Chemistry of Heterocyclic Compounds, Vol. 31, No. 2, 1995

SYNTHESIS OF SEVERAL HETERYLDEHYDROPEPTIDES BY THE OXAZOLONE METHOD

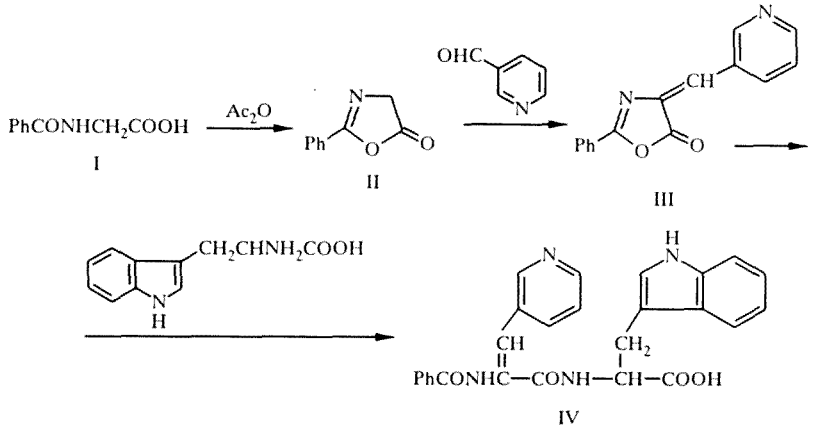
V. A. Slavinskaya, D. É. Sile, M. Katkevich,
É. Kh. Korchagova, I. U. Lipsbergs,
I. V. Turovskii, and É. Lukevits

(E)-N-Benzoyldehydro-3-(3-pyridyl)-alanyltryptophan was synthesized in 89% yield by the reaction of 2-phenyl-4-(3-pyridylidene)-5(4H)-oxazolone with tryptophan. The reaction of 4-[1-(2-furyliden)ethyl]- and 4-(3-pyridyliden)-2-phenyl-5(4H)-oxazolones with alanyltryptophan gives a mixture of the Z *and* E *isomers of the corresponding dehydrotripeptides. Racemization of the alanyl and tryptophan residues was not observed.*

The oxazolone method is commonly used in the synthesis of modified amino acids and peptides [1] and serves as the major method for preparing dehydroamino acids [2] and α-methylamino acids. This method, which is especially fruitful in the synthesis of achiral α,α-dialkylamino acids, gives good yields without requiring the use of expensive reagents. In some cases, the oxazolone method gives higher yields than the dicyclohexylcarbodiimide method. Lewis acids and other catalysts are used in the oxazolone method to prevent epimerization of the amino acid residues [4, 5].

We have used the oxazolone method for the synthesis of derivatives of tryptophan and alanylproline. Dehydrodipeptides containing tryptophan have anti-tumor properties [6]. Alanylproline derivatives hold promise as inhibitors of angiotensin conversion enzyme [7].

N-Benzoyldehydro-3-(3-pyridyl)alanyltryptophan was obtained by the condensation of 2-phenyl-4-(3-pyridyliden)-5(4H)-oxazolone with tryptophan in the presence of triethylamine as the condensing agent. The synthesis was carried out starting from hippuric acid as follows:



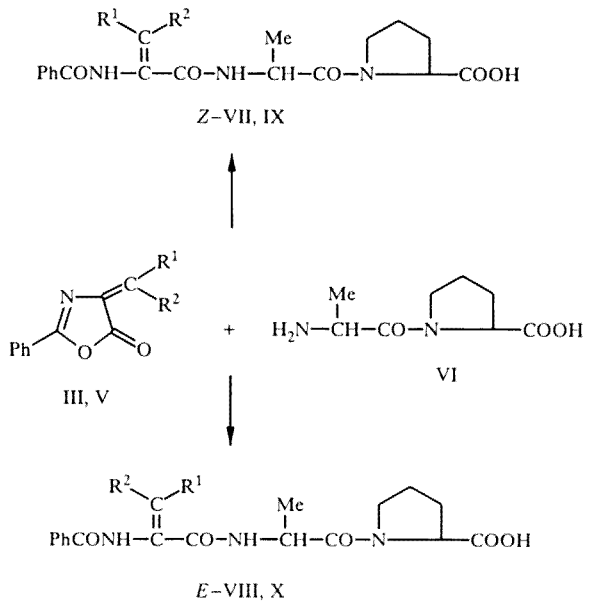
Pyridine derivative III was synthesized by the reaction of hippuric acid with 3-pyridinaldehyde in the presence of acetic anhydride and K_2CO_3 according to a method proposed by Griffith and Harwood [8]. An attempt to condense 2-pyridinaldehyde with hippuric acid proved unsuccessful due to heavy tar formation.

Latvian Institute of Organic Synthesis, LV-1006 Riga, Latvia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 232-235, February, 1995. Original article submitted December 12, 1994.

 0009-3122/95/3102-0202$12.50

Condensation product IV contains virtually only the *E* isomer of the residue of the corresponding dehydroalanine. The product yield is 88.7%. The corresponding tryptophan derivative containing a 2-furyl group in the dehydroalanine residue could not be obtained since this reaction is nonselective.

The condensation of 2-phenyl-4-(3-pyridyliden)-5(4H)-oxazolone (III) and 2-phenyl-4-[1′-(2-furyl)-ethyliden]-5(4H)-oxazolone (V) with alanylproline (VI) leads to the *Z* and *E* isomers of alanylproline derivatives:



III, IX, X R^1 = 3-pyridyl, R^2 = H; V, VII, VIII R^1 = 2-furyl, R^2 = Me

The ratios of the isolated isomers (*Z*-VII:*E*-VIII = 1:2 and *Z*-IX/*E*-X = 1:2.5) indicate the exclusive effect of the amino acid or amino acid residue, with which the derivatives of the corresponding oxazolone form a peptide bond, on the structure of the final product. Separation of the *Z* and *E* isomers of the corresponding alanylproline derivatives could not be achieved under our reaction conditions. Racemization of the amino acid residue directly bound to the dehydroalanine residue was not observed.

EXPERIMENTAL

A sample of hippuric acid was prepared by the acylation of glycine with benzoyl chloride in an alkaline medium [9]. The purity of the sample was 97%. Samples of 2- (98% purity) and 3-pyridinaldehyde (97% purity) were obtained from Fluka Chemie AG, while 2-acetylfuran (96% purity, TU 6-09-16-898-74) was obtained from Biokhimreaktiv Science and Production Firm. Samples of 2-phenyl-4-[1′-(2-furyl)ethyliden]-5(4H)-oxazolone and 2-phenyl-4-(3-pyridyli-den)-5(4H)-oxazolone were obtained according to Chipens et al. [7].

The unreacted starting materials and reaction products were analyzed by liquid chromatography on a DuPont 830 chromatograph using a 4.6×110-mm column. The column was packed with Silasorb SPH C_{18} for the analysis of N-benzoyldehydro-3-(3-pyridyl)-alanyltryptophan (λ 230 nm) and N-benzoyldehydro-3-(3-pyridyl)alanylalanylproline (λ 225 nm). The eluent was 22% acetonitrile and 78% 0.2 M ammonium acetate. The analysis of N-benzoyl- 3-methyl-3-(2-furyl)alanylalanylproline (λ 254 nm) was carried out on a 4.6×150-mm column packed with Zorbax C_8. The eluent was 20% acetonitrile and 80% 0.2 M ammonium acetate.

The desired products were purified on a Büchi preparative chromatograph. The 26×470-mm column was packed with Silasorb C_{18} (LC). The eluent in the separation of N-benzoyldehydro-3-methyl-3-(2-furyl)alanylalanylproline was 25% acetonitrile and 75% 0.1 M ammonium acetate. The eluent in the separation of N-benzoyldehydro-3- (3-pyridyl)-alanylalanylproline was 15% acetonitrile and 85% 0.1 M ammonium acetate.

The PMR spectra of the desired products were taken on a Bruker AM-360 spectrometer in DMSO-D_6 using TMS as the internal standard at 30°C. The *Z* and *E* isomers were identified according to the methods of Tatsuta [10] and Srinivasan [11]. The mass spectra were taken on an AEI MS-50 mass spectrometer at 70 eV.

The elemental analysis for C, H, N for previously unreported compounds corresponded to the calculated values.

N-Benzoyldehydro-3-methyl-(3-(2-furyl)alanylalanylproline (VII, VIII, $C_{23}H_{25}N_3O_6$). A sample of 0.6 g (6 mmoles) triethylamine was added to a solution of 0.719 g (2.99 moles) alanylproline hydrochloride and 0.76 g (3 mmoles) 2-phenyl-4-[1'-(2-furyl)ethyliden]-5(4H)-oxazolone in 15 ml tetrahydrofuran. The reaction mixture was stirred at room temperature for six days until all traces of the dipeptide disappeared. The solvent was evaporated and the dry residue was washed with dry ether. The residue was crystallized from ethanol to give 1.15 g crude product containing 92.8% (1.069 g) of the desired product in 81.2% yield. The desired tripeptide was purified for analytical purposes on a preparative chromatograph. The ratio of the *Z* and *E* isomers was 1:2.

PMR spectrum, δ, ppm: 7.69 (*Z*), 7.73 (*E*) (NH), 2.25 (*E*), 2.31 (*Z*) (CH_3), 6.54, 6.65, 7.45-7.62, 7.95 (4-HFu, 3-HFu, 5-HFu, +*m,p*-HPh, *o*-HP, respectively) — ΔAla, 7.92 (*Z*), 7.97 (*E*) (NH), 4.42 (*Z*), 4.58 (*E*) (α-H), 1.2 (*Z*), 1.26 (*E*) (β-H) — Ala, 4.06 (*Z*), 4.20 (*E*) (α-H), 1.70, 1.90, 2.05, 2.55 (β + γCH_2), 3.30 and 3.40 (*Z*), 3.50 and 3.70 (*E*) (δCH_2) — Pro.*

N-Benzoyldehydro-3-(3-pyridyl)alanylalanylproline (IX, X, $C_{23}H_{24}N_4O_5$). A sample of 0.89 ml triethylamine was added to a solution of 0.77 g (3.2 mmole) alanylproline hydrochloride, 0.89 g (3.5 mmoles) 2-phenyl-4-(3-pyridyl-iden)-5(4H)-oxazolone in 15 ml tetrahydrofuran. The reaction mixture was stirred at room temperature for 12 days until all traces of the dipeptide disappeared and then evaporated. The precipitate obtained was washed with ether and crystallized from acetonitrile to give 1.26 g (2.88 mmoles) product in 90.1% yield. For analytical purposes, the desired tripeptide was purified on a preparative chromatograph. The ratio of the *Z* and *E* isomers was 1:2.5, mp 162°C.

PMR spectrum, δ, ppm: 10.05 (*E*),10.20 (*Z*) (NH), 7.30 (*E*), 7.41 (*Z*) (β-H), 7.38, 7.50-7.70, 7.92, 7.97, 8.36, 8.75 (5-HPy, 4-HPy, *m,p*-HPh, *o*-HPh, 2-HPy, 6-HPy, respectively) — ΔAla, 8.20 (NH), 4.45 (*Z*),4.65 (*E*) (α-H), 1.20 (*Z*), 1.25 (*E*) (β-H) — Ala, 4.22 (α-H), 1.70-2.20 (β+γCH_2), 3.20-3.50 (δCH_2 (*Z*)), 3.52 and 3.70 (δCH_2 (*E*)) — Pro.*

(*E*)-N-Benzoyldehydro-3-(3-pyridyl)alanyltryptophan (IV, $C_{26}H_{22}N_4O_4$). Three drops of triethylamine were added to a solution of 1.12 g (5.5 mmoles) tryptophan and 1.50 g (5.9 mmoles) 2-phenyl-4-(3-pyriliden)-5(4H)-oxazolone in 17 ml tetrahydrofuran. The reaction mixture was stirred at room temperature for about 12 days until all traces of tryptophan disappeared. The solvent was then evaporated. The yellow precipitate was washed with ether and crystallized from ethanol to give 2.4 g product containing 92% desired dipeptide, mp 147°C.

PMR spectrum, δ, ppm: 9.95 (NH), 7.20 (β-H), 7.45-7.65 (NCOC_6H_5), 8.68, 8.45, 7.90, 7.35 (β-HPy, 2-HPy, 6-HPy, 4-HPy, 5-HPy, respectively) — ΔAla, 8.23 (NH), 4.59 (α-H), 3.20, 3.29 (β-H), 12.58 (CO_2H), 10.85 (Trp NH), 7.95, 7.32, 7.19, 7.05, 6.45 (4-H, 7-H, 2-H, 6-H, 5-H Trp, respectively) — Trp.

REFERENCES

1. V. A. Slavinskaya, D. É. Sile, M. Yu. Katkevich, É. Kh. Korchagova, and É. Lukevits, Khim. Geterotsikl. Soedin., No. 6, 829 (1994).
2. G. I. Chipens, V. A. Slavinskaya, A. K. Strautinya, D. É. Sile, D. R. Kreile, and A. Yu. Krikis, Modified Amino Acids and Derived Peptides [in Russian], Zinatne, Riga (1987), p. 67.
3. D. G. Doxerty, J. E. Tietzman, and M. Bergmann, J. Biol. Chem., **147**, 617 (1943).
4. P. Wipf and H. Heimgartner, Helv. Chim. Acta, **69**, No. 5, 1153 (1986).
5. P. Wipf and H. Heimgartner, Helv. Chim. Acta, **71**, No. 1, 140 (1988).
6. E. Etschenberg, W. Opitz, and S. Radatz, German Federal Republic Patent No. 2,659,154; Chem. Abstr. (1978).
7. G. I. Chipens, V. A. Slavinskaya, A. K. Strautinya, D. É. Sile, É. Kh. Korchagova, and O. M. Galkin, in: G. I. Chipens (ed.), Structure and Action of Zinc Enzymes–Kinases II and Enkephalinases, Zinatne, Riga (1990), p. 12.
8. R. K. Griffith and H. J. Harwood, J. Org. Chem., **29**, 2658 (1964).
9. Organic Syntheses [Russian translation], Coll. Vol. 2, Izd. Inos. Lit., Moscow (1949), p. 158.

*β-H see along with γCH_2.

10. K. Tatsuta, S. Miura, H. Gunji, T. Tamai, R. Yoshida, T. Inagaki, and Y. Kurita, Bull. Chem. Soc. Jpn., **67**, 1701 (1994).
11. A. Srinivasan, V. D. Richard, and R. K. Olsen, Tetrahedron Lett., No. 12, 891 (1976).