(±)-β-Methyleneaspartic Acid

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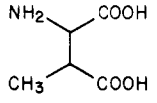
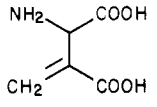
L-*threo*-β-Methylaspartic acid (I)[1] is a principal in the



I

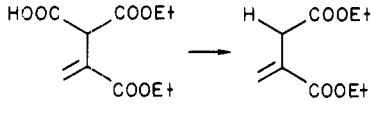
reversible isomerization of β-methylaspartate to glutamate,[2] one of the three known coenzyme B_{12} dependent, enzyme-catalyzed, carbon-skeleton rearrangement reactions. β-Methylaspartic acid (I) also occurs in nature as a component of the polypeptide antibiotics aspartocin[3] and glumamycin.[4] Because there exists a high level of interest in the β,γ-unsaturated amino acids[5] and expressly for the purpose[6] of attachment to the cobalt atom of vitamin B_{12}, the unsaturated analogue of I, β-methyleneaspartic acid (II), has been synthesized. The long-range goal of this



II

research is that of constructing a model intermediate for the β-methylaspartate ⇄ glutamate carbon-skeleton rearrangement reaction.[6]

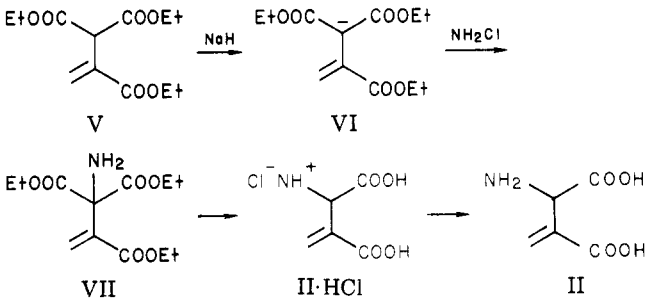
The problem, as it developed, was that initial approaches to the desired unsaturated amino acid II, including Curtius,[7] Schmidt,[8] and Gabriel reactions, were unsuccessful. For example, mixed anhydride[9] and phosphoryl azide[10] methods attempted on the half-ester–half-acid III



III IV

gave high yields of diethyl itaconate, the product of decarboxylation. Indeed, exposure of the half-acid III to triethylamine at room temperature resulted in rapid decarboxylation to diethyl itaconate (IV), accompanied by minor amounts of mesaconate and citraconate. The acid chloride, prepared from the half-acid III, proved to be quite unstable as signaled by the rapid disappearance of the vinyl hydrogens in the NMR spectrum. No well-defined products could be isolated from the latter decomposition reaction.

Scheme I



V VI VII II·HCl II

Attention was then directed to a sequence in which chloramine[11] is used to aminate a malonate anion. Thus, 1,1,2-tricarbethoxyprop-2-ene (V) was reacted with sodium hydride (Scheme I). The resulting anion VI was then treated, in the cold, with a dry solution of chloramine in ether. The product amino triester VII was isolated in 65% yield, following extraction and washing through silica gel. The alternative regioisomer, the result of amination at the methylene group, was neither expected nor observed in this kinetic amination reaction.

The spectral properties of the amino triester VII were in excellent accord with those expected. The proton NMR spectrum showed a pair of terminal vinyl methylene singlets at δ 5.87 and 6.17 together with the absorption of the ethyl ester and amine groups at higher field. The infrared spectrum showed ester carbonyl together with a doublet at 3320 and 3400 cm^{-1} appropriate for the primary amino group. The mass spectrum can be understood in terms enumerated by Biemann, Seibl, and Gapp[12] for diethyl aspartate and diethyl glutamate. Thus, no molecular ion (*m/e* 273) is observed, but an $M^+ + H$ peak is observed at *m/e* 274. The first fragment peak occurs at *m/e* 227 and corresponds to loss of EtOH, presumably with formation of a lactam.[12] The next peak in the spectrum is the base peak at *m/e* 200 resulting from loss of a carbethoxy group from the amine-bearing carbon. The $C_9H_{14}NO_4$ composition, presumed for the *m/e* 200 peak, was firmly established by measurement of its exact mass. The next peak at *m/e* 172 results from loss of ethylene from the *m/e* 200 fragment, as observed for diethyl aspartate.[12] A doublet at *m/e* 154, 153 results from loss of EtOH and EtOH + H from *m/e* 200. A very strong peak at *m/e* 127 results from loss of carbethoxy from the *m/e* 200 fragment. Finally, a strong peak at *m/e* 98 may be ascribed to β-elimination giving rise to ethyl propiolate. Good precedent[12] exists for β-elimination when the leaving carbon is sp^3 hydridized, in which case the fragment is an olefin rather than an acetylene.

The amino triester VII was dissolved in 20% hydrochloric acid and heated at 65 °C for approximately 100 h (see Experimental Section) to effect hydrolysis and decarboxylation. The desired amino acid II was isolated as the hydrochloride, following removal of the aqueous acid medium. The hydrochloride of II is a white, very hygroscopic foam. It is best to carry it forward to the amino acid II, which is simply accomplished by treatment of the crude hydrochloride with 2 N sodium hydroxide. At pH 5 the desired amino acid II precipitates from solution.

Given the relative ease of transformation of the β,γ-unsaturated amino acids to their α,β-unsaturated isomers under the influence of acid, it would appear that the

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success of the present procedure depends upon the reluctance with which the electron-deficient double bond is protonated. Thus, the procedure described here may not be generally applicable to the preparation of other β,γ-unsaturated amino acids, although this remains to be tested by experiment. The chloramine procedure is, however, an effective method for the preparation of the β-methyleneaspartic acid hydrochloride (II·HCl) described here, an instance in which a variety of other methods were not successful.

Experimental Section

1-Amino-1,1,2-tricarbethoxyprop-2-ene (VII). 1,1,2-Tricarbethoxyprop-2-ene (V)[13] (15 g, 0.058 mol) was dissolved in 200 mL of benzene in a 500-mL three-necked, round-bottomed flask equipped with an addition tube charged with sodium hydride (3.6 g, 50% dispersion in mineral oil, 0.075 mol). The reaction flask was evacuated three times and flushed with nitrogen and then cooled to 0 °C. The sodium hydride was added slowly at a rate such that the evolution of hydrogen and attendant foaming were controlled. When the addition was complete, the ice bath was removed and the solution was stirred at room temperature for 1 h. The benzene was removed under vacuum, yielding the white solid sodium salt VI. The solid VI was suspended in 140 mL of ether, placed in a dropping funnel, and added to 185 mL of an ice-cold, stirred solution of chloramine (0.63 M) in ether. When the addition was complete, the reaction mixture was stirred for 1 h at 0 °C. The ice bath was removed and the reaction was allowed to warm to room temperature and stirred for an additional 2-h period. The reaction mixture was then filtered and extracted with four 20-mL portions of a 10% HCl solution. The combined aqueous acid layers were made basic with Na_2CO_3 and extracted with four 20-mL portions of ether. The combined ether layers were dried with $MgSO_4$ and concentrated under vacuum, yielding 9.205 g of a light green oil.

The crude product from three such amination reactions was placed on a column of 65 g of silica gel and eluted with 60:40 hexane–ethyl acetate; 200-mL fractions were collected. The course of chromatographic purification can be followed by using thin-layer chromatography. The desired amino triester VII is characterized by R_f 0.57 in 50:50 benzene–hexane. Fractions 2 and 3 contain pure product and were combined, yielding 31 g (65%) of colorless oil.

The amino triester VII showed in its proton NMR spectrum (CCl_4) a nine-proton methyl triplet (J = 7 Hz) at δ 1.27, a two-proton amine singlet at δ 2.18, a six-proton methylene quartet at δ 4.13, and a pair of one-proton vinyl singlets at δ 5.87 and 6.17. The carbon-13 NMR spectrum ($CDCl_3$) showed peaks at 13.24 (quartet, $\mathbf{C}H_3CH_2O$), 60.51 (triplet, $CH_3\mathbf{C}H_2O$), 61.56 (triplet, $CH_3\mathbf{C}H_2O$), 67.33 (singlet, CNH_2), 125.32 (triplet, $\mathbf{C}H_2{=}C$), 130.37 (singlet, $CH_2{=}\mathbf{C}$), 164.87 (singlet, COOEt), and 169.17 (singlet, COOEt) ppm relative to tetramethylsilane as an internal standard. The infrared spectrum (neat) showed a carbonyl band at 1730 cm^{-1} and NH_2 bands at 3320 and 3400 cm^{-1}. The mass spectrum (70 eV) showed m/e (percent relative intensity) 274 (7.1, M^+ + H), 227 (4.6, M^+ - EtOH), 200 (100, M^+ - COOEt), 172 (12.7, M^+ - COOEt - C_2H_4), 154 (1.06, M^+ - COOEt - EtOH), 153 (11.5, M^+ - COOEt - EtOH - H), 127 (90.1, M^+ - 2 COOEt - H), and 98 (76.1 $HC{=}CCOOEt^+$). Exact mass calcd for $C_9H_{14}NO_4$, 200.0923; found, 200.0916.

β-Methyleneaspartic Acid Hydrochloride (II·HCl). The amino triester VII (2 g, 0.007 mol) was dissolved in 21 mL of a 20% hydrochloric acid solution in a 50-mL round-bottomed flask. The reaction was heated 82 h at 65 °C. The solvent was removed, yielding 1.46 g of white foam. The continued presence of an ethyl ester absorption in the NMR spectrum showed that the reaction was not complete. The residue was taken up in 20 mL of fresh acid solution, and the mixture was heated for 23 h at 65 °C. Evaporation of the aqueous solution yielded 1.462 g of a very hygroscopic noncrystalline product. The NMR spectrum (CD_3OD) showed a one-proton methine singlet at δ 4.97, a pair of one-proton vinyl singlets at δ 6.33 and 6.67, and a three-proton broad singlet (OH and NH) at δ 5.77. When the decarboxylation was carried out in DCl–D_2O the singlet at δ 4.97 was absent from the NMR spectrum. The infrared spectrum (KBr) showed a very broad, strong peak at 3500–2750 cm^{-1} together with expected bands at 1710 and 1630 cm^{-1}.

(±)-β-Methyleneaspartic Acid. A solution of 4.2 g of amino triester VII in 50 mL of 20% hydrochloric acid was heated for 68 h at 74 °C. The solution was then taken to dryness, leaving a yellow hygroscopic solid. An NMR spectrum of the solid showed that the hydrolysis was not complete. The solid was redissolved in 50 mL of fresh 20% hydrochloric acid, and the mixture was heated for an additional 48 h at 74 °C. The reaction mixture was concentrated under vacuum, leaving a solid residue. The solid was treated with small portions of a solution of 2 N sodium hydroxide until the solid dissolved and the pH of the solution became approximately 5 (approaching the isoelectric point). At this point 1.08 g of a white solid precipitated from the solution. The mother liquor was made acidic with 10% hydrochloric acid, concentrated under vacuum, and re-treated with 4 N NaOH, yielding a white solid. Two further repetitions of the latter process gave a total of 0.78 g of white solid of sufficient purity that it was combined with the first crop above. The total crude weight of the desired amino acid II was 1.87 g (84% yield). The product thus obtained was slightly off-color, but the NMR spectrum taken as the hydrochloride (D_2O/DCl, TSP reference) showed only the expected three singlets at δ 5.02, 6.37, and 6.73 together with a solvent singlet at δ 5.16. The carbon-13 NMR spectrum (D_2O/DCl, $CHCl_3$ external reference taken as 77.20 ppm) showed a pair of carboxyl singlets at 167.12 and 169.73 ppm, a vinyl triplet at 136.59 ppm, a vinyl singlet at 131.65 ppm, and a methine doublet at 53.93 ppm.

Crystallization from 15 mL of hot water yielded 1.59 g (72%) of white crystalline product II. The amino acid II does not have a sharp melting point; it begins to decompose at 170 °C, becoming progressively darker in color as the temperature is raised above this point.

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Registry No. (±)-II, 71195-09-0; (±)-II·HCl, 71195-10-3; V, 71195-11-4; VI, 71195-12-5; VII, 71195-13-6.

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Organotellurium Chemistry. 3. (*o*-Nitrophenyl)tellurenyl Bromide: A Highly Stabilized Tellurenyl Halide

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Among the arylchalcogen monohalides, the synthetically valuable arylselenenyl halides[1] have been the object of much more intensive study by organic chemists than their less stable sulfur[2] and tellurium[3] counterparts. The least-studied class of this group has been the aryltellurenyl

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