The aqueous layer from the hydrolysis mixture was extracted in a continuous ether extractor. The ether extract was combined with the ether layer from the hydrolysis mixture, and the ether was removed from the dried (sodium sulfate) ether soution through a Fenske column. The residue was distilled *in vacuo* (5 mm.) through a Vigreux column. The distillate (4.69 g.) was condensed in a receiver which was in a −70° bath. A residue of 0.43 g. remained in the distilling flask. The constituents of this distillate were identified by comparison with authentic samples by v.p.c. (cyanosilicone column). The quantitative v.p.c. analysis of the distillate was carried out by the method of internal normalization.[7] The distillate contained isopropyl alcohol (12.8 mmoles), ethylisopropylcarbinol (36.7 mmoles, 69% yield on the basis of 1 mole of ozonide giving 2 moles of carbinol), and unidentified material (0.14 g.).

(7) R. L. Pecsok, "Principles and Practice of Gas Chromatography," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 143.

A New Synthesis of *p*-Methylaminobenzoyl-L-glutamic Acid[1]

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Received December 8, 1964

The preparation of *p*-methylaminobenzoyl-L-glutamic acid, an intermediate in the synthesis of N^{10}-methylfolic acid and analogs, by the aminolysis of sodium *p*-iodobenzoyl-L-glutamate with methylamine at pH 8–9 has been reported.[2] The desired acid failed to crystallize, and the crude sodium salt was isolated in unspecified yield.

We were unsuccessful with this procedure until the use of sodium hydroxide during the condensation was eliminated. The *p*-methylaminobenzoyl-L-glutamic acid was then isolated in low yield as the dihydrated barium salt from which the free acid was obtained as an oil. There was also a possibility of racemization of the optically active compound in the alkaline solution at elevated temperature. In a procedure here described, *p*-methylaminobenzoyl-L-glutamic acid hydrobromide has been synthesized in high purity and yield suitable for the synthesis of N^{10}-methylfolic acid and derivatives.

Starting with *p*-methylaminobenzoic acid, the methylamino group was protected by carbobenzyloxylation before conversion of the acid into its chloride. The N-*p*-[(carbobenzyloxy)methylamino]benzoyl chloride was allowed to react with diethyl L-glutamate as in the synthesis of derivatives of aminobenzoylglutamic acid.[3] The resulting ester was hydrolyzed by alkali to afford N-{*p*-[(carbobenzyloxy)methylamino]benzoyl}-L-glutamic acid. The carbobenzyloxy group was removed by 40% hydrogen bromide in glacial acetic acid,[4] and the *p*-methylaminobenzoyl-L-glutamic acid was isolated as the hydrobromide. Attempts to remove the hydrogen bromide from the dipeptide with pyridine, triethylamine, or sodium hydrogen carbonate yielded an oily product which could not be reconverted to the crystalline hydrobromide by treatment with hydrogen bromide in ether. The diethyl ester was prepared by the decarbobenzyloxylation of diethyl N-{*p*-[(carbobenzyloxy)methylamino]benzoyl}-L-glutamate and it showed optical rotation identical with that reported.[2] This indicates that no racemization occurred in the earlier aminolysis procedure.[2]

(1) Supported in part by grants from the National Institutes of Health, U. S. Public Health Service, No. CY-3335 and C-6516.

(2) D. B. Cosulich and J. M. Smith, Jr., *J. Am. Chem. Soc.*, **70**, 1922 (1948).

(3) S.-C. J. Fu, *J. Med. Pharm. Chem.*, **5**, 33 (1962).

(4) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

Experimental[5]

Barium *p*-Methylaminobenzoyl-L-glutamate from *p*-Iodobenzoyl-L-glutamic Acid.—*p*-Iodobenzoyl-L-glutamic acid,[2] $\lambda_{max}^{H_2O}$ 252 mμ, 2 g. (5.3 mmoles), 5 ml. of 30% aqueous solution of methylamine, and 10 mg. of fine copper powder was heated in a sealed tube at 150° for 10 hr. The reaction mixture was diluted with 10 ml. of methanol and filtered. Upon concentration under nitrogen, a golden oil resulted, which defied attempts at crystallization and which gave unreproducible refractive indices and erroneous elementary analyses. The oil was redissolved in 5 ml. of methanol and treated with 5 ml. of 0.5 *M* barium chloride in 50% methanol. The precipitated barium *p*-methylaminobenzoyl-L-glutamate was collected and washed with methanol; yield 0.6 g. (24%), $\lambda_{max}^{H_2O}$ 291 mμ.

Anal. Calcd. for $C_{13}H_{14}BaN_2O_5 \cdot 2H_2O$: C, 34.6; H, 4.0; N, 6.2. Found: C, 34.1; H, 4.0; N, 6.0.

Treatment of the barium salt with 1 *N* sulfuric acid to pH 6 afforded the free dipeptide as an oil which again gave unreproducible refractive indices and erroneous elementary analyses.

N-*p*-[(Carbobenzyloxy)methylamino]benzoic Acid.—*p*-Methylaminobenzoic acid (2 g., 13.3 mmoles) purified by the nitrosation procedure[6] was dissolved in 10 ml. of 2 *N* sodium hydroxide. To this solution was added carbobenzyloxy chloride (2.3 ml., 16 mmoles) alternately with 17 ml. of 2 *N* sodium hydroxide at 0°. Upon acidification to pH 3, the crude compound precipitated; it was collected and washed with cold water. The pure N-*p*-[(carbobenzyloxy)methylamino]benzoic acid was obtained after two recrystallizations from glacial acetic acid; yield 66%, m.p. 149.5–151.5°.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.3; N, 4.9. Found: C, 67.3; H, 5.4; N, 4.9.

Diethyl N-{*p*-[(Carbobenzyloxy)methylamino]benzoyl}-L-glutamate.—The N-*p*-[(carbobenzyloxy)methylamino]benzoyl chloride was prepared by treating N-*p*-[(carbobenzyloxy)methylamino]benzoic acid (1.4 g., 5 mmoles) with phosphorus pentachloride (1.2 g., 5.5 mmoles) in 20 ml. of anhydrous ether. The acid chloride was not isolated; the ether solution was washed with 10 ml. of ice-cold water and immediately poured into a mixture of diethyl L-glutamate hydrochloride[7] (1.2 g., 5 mmoles) and sodium hydrogen carbonate (3.3 g., 40 mmoles) in 20 ml. of ethyl acetate and 20 ml. of water. This was stirred at 0° for 15 min. and then at 25–30° for 1 hr. The organic phase was separated and washed successively with 10 ml. each of water, 2 *N* hydrochloric acid, and water. The crude product obtained after evaporation of the solvent was recrystallized from ethyl acetate–*n*-hexane (1:5) and acetone–*n*-hexane (1:5); yield 79%, m.p. 85°, sintered at 64–66°.

Anal. Calcd. for $C_{25}H_{30}N_2O_7$: C, 63.8; H, 6.4; N, 6.0. Found: C, 63.7; H, 6.2; N, 6.0.

N-{*p*-[(Carbobenzyloxy)methylamino]benzoyl}-L-glutamic Acid Hydrate.—Diethyl N-*p*-[(carbobenzyloxy)methylamino]-benzoyl-L-glutamate (2.4 g., 5 mmoles) was hydrolyzed in 1 *N* sodium hydroxide (11 ml., 11 mmoles) and 11 ml. of methanol, first at 0° for 10 min. and then at 25–30° for 1 hr. The resulting

(5) All melting points are corrected. Optical rotation was measured with a Bellingham and Stanley polarimeter. Ultraviolet absorption spectra were recorded with a Cary Model 15 spectrophotometer. The elementary analyses were performed by Dr. C. K. Fitz, Needham Heights, Mass.

(6) (a) A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **66**, 2127 (1944); (b) F. Klaus and O. Baudisch, *Ber.*, **51**, 1036 (1918).

(7) $[\alpha]^{25}D$ +23.0° (absolute ethanol). $[\alpha]D$ +22.4° (water) is given in J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1961, p. 932.

clear solution was acidified to pH 3 with 6 *N* hydrochloric acid. The crude waxy crystals were recrystallized from acetone–*n*-hexane (1:5). The yield was quantitative; m.p. 74–75°.

Anal. Calcd. for $C_{21}H_{22}N_2O_7 \cdot H_2O$: C, 58.3; H, 5.6; N, 6.5. Found: C, 58.6; H, 6.0; N, 6.5.

***p*-Methylaminobenzoyl-L-glutamic Acid Hydrobromide.**— To N-{*p*-[(carbobenzyloxy)methylamino]benzoyl}-L-glutamic acid (1 g., 2.4 mmoles), 3 ml. of 40% hydrobromic acid in glacial acetic acid[4] was added with vigorous stirring at 25° for 1 hr. The evolution of carbon dioxide had almost subsided in 15 min. and the clear solution was stirred for another 30 min. Anhydrous ether (30 ml.) was added and the mixture was stirred continuously at 4° for 20 hr. After decantation of the ether, the semisolid was dried *in vacuo* over phosphorus pentoxide, concentrated sulfuric acid, and sodium hydroxide pellets. A white hygroscopic crystalline powder was obtained and no further purification was necessary. The yield was 78%; m.p. 72–74° dec. (sealed tube), $\lambda_{max}^{H_2O}$ 291 mμ (ε 15,050), $[\alpha]^{25}D$ −7.45° (H_2O).

Anal. Calcd. for $C_{13}H_{16}N_2O_5 \cdot HBr$: C, 43.2; H, 4.8; Br, 22.1; N, 7.8. Found: C, 43.2; H, 5.2; Br, 21.8; N, 7.7.

Diethyl *p*-Methylaminobenzoyl-L-glutamate.—Diethyl N-{*p*-[(carbobenzyloxy)methylamino]benzoyl}-L-glutamate (1 g., 2.4 mmoles) and 3.5 ml. of 40% hydrobromic acid in glacial acetic acid were stirred at 25° for 45 min., by the end of which time evolution of carbon dioxide had subsided. Anhydrous ether (30 ml.) was added and the reaction mixture was continuously stirred at 4° for 20 hr. The ether was decanted and the residual semisolid was dried *in vacuo* over phosphorus pentoxide, concentrated sulfuric acid, and sodium hydroxide pellets. The crude diethyl *p*-methylaminobenzoyl-L-glutamate hydrobromide was obtained as a white hygroscopic powder.

The crude product (0.65 g.) was dissolved in 8 ml. of absolute ethanol and filtered through Darco.[8] To the clear solution were added 0.5 ml. of pyridine, a few crystals of sodium hydrogen sulfite, and 40 ml. of water. The crystallization of diethyl *p*-methylaminobenzoyl-L-glutamate was complete at the end of 72 hr. at 0°. The yield was 75%; white needles from either ethyl acetate–*n*-hexane (1:5) or dilute ethanol, m.p. 89–91°, $[\alpha]^{25}D$ −20.50° (1 *N* HCl); lit.[2] m.p. 89.8–91.0°, $[\alpha]^{25}D$ −21° (1 *N* HCl).

Anal. Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.7; H, 7.2; N, 8.3. Found: C, 61.0; H, 7.3; N, 8.5.

This ester was also formed when a solution of 1 g. (2.8 mmoles) of *p*-methylaminobenzoyl-L-glutamic acid hydrobromide in 10 ml. of absolute ethanol saturated with hydrogen chloride was allowed to stand in a closed vessel for 36 hr. at room temperature. After removal of the solvent under reduced pressure, the residue was treated with pyridine and then twice recrystallized from ethyl acetate–*n*-hexane (1:5). The pure diethyl *p*-methylaminobenzoyl-L-glutamate was obtained in 60% yield; the physical properties were the same as those described above.

Anal. Found: C, 60.9; H, 7.1; N, 8.3.

Acknowledgment.—The authors wish to express their appreciation to Dr. Leonard T. Capell, Chemical Abstracts Service, for discussion of the nomenclature.

(8) Darco, grade G-60, Atlas Chemical Industries, Wilmington, Del.

The Synthesis of Cyanovinylguanidines

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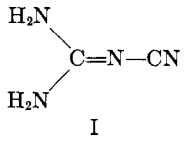
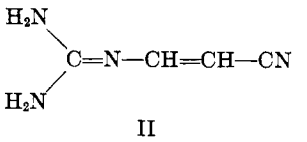
Received December 1, 1964

Cyanoguanidine (I) has enjoyed considerable utility as a reagent in organic synthesis.[1] The vinylogous cyanoguanidine system II is, however, unknown. In this communication, we describe the preparation and properties of *trans*- and *cis*-tetramethylcyanovinylguanidines VII and VIII, substituted examples of structure II, and our unsuccessful efforts to isolate II itself.

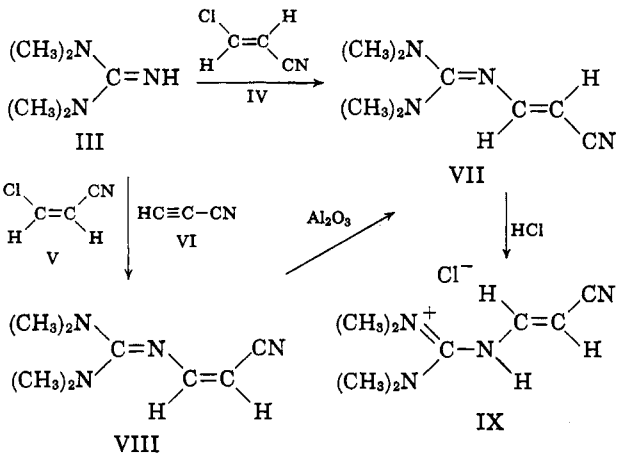


I



II

The first synthetic route employed was predicated upon conjugate addition of tetramethylguanidine (III) to 3-chloroacrylonitrile. Single different products were obtained when *trans*- and *cis*-3-chloroacrylonitrile (IV and V) were used. The spin–spin coupling constants (14 and 7 c.p.s.) of the olefinic protons in the n.m.r. spectra of the respective isomeric products indicated[2] that they were *trans*- and *cis*-2-(2-cyanovinyl)-1,1,3,3-tetramethylguanidine (VII and VIII).



These stereochemical results imply that a likely course of reaction is addition of the guanidine to the acrylonitrile, followed by rotation about the central C–C bond of the anion to achieve the *trans* coplanarity necessary for elimination of chloride. The sequence is illustrated for the *trans* and *cis* isomers by eq. 1 and 2. These results are in complete accord with the recently published observations of Scotti and Frazza[4] on the addition of other nucleophiles to 3-chloroacrylonitrile.

A second synthetic route consisted of the addition of tetramethylguanidine to propiolonitrile (VI). As expected, the product formed by *trans* addition to the acetylenic bond[5] was the *cis*-cyanovinylguanidine VIII.

trans-Cyanovinylguanidine VII formed a crystalline hydrochloride. Evidence for protonation on the central nitrogen (IX) was found in the ultraviolet spectrum, which showed a marked hypsochromic shift relative to the base. The *trans* isomer VII appears to be more stable than *cis* isomer VIII, as shown by the conversion of VIII to VII with basic alumina.

(1) V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947.

(2) It has been shown[3] that the magnitude of the spin–spin splitting constant falls between 11 and 18 c.p.s. for *trans* olefinic protons and between 6 and 14 c.p.s. for *cis* olefinic protons. When values for a pair of isomers fall outside the range of overlap, structural assignments may be made with reasonable certainty.

(3) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p. 85.

(4) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).

(5) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 349.