NOTES

Ethyl Formylaminomalonate: An Intermediate in the Synthesis of Amino Acids

By Alexander Galat

Several acyl derivatives of aminomalonic ester have been employed as intermediates in the synthesis of amino acids, but there appears to be no record of the use for this purpose of the simplest and perhaps the most accessible member of this series, formylaminomalonic ester.

Ethyl formylaminomalonate was readily prepared in an over-all yield of 55% by nitrosation of ethyl malonate with sodium nitrite and acetic acid, followed by reduction with zinc and formic acid, according to the procedure of Conrad and Schulze.[1] When the nitrosation was carried out with butyl nitrite[2] the over-all yield was 63%. Since ethyl formylaminomalonate can thus be prepared in a substantially higher yield than ethyl acetylaminomalonate (40%)[3] and, unlike the latter, does not require the use of a catalytic reduction under pressure, this ester offers definite advantages as a convenient intermediate in the synthesis of amino acids.

Ethyl formylaminomalonate was condensed with benzyl chloride, ethyl chloroacetate and acrylonitrile under the general conditions described for acetylaminomalonic ester,[4] and the condensation products were subjected, without isolation, to acid hydrolysis, thus yielding *dl*-phenylalanine (60%), *dl*-aspartic acid (55%) and *dl*-glutamic acid (57%), respectively. Other amino acids may undoubtedly be synthesized by the same method and the use of formylaminomalonic ester may be considered a convenient variation of the Sörensen method.

Experimental

Ethyl Formylaminomalonate.—To a mixture of 30.4 ml. (0.2 mole) of ethyl malonate and 34 ml. (0.6 mole) of glacial acetic acid was added a solution of 38 g. (0.55 mole) of sodium nitrite in 55 ml. of water. The mixture was stirred during the addition of the nitrite and maintained at below 20°. After the addition had been completed, the mixture was stirred for an additional four and one-half hours at room temperature, extracted with chloroform and the solvent removed *in vacuo* on a water-bath. The residue, a yellow oil weighing about 38 g., was dissolved in 160 ml. of technical formic acid (a 90% acid was used without detriment instead of the less readily available 99–100% acid recommended by Conrad and Schulze), and the mixture was transferred into a three-neck flask provided with a thermometer, a stirrer and a reflux condenser. A small amount of technical zinc dust was added and the mixture was stirred and heated until the reaction started. There usually was an induction period of several minutes after which the reaction proceeded with violence, unless only a small amount of zinc was present at this stage. Thirty grams of zinc dust was then added through the condenser at such a rate that the temperature was maintained at 75–80° without external heating. After the addition of zinc had been completed (fifteen to twenty minutes), the mixture was filtered hot, the filter-cake of zinc formate thoroughly washed with formic acid and the filtrate evaporated *in vacuo* on a water-bath. The residue, which was an oil containing a small amount of zinc formate, was fractionally distilled *in vacuo* and the fraction boiling between 130 and 132° at 2–3 mm. of mercury was collected. It solidified into a white crystalline mass which had a setting point of 48–49°; yield, 22.2 g. (54.7%).

Anal. Calcd. for $C_8H_{13}O_5N$: C, 47.3; H, 6.4; N, 6.9. Found: C, 47.6; H, 6.6; N, 7.1.

***dl*-Aspartic Acid.**—To a solution of 1.2 g. (0.052 mole) of sodium in 100 ml. of absolute alcohol was added 10.15 g. (0.05 mole) of ethyl formylaminomalonate. To the resulting solution was added 5.4 ml. (0.052 mole) of dry ethyl chloroacetate (Dow) and a few crystals of sodium iodide. The mixture was allowed to stand at room temperature for two days during which much sodium chloride precipitated. It was then heated for two and one-half hours on the water-bath, sodium chloride removed by filtration and the filtrate evaporated *in vacuo* to dryness. There remained a brown sirup containing some crystals. This mixture was treated with 75 ml. of concentrated hydrochloric acid and refluxed for three hours. The brown solution was then evaporated *in vacuo* to dryness, the residue dissolved in 30 ml. of water, treated hot with charcoal and filtered, yielding a colorless filtrate. Concentrated ammonia was added until a *p*H of 3, the solution evaporated to a small volume and chilled for twenty-four hours. *dl*-Aspartic acid which crystallized was collected by filtration, washed with cold water and alcohol and recrystallized from a small amount of water; yield, 3.55 g. (54.7%). The material decomposed above 300°, gave a hydrochloride which melted at 180–185° (dec.) and the N-benzoyl derivative melting at 160–162°.

Anal. Calcd. for $C_4H_7O_4N$: C, 36.1; H, 5.27; N, 10.53. Found: C, 36.3; H, 5.30; N, 10.3.

Galat Chemical Development, Inc.
61 So. Broadway
Yonkers, N. Y.

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(1) Conrad and Schulze, *Ber.*, **42**, 733 (1909).

(2) Redemann and Dunn, *J. Biol. Chem.*, **130**, 345 (1939).

(3) Snyder and Smith, This Journal, **66**, 350 (1944).

(4) Albertson and Archer, *ibid.*, **67**, 308 (1945). Snyder, Skeleton and Lewis, *ibid.*, **67**, 310 (1945).

Methylcyclopropane: Infrared Absorption Spectrum and Synthesis from *i*-Butyl Chloride

By Francis E. Condon and Dan E. Smith

Cyclopropanes have been obtained from the reaction of sodium or sodium alkyls with neoalkyl chlorides.[1] The present work extends this reaction to *i*-butyl chloride.

From 117.5 g. of *i*-butyl chloride and 10.2 g. of sodium (*cf.* ref. 1a) there was obtained 3.1 g. of methylcyclopropane; other products were 8.8 g. of *i*-butane, 4.7 g. of *i*-butylene and 5.5 g. of 2,5-dimethylhexane; 78 g. of *i*-butyl chloride was recovered. The reaction of 80.7 g. of *i*-butyl chloride, 146.5 g. of dipropylmercury and 22.5 g. of sodium in 218.3 g. of *n*-heptane (*cf.* ref. 1c) resulted in 9.6 g. of methylcyclopropane; lower-boiling products were

(1) (a) Whitmore, Popkin, Bernstein and Wilkins, This Journal, **63**, 124 (1941); (b) Whitmore and Carney, *ibid.*, **63**, 2633 (1941); (c) Whitmore and Zook, *ibid.*, **64**, 1783 (1942); (d) Whitmore, Weisberger and Shabica, *ibid.*, **65**, 1469 (1943).

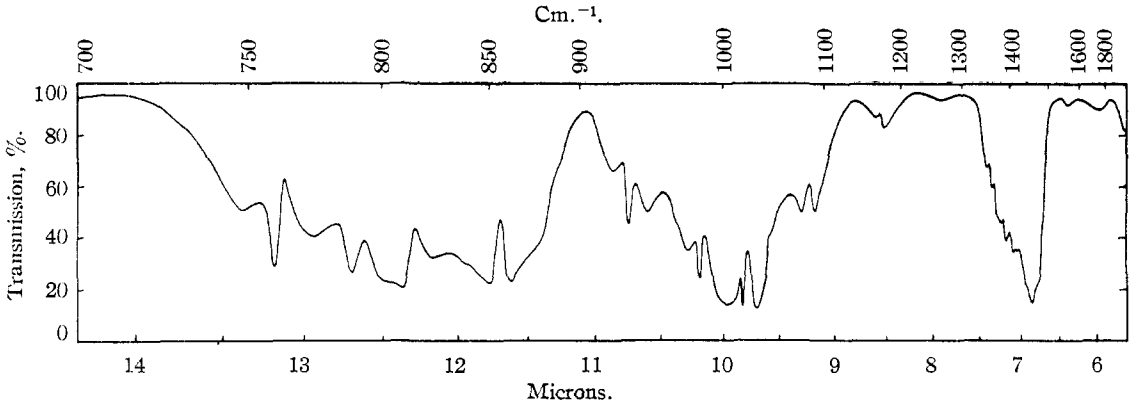

Fig. 1.—Infrared absorption spectrum of methylcyclopropane: pressure, 45.1 mm.; cell, 43 cm.

0.5 g. of propylene, 15.6 g. of propane, 1.1 g. of *i*-butane, and 14 g. of *i*-butylene.

The methylcyclopropane boiled constantly at 0° at 750 mm. rather than at 4–5°.[2] Its vapor pressure was 752 mm. at 0° (melting ice) and 128 mm. at −38.9° (melting mercury). Its infrared absorption spectrum, Fig. 1, was obtained with the instrument at the University of Oklahoma Research Institute.[3] Comparison with the already well-known spectra of *n*-butane, *i*-butane, 1-butene, *cis*- and *trans*-2-butenes, *i*-butylene, 1,2- and 1,3-butadienes, and ethylacetylene eliminated the possibility that the material on hand was any one of these or that it was seriously contaminated with any one of these. The boiling point, vapor pressure and infrared absorption spectrum of a different sample of methylcyclopropane, which was prepared from 1,3-dibromobutane by reduction with zinc in 80% ethanol (*cf.* ref. 2), agreed with those of the methylcyclopropane obtained from *i*-butyl chloride and propylsodium.

Acknowledgments.—The infrared absorption spectra were obtained by Miss Annette Herald and were interpreted by Mr. Vernon Thornton. Phillips Petroleum Company granted permission to publish the data.

(2) (a) Demjanow, *Ber.*, **28**, 21 (1895); (b) Lott and Christiansen, *J. Am. Pharm. Assoc.*, **27**, 126 (1938).

(3) Nielsen and Don C. Smith, *Ind. Eng. Chem., Anal. Ed.*, **15**, 609 (1943).

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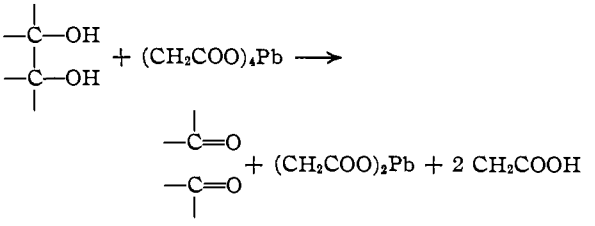
The Structure of Adenosine Triphosphate

BY GEORGE FAWAZ[1] AND KRIKOR SERAIDARIAN

The presence of a free α-glycol grouping in adenosine di- and triphosphate, a long debated question, has received support from the work of Lythgoe and Todd.[1a] These authors used Malparade's method of titration with periodate and found that each of the nucleotides consumed almost exactly one mole of the reagent.

We have utilized Criegee's method of titration with lead tetraacetate and came to the same conclusion. Thus, each of the following three compounds consumed one mole of lead tetraacetate: adenosine triphosphate[2] (sodium salt), muscle adenylic acid[3] and adenosine.[4] These results are to be expected if the compounds named contained one free α-glycol grouping according to the equation



Yeast adenylic acid,[5] on the other hand, was not oxidized by the reagent nor was adenosine itself altered.

Experimental

The reagent was a 0.152 *N* colorless solution of lead tetraacetate in glacial acetic acid, standardized according to Hockett and McClenahan.[6] In each case 0.05 millimole of the substance to be titrated was dissolved in 2 cc. of water, and 2 cc. of 0.152 *N* lead tetraacetate was added. After standing at room temperature for five minutes, 4 cc. of a solution containing 25 g. of sodium acetate and 2 g. of potassium iodide per 100 cc. was added and the liberated iodine was titrated with 0.1 *N* thiosulfate. In parallel control experiments it was found that the addition of 2 cc. of the reagent to 2 cc. of water followed after five minutes with 4 cc. of the acetate-iodide solution resulted in no measurable hydrolysis of the reagent.

The results are expressed in cc. of 0.1 *N* thiosulfate and represent the difference between the back titration of the above-mentioned control and that of the substance tested: adenosine triphosphate 0.98 cc.; muscle adenylic acid 1.00 cc.; adenosine 1.04 cc.; yeast adenylic acid 0.002 cc.; adenine 0.00 cc.

Baer, *et al.*,[7] were the first to utilize the lead tetraacetate method in aqueous medium. They recommended its use for preparative purposes in those cases where the rate of oxidation of the compound is greater than the rate of hydrolysis of the reagent. The results shown above, however, in particular the fact that there is no measurable hydrolysis of the reagent in 50% acetic acid

(1) Present address: Converse Memorial Laboratory, Chemistry Department, Harvard University, Cambridge, Mass.

(1a) Lythgoe and Todd, *Nature*, **155**, 695 (1945).

(2) Kerr, *J. Biol. Chem.*, **139**, 121 (1941).

(3) *Ibid.*, **139**, 131 (1941).

(4) Purchased from A. D. MacKay, New York City.

(5) Purchased from E. Machlett and Son, New York City, N. Y.

(6) Hockett and McClenahan, THIS JOURNAL, **61**, 1670 (1939).

(7) Baer, Grosheintz and Fischer, *ibid.*, **61**, 2607 (1939).