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Amino Acids from Methyl Formamidomalonate

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Phenylalanine, tyrosine, norleucine, and aspartic acid have been prepared from methyl formamidomalonate. Its alkylated products have higher melting points and are more easily hydrolyzed than corresponding ethyl acetamidomalonates.

One of the classical methods of producing α-amino acids is to make an α-haloacid and then treat it with concentrated ammonium hydroxide. This method has sometimes proved unsatisfactory because of the lengthy procedure involved in the isolation of a product free from ammonium halide.

Goldeckemeyer[2] condensed an α-haloester (ethyl chloroacetate) with potassium phthalimide and then hydrolyzed with concentrated hydrochloric acid at 200° in a sealed tube.

The next advancement was made by Sorensen[3] who condensed potassium phthalimide with ethyl bromomalonate. The resulting ethyl phthalimidomalonate was then alkylated and upon hydrolysis as before gave an amino acid. The malonic acid was decarboxylated during the hydrolysis. This method eliminated the need of a variety of α-haloacids or their esters and substituted the use of readily available alkyl halides.

Thirty-seven years later Redemann and Dunn[4] used ethyl benzamidomalonate as a reagent for the preparation of amino acids; thus, the ease of hydrolysis and decarboxylation was improved. Ethyl acetamidomalonate was prepared by Cerchez[5] in 1931, but he did not use it to prepare amino acids. Its use for this purpose was suggested by M. Tishler.[6] The acetamido group is more easily hydrolyzed than the benzamido group, but the ultimate in an acyl group appeared when Galat[7] used ethyl formamidomalonate in 1947. The acyl group cannot be eliminated without exposing the nitrogen atom to competing alkylation.[4] The sole remaining simplification is the use of methyl formamidomalonate. This compound was reported by Conrad and Schulze[8] in 1909, but its use to prepare amino acids was not reported until Hellmann and Lingens[9] used it to prepare precursers for tryptophan and glutamic acid.

Methyl formamidomalonate appeared to us to have two advantages over ethyl formamidomalonate. The first of these is that methyl esters generally have higher melting points than the corresponding ethyl esters. This has also been pointed out by Hellmann and Lingens. Secondly, methyl esters hydrolyze more readily than ethyl esters. The working time from alkyl halide to amino acid is then less because of greater ease in getting a crystalline intermediate and in carrying out its cleavage. This aids in the preparation of unsaturated amino acids where γ-δ unsaturated alkyl malonates on acid cleavage give lactones.[10] Although methyl esters are less hindered than ethyl esters, alkylation with secondary C_4 halides was not successful with methyl formamidomalonate.

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To see how the melting points varied with structure, the following table was completed by synthesizing the unknown compounds:

Compound	M.P.	M.P. of *n*-Butyl	Derivative
Ethyl acetamidomalonate	97°[11]	42°[10]	oil[12]
Methyl acetamidomalonate	128.5°[9]	100°	
Ethyl formamidomalonate	48°[8]	83°[13]	
Methyl formamidomalonate	85°[8]	109.5°	

Since the condensation of ethyl acetamidomalonate with ethyl bromoacetate gave an oil,[14] a similar reaction was tried with methyl formamidomalonate. The product was readily crystallized and melted at 94°. The yield was 80%. Galat condensed ethyl formamidomalonate with ethyl chloroacetate and obtained a brown syrup containing some crystals. This was hydrolyzed to aspartic acid with a yield of 55%.[7]

The rate of hydrolysis in base is twice as great for methyl esters as for the corresponding ethyl esters.[15] In acid hydrolysis the difference is not so large, but the methyl esters still hydrolyze at a slightly faster rate.

As was expected, the hydrolysis of our methyl esters occurred quite rapidly. The esters were placed in constant boiling hydrobromic acid and were heated under a reflux condenser. From the top of the condenser a drying tube containing sodium hydroxide was led to a solution of silver nitrate. The end of a hydrolysis or cleavage of an ether group was found by noting when fresh silver nitrate no longer gave a silver bromide precipitate. Corresponding ethyl esters required three to four hours before the test was negative. Aspartic acid was synthesized from ethyl carbethoxymethylacetamidomalonate by refluxing with 7 hr. constant-boiling hydrochloric acid.[14] The ethyl carboethoxyformamidomalonate was heated for 3 hr.[7] Our methyl carbethoxymethylformamidomalonate hydrolyzed completely in 60 minutes. Albertson and Archer[16] synthesized phenylalanine by condensing ethyl acetamidomalonate with benzyl chloride and then heating the intermediate under reflux with constant-boiling hydrobromic acid for 7.5 hr. The melting point of this ethyl acetamidobenzylmalonate was 104° and the overall yield was 60%. We found that methyl benzylformamidomalonate melted at 153°, its hydrolysis took 60 minutes, and the overall yield was 73%.

To check further the speed of hydrolysis, tyrosine was synthesized by chloromethylating anisole, condensing it with methyl formamidomalonate and then heating with hydrobromic acid. In this preparation an ether cleavage was involved as well as hydrolysis and decarboxylation, but again the silver nitrate test was negative at the end of 60 minutes. Formamido compounds dissolve in hot hydrobromic acid in a few minutes as the formyl group comes off readily to form an amine salt. This rapid solution facilitates hydrolysis of the ester groups above that which would be found for acetamido or benzamidomalonates. As the average atmospheric pressure at the University of Colorado is about 630 mm. of mercury, solutions come to a boil at lower temperatures. As a result the length of time needed for hydrolysis may be less elsewhere.

EXPERIMENTAL

Methyl malonate. Methyl malonate is available commercially but is considerably more expensive than ethyl malonate. Therefore, some was prepared by ester interchange between ethyl malonate and methanol,[17] and by use of cyanoacetic acid and methanol following Ross and Bibbins[18] procedure for ethyl malonate.

Methyl formamidomalonate. Methyl formamidomalonate was prepared by a modification of Galat's preparation of ethyl acetamidomalonate.[7] The product was crystallized from aqueous methanol and obtained in a 41% yield, m.p. 83–84°. The subsequent preparation reported by Hellmann and Lingens[9] appears much superior to ours and they report a 96% overall yield and a melting point of 85.5°.

Methyl acetamidomalonate. An almost quantitative yield is reported by Hellmann and Lingens for methyl acetamidomalonate melting at 128.5°. Our material melted at 128°.

Ethyl formamidomalonate. This was prepared by Galat's method.[7] Subsequently Shaw and Nolan[11] have published an improved method.

Alkylations of methyl formamidomalonate. The alkylations followed a procedure of Albertson.[11] Ten g. of methyl formamidomalonate, 50 ml. of absolute methanol, 5.4 g. of sodium methoxide, and 9 g. of *n*-butyl bromide were heated under a reflux condenser for 12 hr. Then 50 ml. of water was added. Chloroform extraction gave 5 g. of crude material. Treatment with decolorizing charcoal and crystallization from methanol gave 1.75 g. of starting material and a 37% yield of methyl *n*-butylformamidomalonate, m.p. 108–109°. Aqueous methanol was used to prepare an analytical sample, m.p. 109.5°.

Anal. Calcd. for $C_{10}H_{17}NO_5$: N, 6.06. Found: 5.88; 5.98.

In a similar fashion 10.8 g. of ethyl bromoacetate gave after crystallization from aqueous methanol 7 g. of methyl carbethoxymethylformamidomalonate, m.p. 87–90° (47%). Further recrystallizations raised the melting point to 93–94°.

Anal. Calcd. for $C_{10}H_{15}NO_7$: N, 5.36. Found: N, 5.53; 5.47.

Anisole was chloromethylated as directed by Quelet and Allard.[19] Ten g. of *p*-methoxybenzyl chloride and 8.5 g. of methyl formamidomalonate gave 6.6 g. of crude methyl *p*-

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methoxybenzylformamidomalonate, m.p. 102–106°. In addition 1.9 g. of methyl formamidomalonate was recovered. Crystallization from methanol and benzene raised the melting point to 120–120.5°.

Anal. Calcd. for $C_{14}H_{17}NO_6$: N, 4.84. Found: N, 4.72.

Ten g. of methyl formamidomalonate and 5.5 g. of benzyl chloride gave 13 g. (75%) of crude product, m.p. 148–150°. Crystallization from aqueous methanol raised the melting point of the methyl benzylformamidomalonate to 153–154°.

Anal. Calcd. for $C_{13}H_{15}NO_5$: N, 5.29. Found: N, 5.16.

Alkylation of ethyl formamidomalonate with n-butyl bromide. Ten g. of ethyl formamidomalonate, 3.4 g. of sodium ethoxide and 9 g. of *n*-butyl bromide were heated for 8 hr. in absolute ethanol. One crystallization from aqueous ethanol gave 7.9 g. (62%) of ethyl *n*-butylformamidomalonate, m.p. 79–81°. Further recrystallization raised the melting point to 81.0–81.8°. This compound has also been prepared in this laboratory by hydrogenation of ethyl allylcarbinylformamidomalonate.[13] Previously conflicting melting points of 101°[20] and 77–80°[21] have been reported.

Anal. Calcd. for $C_{12}H_{21}NO_5$: N, 5.21. Found: N, 5.51, 5.44.

Alkylation of methyl acetamidomalonate with n-butyl bromide. One g. of methyl acetamidomalonate and 1 g. of *n*-butyl bromide were placed in 5 ml. of absolute methanol to which 0.5 g. of sodium had been added. The mixture was heated under a reflux condenser for 4 hr. and was allowed to stand overnight. Five ml. of water was added, and then a chloroform extraction gave 280 mg. of long cylindrical needles, m.p. 96–98°. The analytical sample of methyl *n*-butylacetamidomalonate was prepared by dissolving the product in benzene and diluting with petroleum ether. The melting point was 99–100° and the analysis was performed by Galbraith Laboratories.

Anal. Calcd. for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.81. Found: C, 53.67; H, 7.65.

Hydrolysis with hydrobromic acid. The malonates were refluxed with constant boiling hydrobromic acid and the vapors were passed through a tower of sodium hydroxide pellets and then into a 4% alcoholic solution of silver nitrate. The rate of hydrolysis was followed by observing the appearance of silver bromide. When the hydrolysis was completed, there was no further precipitate of silver bromide.

It took from 3 to 4 hr. to hydrolyze ethyl *n*-butylacetamidomalonate, ethyl *n*-octylacetamidomalonate, and ethyl *n*-butylformamidomalonate. Complete hydrolysis for the methyl formamidomalonate intermediates took place in an hour for all the compounds studied.

Two hundred mg. of *p*-methoxybenzylformamidomalonate was refluxed with 50 ml. of constant boiling hydrobromic acid. Complete hydrolysis took place in 1 hr. but was continued for an additional 0.5 hr. The hydrobromic acid was removed *in vacuo* and the residue purified on an ion exchange column containing the Duolite resin A2. One hundred ten mg. of *dl*-tyrosine was obtained, yield 98%, m.p. 295–298° dec.; reported m.p. 290–295° dec.[22]

Identification of the tyrosine was obtained by making the *N*-benzoyl-*dl*-tyrosine, m.p. 196–198°; reported 195–197°.[22]

One g. of methyl carboethoxmethylformamidomalonate was refluxed with 50 ml. of constant boiling hydrobromic acid. Hydrolysis was complete in an hour but was continued for another 0.5 hr., yield 80%, m.p. 300–303° dec.; reported, above 300°.[7] Identification of the *dl*-aspartic acid was obtained by a spot test developed by Inukai, Tsurumi, and Sakai.[23]

Four hundred seventy mg. of methyl *n*-butylformamidomalonate was refluxed with 50 ml. of constant boiling hydrobromic acid, hydrolysis was complete in 1 hr. The hydrobromic acid was removed *in vacuo* and the residue purified on an ion exchange column containing the Duolite resin A2, yield 85%, m.p. 274–276°.

Identification of the norleucine was obtained by preparing the *N*-formylnorleucine, m.p. 109–111°, reported 113–115°.[24]

The hydrolysis of methyl benzylformamidomalonate was complete in an hour. The yield was practically quantitative and the product melted at 269–272° with decomposition, reported 271–273°;[25] 257° dec.[16]

Identification of the phenylalanine was obtained by preparing the *N*-benzoyl-*dl*-phenylalanine, m.p. 187–188°; reported 187–188°.[26]

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Synthesis of (+)(S)-3-Methyl-1-pentene

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(+)(S)-3-Methyl-1-pentene (*i.e.*, L-3-methyl-1-pentene) having an optical purity of at least 86% has been prepared in five steps starting from (−)(S)-2-methyl-1-butanol with an over-all yield of 18% and a maximum per cent of racemization of 12.6%. The optical purity of the (+)(S)-3-methyl-1-pentene was calculated by regenerating the (+)(S)-3-methyl-1-pentanol by addition of the olefin to diisobutylaluminum monohydride and by oxidation followed by hydrolysis of the trialkylaluminum thus obtained.

The preparation and the determination of optical purity of aliphatic olefins do not seem to have been investigated extensively. No data have been found in the literature (up to 1957) on the simplest optically active α-olefin, 3-methyl-1-pentene. For the mixture of 4-methyl-hexenes prepared by dehydration of the optically active 4-methyl-2-hexanol over alumina, α_D^{26} (l = 1) +13.7° is reported.[1] For 5-methyl-1-heptene, two very different values (+6.84°[2] and +10.2°[3]) have been reported for the

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