Glutamic acid analogues. The synthesis and identification of 4-isopropyl-3,5-dicarbethoxy-2-pyrrolidinone[1]

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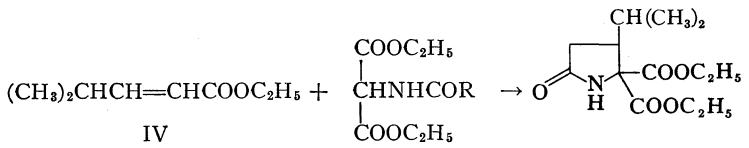
During an investigation involving the synthesis of 3-alkylglutamic acids (1), a series of 4-alkyl-3,5,5-tricarbethoxy-2-pyrrolidinones was treated with hydrochloric acid. The hydrolysates were concentrated to dryness followed by treatment at an elevated temperature to obtain the corresponding 4-alkyl-5-carboxy-2-pyrrolidinones.

With 4-isopropyl-3,5,5-tricarbethoxy-2-pyrrolidinone (I), however, the same treatment led to an isolable acid, $C_9H_{13}NO_5$, m.p. 186–187° (decomp.). When this acid was heated at 220°, it underwent decarboxylation, with subsequent formation of 4-isopropyl-5-carboxy-2-pyrrolidinone (2). Elemental analysis, the neutralization equivalent, and a negative ninhydrin test strongly suggested that this unknown was the dicarboxylic acid of either 4-isopropyl-3,5-dicarbethoxy-2-pyrrolidinone (II) or 4-isopropyl-5,5-dicarbethoxy-2-pyrrolidinone (III). We now have determined its structure.

The unknown dicarboxylic acid was esterified to the diethyl ester, m.p. 106–108°. III was prepared by a known method (1); the Michael reaction of ethyl 4-methyl-2-pentenoate (IV) and diethyl acetamidomalonate (V, R = CH_3) gave an addition–cyclization product identified as III, m.p. 98–99°. Reaction of IV with diethyl propionamidomalonate (V, R = C_2H_5) also gave III. The mixed melting point of III and the diethyl ester of the unknown acid was depressed by a magnitude of 20°. The two esters gave different infrared and nuclear magnetic resonance spectra, thus eliminating III as the possible unknown.

The nuclear magnetic resonance spectrum ($CDCl_3$) of the diethyl ester of the unknown acid agreed well with that expected for structure II. There was a multiplet centered at τ 7.18, a doublet (J = 11.0 c.p.s.) at τ 6.60, and another doublet (J = 7.6 c.p.s.) at τ 5.75,[3] for which we have assigned the C_4, C_3, and C_5 protons, respectively. Each of these peaks integrated for one proton.[4] When II was treated with hexadeuteriodimethyl sulfoxide in the presence of a catalytic amount of potassium *t*-butoxide (room temperature, 24 h), the doublet at τ 6.60 disappeared. In the spectrum of 2-pyrrolidinone (VI), the C_5-methylene protons (τ 6.60) were observed at lower field than the C_3-methylene pro-



IV V, R = CH_3 or C_2H_5 III

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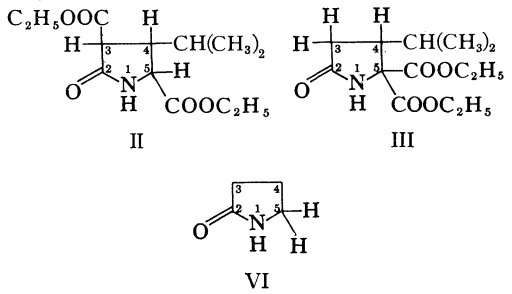
[3]This doublet was buried among the two carbethoxyl methylene quartets, but was clearly observed upon expansion of the spectrum.

[4]Integration of the doublet at τ 5.75 and the two quartets overshadowing it amounted to five protons, indicating that the doublet at τ 5.75 is represented by one proton. The unknown dicarboxylic acid showed a similar doublet (J = 7.5 c.p.s.) at τ 5.90.



II III

VI

tons (3). This lends support to the present assignment of the C_5 proton to the doublet at τ 5.75 and not to the doublet at τ 6.60; since both the C_3 and C_5 positions carry a carbethoxyl group, the relative chemical shifts of the C_3 and C_5 protons of II are expected to be the same as in VI. That only one doublet has been observed for both the C_3 and C_5 protons seems to suggest that II might exist mainly in one stereoisomer (probably 3,4-*trans*-4,5-*trans*). Thin-layer chromatography (silica gel) showed only a single spot on the plate.

Compound III, on the other hand, showed the C_4 proton as a multiplet centered at τ 7.08, and the C_3-methylene protons in four peaks at τ 7.76, τ 7.68, τ 7.62, and τ 7.54.[5]

Compounds II and III and the triester I all showed two doublets for the isopropyl methyl groups (see Experimental), indicating that the two methyl groups are magnetically non-equivalent. This two-doublet phenomenon persisted at 150°.[6] The unknown dicarboxylic acid also exhibited two doublets for the isopropyl methyls both at room temperature and at 130°. This magnetic non-equivalence could occur if these compounds exist mainly in one particular conformational isomer, probably the one in which the C_4-hydrogen and the methine hydrogen of the isopropyl substituent are *trans* to each other. Examples of the magnetic non-equivalence involving the isopropyl group have been cited previously (4, and references therein).

[5]We were not able to determine the coupling constants involved in these protons.

[6]The nuclear magnetic resonance spectra at elevated temperatures were measured in hexadeuteriodimethyl sulfoxide solution.

EXPERIMENTAL

All melting points were taken in open capillary tubes on a Mel-Temp apparatus and are corrected. Elemental analyses were carried out by Strauss and Weiler, Oxford, England. Nuclear magnetic resonance spectra were measured on a Varian Associates model A-60 spectrometer with tetramethylsilane as an internal reference. Infrared spectra were measured with a Unicam SP.200 spectrophotometer.

4-Isopropyl-3,5,5-tricarbethoxy-2-pyrrolidinone (I)

This was prepared according to a previously described procedure (1), m.p. 79–80°. Nuclear magnetic resonance ($CDCl_3$): τ 9.17 (d) and τ 8.99 (d) ($CH(\mathbf{CH_3})_2$), τ 8.71 (t) ($COOCH_2\mathbf{CH_3}$), τ 8.23 (m) ($\mathbf{CH}(CH_3)_2$), τ 6.80 (m) (C_4—**H** and C_3—**H**), τ 5.85 (q) and τ 5.78 (q) ($COO\mathbf{CH_2}CH_3$), τ 1.83 (s) (N**H**).

4-Isopropyl-3,5-dicarboxy-2-pyrrolidinone

4-Isopropyl-3,5,5-tricarbethoxy-2-pyrrolidinone (10 g, 0.029 mole) was dissolved in 80 ml of concentrated hydrochloric acid and refluxed for 3 h; then the reaction mixture was concentrated to 20 ml at a temperature below 70°. The precipitate thus obtained was recrystallized from water–ethanol (4:1), 2.9 g (46.4%), m.p. 186–187° (decomp.).

Anal. Calcd. for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51; neutralization equiv. 107.6. Found: C, 50.65; H, 6.08; N, 6.62; neutralization equiv. 108.1, 108.3.

Infrared (Nujol): 3.0–4.0 μ (a broad band typical of COOH), 5.74 μ and 6.02 μ (C=O). Nuclear magnetic resonance (dimethyl sulfoxide-d_6): τ 9.15 (d) and τ 9.01 (d) ($CH(\mathbf{CH_3})_2$), τ 8.45 (m) ($\mathbf{CH}(CH_3)_2$), τ 7.43 (m) (C_4—**H**), τ 6.85 (J = 11 c.p.s.) (C_3—**H**), τ 5.90 (J = 7.5 c.p.s.) (C_5—**H**), τ 1.76 (s) (N**H**), τ 0.63 (broad) (COO**H**).

4-Isopropyl-3,5-dicarbethoxy-2-pyrrolidinone (II)

Hydrogen chloride gas was passed into 70 ml of anhydrous ethanol until it was saturated. To this solution was added 2.0 g (0.0093 mole) of 4-isopropyl-3,5-dicarboxy-2-pyrrolidinone, and the flask was stoppered and allowed to remain at room temperature for 2 days. The reaction mixture was transferred to a flash evaporator and the solvent removed at a temperature below 60°. The residual liquid was treated with 20 ml of cold water, whereupon the residue crystallized. The crystals were collected and recrystallized from ethanol, 1.5 g (59.5%), m.p. 106–108°.

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.41; H, 7.64; N, 5.18.

Infrared (CCl_4): 2.87 μ, 3.08 μ, and 3.20 μ (NH); 5.76 μ (CO, ester); 5.86 μ (CO, lactam). Nuclear magnetic resonance ($CDCl_3$): τ 9.13 (d) and τ 8.96 (d) ($CH(\mathbf{CH_3})_2$), τ 8.71 (t) ($COOCH_2\mathbf{CH_3}$), τ 8.51 (m) ($\mathbf{CH}(CH_3)_2$), τ 7.18 (m, τ 6.95 – τ 7.42) (C_4—**H**), τ 6.60 (d, J = 11.0 c.p.s.) (C_3—**H**), τ 5.75 (d, J = 7.6 c.p.s.) (C_5—**H**), τ 5.80 (q) and τ 5.76 (q) ($COO\mathbf{CH_2}CH_3$), τ 2.40 (s) (N**H**).

4-Isopropyl-5,5-dicarbethoxy-2-pyrrolidinone (III)

Diethyl acetamidomalonate (5.43 g, 0.025 mole), 3.65 g (0.025 mole) of IV, and 0.3 g (0.013 g-atom) of

sodium metal dissolved in 70 ml of absolute alcohol were refluxed for 10 h. Work-up of the reaction mixture followed by recrystallization from ethanol gave 4.3 g (63.4%) of crystals, m.p. 98–99°. By replacing diethyl acetamidomalonate (V, R = CH_3) with diethyl propinonamidomalonate (V, R = C_2H_5) the identical product was obtained in a yield of 28.4%.

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.70; H, 7.69; N, 5.12.

Infrared (CCl_4): 2.89 μ, 3.10 μ, and 3.20 μ (NH); 5.78 μ (CO, ester); 5.88 μ (CO, lactam). Nuclear magnetic resonance ($CDCl_3$): τ 9.14 (d) and τ 9.00 (d) ($CH(CH_3)_2$); τ 8.71 (t) ($COOCH_2CH_3$); τ 8.18 (m) ($CH(CH_3)_2$); τ 7.76, τ 7.68, τ 7.62, and τ 7.54 (C_3—H_2); τ 7.08 (m) (C_4—H); τ 5.76 (q) and τ 5.73 (q) ($COOCH_2CH_3$); τ 2.80 (s) (NH).

1. Y. C. Kim and G. H. Cocolas. J. Med. Chem. **8**, 509 (1965).
2. Y. C. Kim. M.Sc. Thesis, University of North Carolina, Chapel Hill, North Carolina. 1962.
3. N. S. Bhacca, L. F. Johnson, and J. N. Shoolery. NMR Spectra Catalogue. Vol. 1. Varian Associates, Palo Alto, California. 1962. Spectrum No. 68.
4. N. S. Bowman, D. E. Rice, and B. R. Switzer. J. Am. Chem. Soc. **87**, 4477 (1965).

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The reaction of all-*cis* cyclopentanetetracarboxylic acid dianhydride with primary amines

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Although Alder and his co-workers (1) have thoroughly investigated the stereochemistry of the cyclopentanetetracarboxylic acids, the reaction of the all-*cis* dianhydride I with primary amines has not been reported. This note reports the reaction of I with different primary amines.

The *cis*-dianhydride gave primarily *cis*-diimides II. However, the isomeric *trans*-diimides III could also be isolated, as well as an imide-*trans*-diamide IV (Reaction Scheme 1).

The exact mechanism of imide formation has not been unequivocally demonstrated, but probably is as shown in Reaction Scheme 2 (2). The first step involves nucleophilic attack of the base on the carbonyl carbon to form the intermediate A, which quickly loses a proton to the basic medium to form B; this then picks up a proton from solution to form C, the amide-carboxylic acid.

Apparently, an imide may be formed in two ways: either by the elimination of water from the amide-acid (heating succinanilic acid just above the melting point for $\frac{1}{2}$ h gives an 18% yield of *N*-phenylsuccinimide) (Reaction Scheme 3), or by the formation of a diamide, which easily loses an amine to give the imide (3) (steps 6–8; Reaction Scheme 4).

In this latter sequence, step 6 (internal nucleophilic attack of the amide nitrogen on the adjacent carbonyl) is of great significance. It seems logical that the less basic the amine, the slower the rate of the nucleophilic attack. However, in this work, no definite conclusion can be drawn concerning the basicity of the amine in relation to the final isolable products. This is due to the difficulty of isolation of the various products of the reaction. A significant reaction competing with step 6 is the base-catalyzed isomerization at carbon 2 (Reaction Scheme 5).

Carbon 2 is the logical place for the first inversion because of the steric crowding. Since, in structure E, the group at position 1 has a hydrogen on one side and an amide group on the other side, whereas the group at position 2 has amide and anhydride groups on either side, inversion at carbon 2 is the easiest way to decrease crowding and increase stability, and thus give rise to a structure like IV*a*. Alder (1) gave

[1]Taken in part from the M.S. thesis of Rose Ann Blau, Loyola University, Chicago, Illinois, June 1966.