p*-nitrophenyl ester of N-acetyl-S-benzyl-L-cysteine for the preparation of a protected nonapeptide which in turn was to be used for the synthesis of an acetyl derivative of lysine-vasopressin. The *p*-nitrophenyl ester of the N-carbobenzoxy derivative of S-benzyl-L-cysteine has been used in the synthesis of several peptides without any apparent racemization of the cysteine residue being encountered.[1-4] It was not known, however, whether the *p*-nitrophenyl ester of the N-acetyl derivative could be used similarly. The question of racemization was particularly important since optically active N-acetyl amino acids undergo conversion to their racemic form during peptide synthesis by most of the usual methods.[5,6] It was necessary, therefore, before the desired nonapeptide could be synthesized, to study the ability of *p*-nitrophenyl N-acetyl-S-benzyl-L-cysteinate to form a peptide bond without the configuration of the cysteine simultaneously being changed. The present report describes the preparation of this active ester and its use in the synthesis of two optically active N-acetyl dipeptides.

p-Nitrophenyl esters have been prepared routinely in this laboratory from the protected amino acid and *p*-nitrophenol with the aid of dicyclohexylcarbodiimide.[2,7,8] When the synthesis of *p*-nitrophenyl N-acetyl-S-benzyl-L-cysteinate from N-acetyl-S-benzyl-L-cysteine was attempted by this procedure, only the racemic product could be isolated. Likewise, the mixed anhydride method[9] yielded the optically inactive *p*-nitrophenyl ester. The desired optically active *p*-nitrophenyl ester could be obtained, however, by allowing *p*-nitrophenyl S-benzyl-L-cysteinate hydrobromide[10] to stand overnight in a solution of acetic anhydride in glacial acetic acid. *p*-Nitrophenyl esters of other amino acids with unprotected amino groups have been acylated previously without any apparent loss of optical activity.[10,11]

Ethyl N-acetyl-S-benzyl-L-cysteinylglycinate and methyl N-acetyl-S-benzyl-L-cysteinyl-L-tyrosinate were prepared from the corresponding N-carbobenzoxy dipeptides by acetylation of their decarbobenzoxylation products, a synthetic pathway in which there is considered to be no significant danger of racemization.[2,6,12] Ethyl N-acetyl-S-benzyl-L-cysteinylglycinate then was prepared from *p*-nitrophenyl N-acetyl-S-benzyl-L-cysteinate and ethyl glycinate hydrochloride. Likewise, methyl N-acetyl-S-benzyl-L-cysteinyl-L-tyrosinate was prepared from the active ester and methyl L-tyrosinate. The analytically pure products were isolated in 49 and 81% yield, respectively. Their melting points and optical rotations were in close agreement with the corresponding values for the products obtained by the more conventional synthetic procedure. Although the complete absence of racemization has not been demonstrated, these experiments indicate that the *p*-nitrophenyl ester of N-acetyl-S-benzyl-L-cysteine can be used for the preparation of optically active N-acetyl peptides. It remains to be established, of course, whether the *p*-nitrophenyl esters of other optically active N-acetyl amino acids can be used in peptide synthesis with similar retention of optical activity.

Experimental

All melting points were determined in capillary tubes and are corrected.

N-Acetyl-S-benzyl-L-cysteine.—This compound was prepared by a modification of a procedure reported earlier

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(4) J. Meienhofer and V. du Vigneaud, *ibid.*, **83**, 142 (1961).
(5) M. B. North and G. T. Young, *Chem. Ind.* (London), 1597 (1955).
(6) St. Guttmann and R. A. Boissonnas, *Helv. Chim. Acta*, **41**, 1852 (1958).
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(8) M. Rothe and F. W. Kunitz, *Ann.*, **609**, 88 (1957).
(9) M. Bodanszky, *Acta Chim. Acad. Sci. Hung.*, **10**, 335 (1957).
(10) M. Goodman and K. C. Stueben, *J. Am. Chem. Soc.*, **81**, 3980 (1959).
(11) B. Iselin and R. Schwyzer, *Helv. Chim. Acta*, **43**, 1760 (1960).
(12) K. Hofmann, T. A. Thompson, H. Yajima, E. T. Schwartz, and H. Inouye, *J. Am. Chem. Soc.*, **82**, 3715 (1960).

from this laboratory.[13] S-benzyl-L-cysteine[14] (2.1 g.), 7 *N* sodium hydroxide (2.0 ml.), and Bogen's universal indicator solution[15] (3 drops) were added to water (12 ml.). The resulting solution was green in color because of the presence of the indicator in the alkaline medium. The solution was cooled to about 5° and was stirred at this temperature while acetic anhydride (4.0 ml.) was added in eight portions over a period of 20 min. along with sufficient 1-ml. portions of 7 *N* sodium hydroxide to prevent the green color from fading. Stirring was continued without further cooling for 20 min., 7 *N* sodium hydroxide again being added as necessary to maintain the green color. A total volume of 12.0 ml. of 7 *N* sodium hydroxide was required to prevent the change in color of the indicator. The reaction mixture was cooled again to about 5° and 7 *N* sulfuric acid (13.1 ml., the exact amount required to neutralize to a phenolphthalein end point the 14.0 ml. of 7 *N* sodium hydroxide used in the earlier steps of the preparation) was added slowly with stirring. The crystalline precipitate was filtered and washed with water (25 ml.). The crude product was dissolved in hot 50% ethanol (40 ml.). Charcoal (0.5 g.) was added to the resulting solution and the mixture was heated at the boiling point for 10 min. The mixture was filtered and the charcoal was washed on the funnel with hot 50% ethanol (10 ml.). The filtrate and washings were combined and heated again to the boiling point. Hot water (65 ml.) was added. The mixture was allowed to cool gradually to room temperature. The crystalline product was filtered and washed with water (50 ml.); wt. 1.8 g., m.p. 143.5–145.5°, $[\alpha]^{22}D$ −46.1° (*c* 1, 95% ethanol). Reported,[13] m.p. 143–144°, $[\alpha]^{26}D$ −41.5° (95% ethanol).

Anal. Calcd. for $C_{12}H_{15}O_2NS$: C, 56.9; H, 5.97; N, 5.53. Found: C, 56.9; H, 6.05; N, 5.58.

p-Nitrophenyl N-Acetyl-S-benzyl-DL-cysteinate.—N-Acetyl-S-benzyl-L-cysteine (5.1 g.) and *p*-nitrophenol (3.3 g.) were dissolved in tetrahydrofuran (80 ml.). The resulting solution was cooled to about 5° and stirred at this temperature while a solution of dicyclohexylcarbodiimide (4.1 g.) in tetrahydrofuran (20 ml.) was added in 1-ml. portions over a period of 20 min. Stirring was continued for 40 min. at 5° and then at room temperature for 4 hr. The reaction mixture was filtered and the solid on the funnel was washed with tetrahydrofuran (40 ml.). Tetrahydrofuran was removed *in vacuo* from the combined filtrate and washings. The residue was dissolved in hot propanol (30 ml.) and crystallization was induced by the addition of hexane (60 ml.). The mixture was allowed to stand for 16 hr. and then the product was filtered. It was washed with propanol–hexane (1:2) (30 ml.) and then with hexane (70 ml.); wt. 5.0 g. The product was recrystallized from propanol (25 ml.) and hexane (50 ml.); wt. 4.2 g., m.p. 113–114°, $[\alpha]^{21}D$ 0° (*c* 1, tetrahydrofuran).

Anal. Calcd. for $C_{18}H_{18}O_5N_2S$: C, 57.7; H, 4.85; N, 7.48. Found: C, 57.8; H, 4.97; N, 7.27.

p-Nitrophenyl S-Benzyl-L-cysteinate Hydrobromide.—*p*-Nitrophenyl S-benzyl-N-carbobenzoxy-L-cysteinate[1] (10.0 g.) was dissolved in 4 *N* hydrogen bromide in glacial acetic acid (50 ml.). The solution was allowed to stand at room temperature for 20 min. and then anhydrous ether (650 ml.) was added. The crystalline precipitate was filtered and was washed with ether (150 ml.); wt. 8.6 g., m.p. 155.5–157°, $[\alpha]^{21}D$ −14.0° (*c* 1, tetrahydrofuran), $[\alpha]^{21}D$ + 12.9° (*c* 2.1, ethanol). Reported,[10] m.p. 155–155.5°, $[\alpha]D$ +14.6° (ethanol).[16]

A portion of the product (1.0 g.) was recrystallized from glacial acetic acid (25 ml.) and ether (60 ml.); wt. 0.9 g. The melting point and optical rotation were the same as before recrystallization.

Anal. Calcd. for $C_{16}H_{16}O_4N_2S \cdot HBr$: C, 46.5; H, 4.15; N, 6.78. Found: C, 46.4; H, 4.17; N, 6.68.

p-Nitrophenyl N-Acetyl-S-benzyl-L-cysteinate.—*p*-Nitrophenyl S-benzyl-L-cysteinate hydrobromide (2.0 g.) was dissolved in a solution of acetic anhydride (25 ml.) in glacial acetic acid (25 ml.). The solution was stirred for 15 hr. at room temperature. Acetic anhydride and acetic acid were removed *in vacuo*. The residue was dissolved in hot propanol (20 ml.) and hot hexane (40 ml.) was added. The product began to crystallize as the mixture was allowed to cool gradually. The mixture was stored at 5° for 15 hr. and the crystalline product was filtered. It was washed with propanol–hexane (1:2) (50 ml.) and then with hexane (50 ml.); wt. 1.3 g., m.p. 115.5–116.5°, $[\alpha]^{21}D$ −28.0° (*c* 1, tetrahydrofuran).

Anal. Calcd. for $C_{18}H_{18}O_5N_2S$: C, 57.7; H, 4.85; N, 7.48. Found: C, 57.8; H, 4.95; N, 7.41.

Ethyl S-Benzyl-N-carbobenzoxy-L-cysteinylglycinate.—Ethyl glycinate hydrochloride (5.0 g.) and triethylamine (5.4 ml.) were suspended in chloroform (70 ml.). *p*-Nitrophenyl S-benzyl-N-carbobenzoxy-L-cysteinate (14.0 g.) was added. The reaction mixture was allowed to stand at room temperature for 24 hr. Chloroform was removed *in vacuo*. Ether (100 ml.) was added to the residue. The crystalline solid was filtered and washed with ether (20 ml.). It then was washed successively by trituration with 5% sodium bicarbonate (300 ml.), water (20 ml.), *N* hydrochloric acid (100 ml.), and water (200 ml.); wt. 11.2 g., m.p. 96.5–98°.

A portion of the product (8.4 g.) was recrystallized from ethyl acetate (50 ml.) and hexane (50 ml.); wt. 7.5 g., m.p. 96.5–98°, $[\alpha]^{20}D$ −35.0° (*c* 2, ethanol), $[\alpha]^{20}D$ −40.6° (*c* 4.32, dioxane). Reported, m.p. 94°,[17] 98–99°,[18,19] $[\alpha]D$ −39.6° (dioxane).[17]

Anal. Calcd. for $C_{22}H_{26}O_5N_2S$: C, 61.4; H, 6.09; N, 6.51. Found: C, 61.2; H, 6.09; N, 6.50.

Ethyl N-Acetyl-S-benzyl-L-cysteinylglycinate. Method A.—Ethyl S-benzyl-N-carbobenzoxy-L-cysteinylglycinate (2.15 g.) was dissolved in 4 *N* hydrogen bromide in glacial acetic acid (10 ml.). The solution was allowed to stand at room temperature for 15 min. and then anhydrous ether (90 ml.) was added. The decarbobenzoxylation product settled out as a viscous oil on the sides of the reaction vessel. Ether was removed by decantation. The product was washed with ether (90 ml.) and the ether was removed again by decantation. 0.5 *N* potassium bicarbonate (50 ml.) was added to the oily product and the resulting suspension was extracted four times with 25-ml. portions of ethyl acetate. The ethyl acetate extracts were combined, dried over anhydrous magnesium sulfate, and filtered. *p*-Nitrophenyl acetate[20] (0.91 g.) was added to the filtrate. The resulting solution was concentrated *in vacuo* to a volume of about 6 ml. The concentrated solution was allowed to stand at room temperature for 16 hr. during which time the product crystallized. Ether (50 ml.) was added. The crystalline product was filtered and washed with ether (20 ml.); wt. 1.05 g., m.p. 115–116.5°.

A portion of the product (0.95 g.) was recrystallized from hot water (80 ml.); wt. 0.80 g., m.p. 116.5–117.5°, $[\alpha]^{21}D$ −43.7° (*c* 1, tetrahydrofuran).

Anal. Calcd. for $C_{16}H_{22}O_4N_2S$: C, 56.8; H, 6.55; N, 8.28. Found: C, 56.7; H, 6.59; N, 8.29.

Method B.—*p*-Nitrophenyl N-acetyl-S-benzyl-L-cysteinate (1.12 g.), ethyl glycinate hydrochloride (0.50 g.), and

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(14) J. L. Wood and V. du Vigneaud, *ibid.*, **130**, 109 (1939).

(15) E. Bogen, *J. Am. Med. Assoc.*, **89**, 199 (1927).

(16) When this compound was allowed to stand in ethanol or methanol, the optical rotation gradually became less positive. This may account for the discrepancy between the observed and reported rotations.

(17) K. C. Hooper, H. N. Rydon, J. A. Schofield, and G. S. Heaton, *J. Chem. Soc.*, 3148 (1956).

(18) S. Goldschmidt and G. Rosculet, *Chem. Ber.*, **93**, 2387 (1960).

(19) J. Honzl and J. Rudinger, *Collection Czech. Chem. Commun.*, **26**, 2333 (1961).

(20) C. Huggins and J. Lapides, *J. Biol. Chem.*, **170**, 467 (1947).

triethylamine (0.51 ml.) were added to chloroform (8 ml.). The resulting suspension was stirred at room temperature for 15 min. and then allowed to stand at room temperature without further stirring for 16 hr. Chloroform was removed *in vacuo* and ether (50 ml.) was added to the residue. The mixture was allowed to stand at room temperature for 3 hr. The solid product was filtered and washed successively with ether (40 ml.) and water (13 ml.). It then was dissolved in glacial acetic acid (6 ml.) and water (35 ml.) was added in small portions while the solution was heated to about 60°. The solution was allowed to cool gradually to room temperature during which time the product began to crystallize. The mixture was allowed to stand at 5° for 6 days. The product was filtered and washed with water (20 ml.); wt. 0.50 g., m.p. 115.5–116.5°, $[\alpha]^{21}D$ −44.0° (*c* 1, tetrahydrofuran).

Anal. Found: C, 56.6; H, 6.56; N, 8.29.

Ethyl N-Acetyl-S-benzyl-DL-cysteinylglycinate.—This compound was prepared from *p*-nitrophenyl N-acetyl-S-benzyl-DL-cysteinate and ethyl glycinate hydrochloride by the procedure described for the preparation of ethyl N-acetyl-S-benzyl-L-cysteinylglycinate from the L *p*-nitrophenyl ester and ethyl glycinate hydrochloride. The reaction was carried out on the same scale and the product was purified by exactly the same procedure; wt. 0.48 g., m.p. 86.5–87.5°, $[\alpha]^{21}D$ 0° (*c* 1, tetrahydrofuran).

Anal. Calcd. for $C_{16}H_{22}O_4N_2S$: C, 56.8; H, 6.55; N, 8.28. Found: C, 56.9; H, 6.57; N, 8.26.

Methyl N-Acetyl-S-benzyl-L-cysteinyl-L-tyrosinate. Method A.—Methyl S-benzyl-N-carbobenzoxy-L-cysteinyl-L-tyrosinate[21] (1.57 g.) was dissolved in 4 *N* hydrogen bromide in glacial acetic acid (8 ml.). The solution was allowed to stand at room temperature for 20 min. and then anhydrous ether (240 ml.) was added. The decarbobenzoxylation product settled out as a viscous oil on the sides of the reaction vessel. Ether was removed by decantation. The product was washed with two 25-ml. portions of ether, the ether again being removed by decantation. The oily product was dissolved in water (50 ml.). Potassium bicarbonate (3.8 g.) was added and the resulting suspension was extracted four times with 30-ml. portions of ethyl acetate. The ethyl acetate extracts were combined, dried over anhydrous magnesium sulfate, and filtered. *p*-Nitrophenyl acetate[20] (0.54 g.) was added to the filtrate. The resulting solution was concentrated *in vacuo* to a volume of about 5 ml. and the concentrated solution was allowed to stand at room temperature for 3 days. Ethyl acetate was removed *in vacuo*. The residue was dissolved in glacial acetic acid (10 ml.) and then water (50 ml.) was added in an unsuccessful attempt to crystallize the product. The oily suspension was extracted five times with 25-ml. portions of ethyl acetate. The ethyl acetate extracts were combined, dried over anhydrous magnesium sulfate, and filtered. Ethyl acetate and acetic acid were removed *in vacuo* from the filtrate. The oily residue was dissolved in ethyl acetate (10 ml.) and hexane (20 ml.) was added. The crystalline product was filtered; wt. 0.50 g., m.p. 130–135°. It was recrystallized twice from glacial acetic acid (5 ml.) and water (20 ml.); wt. 0.26 g., m.p. 138.5–141.5°, $[\alpha]^{21}D$ −20.0° (*c* 1, tetrahydrofuran).

Anal. Calcd. for $C_{22}H_{26}O_5N_2S$: C, 61.4; H, 6.09; N, 6.51. Found: C, 61.5; H, 6.13; N, 6.47.

Method B.—*p*-Nitrophenyl N-acetyl-S-benzyl-L-cysteinate (1.12 g.) and methyl L-tyrosinate[22] (0.64 g.) were dissolved in tetrahydrofuran (34 ml.). The solution was allowed to stand at room temperature for 3 days. Tetrahydrofuran was removed *in vacuo* and the residue was dissolved in glacial acetic acid (10 ml.). Water (50 ml.) was added in small portions while the solution was heated to about 60°. The solution was allowed to cool gradually to room temperature during which time the product began to crystallize. The mixture was stored at 5° for 16 hr. The product was filtered and washed with water (25 ml.); wt. 1.18 g. It was recrystallized from ethyl acetate (20 ml.) and hexane (40 ml.), wt. 1.05 g., m.p. 141.5–142.5°, $[\alpha]^{20}D$ −20.0° (*c* 1, tetrahydrofuran).

Anal. Found: C, 61.4; H, 6.25; N, 6.46.

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(21) This compound was prepared by the *p*-nitrophenyl ester method following a procedure reported earlier from this laboratory (ref. 1). In the reported procedure the crude dipeptide methyl ester was saponified and the resulting free acid was purified. In the present work the crude ester was purified by recrystallization from methanol and water, m.p. 110–112°, $[\alpha]^{20}D$ −27.6° (*c* 2.1, dimethylformamide), $[\alpha]^{19}D$ −20.8° (*c* 2, 95% ethanol). The methyl ester prepared by the dicyclohexylcarbodiimide method (ref. 1) when recrystallized from methanol and water melted at 109–110° and possessed a rotation of −27.5° in dimethylformamide (M. Bodanszky, unpublished). This same dipeptide ester synthesized by the azide method has been reported to melt at 110–111° and to possess an optical rotation of −30.5° in 95% ethanol [H. S. Bachelard and V. M. Trikojus, *J. Chem. Soc.*, 4541 (1958)]. Since the observed rotation in 95% ethanol was not in agreement with the reported value, the dipeptide ester was synthesized in this laboratory by the azide method and also by the mixed anhydride method [J. R. Vaughan, Jr., and J. A. Eichler, *J. Am. Chem. Soc.*, **75**, 5556 (1953)]. It was not possible by either of these procedures to obtain material with a rotation significantly different from −20.8° in 95% ethanol, the value found for the product prepared by the *p*-nitrophenyl ester method.

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Partially Fluorinated Aliphatic Compounds by Reductive Desulfurization of Substituted Thiophene

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The reductive desulfurization of substituted thiophenes has been proposed as a synthetic route for the preparation of long-chain acids, ketones, alcohols, and hydrocarbons.[1] The preparation of a straight-chain saturated hydrocarbon was accomplished by the condensation of thiophene and an acid in the presence of phosphorus pentoxide, Clemmensen reduction of the resulting ketone, and finally, desulfurization with Raney nickel. Lengthening of the chain can be accomplished by further reaction in the 5-position of thiophene. Various branched-chain compounds can be prepared by the use of suitably β-substituted thiophenes.

The purpose of our investigation was to determine whether this synthetic technique could be utilized for the preparation of partially fluorinated

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