[CONTRIBUTION FROM THE LABORATORY FOR THE STUDY OF HEREDITARY AND METABOLIC DISORDERS, AND THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND MEDICINE, UNIVERSITY OF UTAH]

# Improved Preparation of Diethyl Oximino-, Formamido- and Acetamidomalonates[1]

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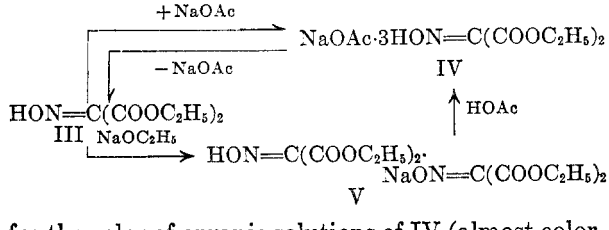
Diethyl malonate was converted by the action of sodium nitrite and acetic acid to diethyl oximinomalonate, which was isolated in 93% yield as a crystalline 3:1 addition compound with sodium acetate. The properties of this new compound are described. The addition compound was reduced with zinc and formic acid to diethyl formamidomalonate in 87% yield, and with zinc, acetic acid, and acetic anhydride to diethyl acetamidomalonate in 100% yield.

Diethyl formamidomalonate (I)[2] and diethyl acetamidomalonate (II)[3,4] have been known for many years, but only recently were introduced as intermediates for the synthesis of various amino acids.[5–9] These and other acylamidomalonates have usually been obtained by reductive acylation of diethyl oximinomalonate (III). Improvements in the preparation of these compounds are presented in this paper.

The oxime III has been synthesized from diethyl sodiomalonate and "nitrous gases",[10,11] or methyl nitrite,[12,13] or *n*-butyl nitrite,[5,14] and from diethyl malonate, sodium nitrite and acetic acid.[5,6,15–21] The last method is convenient, but has been criticized[14] on the grounds that the original yield (80–90%)[15,16] cannot be reproduced. High yields of crude oxime III of uncertain purity have been reported by some investigators[5,17] using this method, but the yield of pure oxime III recorded by others[18,21] has not exceeded 63%. The reaction of diethyl malonate with sodium nitrite and acetic acid was used in the present work, and III was isolated in 93% yield as a crystalline 3:1 addition compound (IV) with sodium acetate, which melts at 87–88°. It is probable that a crystalline substance, m.p. 86.5–88°, which was designated as the oxime III in a recent patent,[20] may actually have been IV.

The addition compound IV is purified more readily than the oily oxime III, and is thus more suitable as an intermediate for other syntheses. IV is stable under normal storage conditions and crystallizes readily from dichloromethane, chloroform, benzene, or toluene. IV undergoes partial dissociation into the oxime III and sodium acetate in ethyl acetate, or in organic solutions in contact with water. In diethyl ether, however, dissociation is complete. This behavior in ether was used to establish the nature of the addition compound IV; quantitative recovery of sodium acetate was effected, and the resulting oxime III was then combined with authentic sodium acetate to reconstitute IV.

The acid sodium salt (V) of the oxime III, which had been encountered in an earlier synthesis of III,[12] was obtained as a minor (2%) contaminant of the addition compound IV. The nature of V was established by its alternate preparation from the oxime III by the action of sodium ethoxide, and by its conversion to the addition compound IV upon treatment with acetic acid. Varying small amounts of the acid salt V are produced when the addition compound IV is heated *in vacuo* and are responsible




for the color of organic solutions of IV (almost colorless to yellow). The acid salt V is of potential inter-

(1) Supported by research grants from the National Institutes of Health, U. S. Public Health Service.

(2) M. Conrad and A. Schulze, *Ber.*, **42**, 729 (1909).

(3) R. Locquin and V. Cerchez, *Bull. soc. chim. France*, [4], **43**, 932 (1928); [4], **49**, 42 (1931).

(4) V. Cerchez, *Bull. soc. chim. France*, [4], **49**, 45 (1931).

(5) A. Galat, *J. Am. Chem. Soc.*, **69**, 965 (1947).

(6) H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944).

(7) H. R. Snyder, J. F. Shekleton, and C. D. Lewis, *J. Am. Chem. Soc.*, **67**, 310 (1945).

(8) N. F. Albertson, S. Archer, and C. M. Suter, *J. Am. Chem. Soc.*, **66**, 500 (1944).

(9) N. F. Albertson and S. Archer, *J. Am. Chem. Soc.*, **67**, 308 (1945).

(10) M. Conrad and C. A. Bischoff, *Ber.*, **13**, 595 (1880); *Ann.*, **209**, 211 (1881).

(11) F. Ratz, *Monatsh.*, **25**, 55 (1904).

(12) L. Bouveault and A. Wahl, *Compt. rend.*, **137**, 196 (1903); *Bull. soc. chim. France*, [3], **29**, 628, 960 (1903).

(13) N. J. Putochkin, *Ber.*, **56**, 2213 (1923).

(14) C. E. Redemann and M. S. Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

(15) R. Locquin and V. Cerchez, *Compt. rend.*, **186**, 1360 (1928); *Bull. soc. chim. France*, [4], **47**, 1274 (1930).

(16) V. Cerchez, *Bull. soc. chim. France*, [4], **47**, 1279 (1930).

(17) Z. J. Vejdělek, *Chem. Listy*, **44**, 73 (1950) [*Chem. Abstr.*, **45**, 8004 (1951)].

(18) J. A. Spring, U. S. Patent **2,635,960** [*Chem. Abstr.*, **47**, 8565 (1953)].

(19) M. Vignau, *Bull. soc. chim. France*, 638 (1952).

(20) J. C. Vander Weele, E. C. Britton, and H. C. White, U. S. Patent **2,649,474** [*Chem. Abstr.*, **48**, 8818 (1954)]; Brit. Patent **713,144** [*Chem. Abstr.*, **49**, 2492 (1955)].

(21) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5579 (1954).

est as an intermediate in syntheses where the addition compound IV may be unsuitable because of its sodium acetate component. The unusual solubility of IV and V in benzene and dichloromethane indicates covalent bonding and probable chelation of sodium in these compounds; other similar examples of chelated sodium compounds are well known.

Diethyl formamidomalonate (I) has been prepared from the oxime III by the action of zinc and formic acid[2,5,15,17]; a 55–70% yield of impure I was reported. "Very poor results"[21] have been indicated more recently with this reaction, and may have been related to partial decomposition of I during vacuum distillation and to incomplete recovery because of its low melting point and tendency to form oils.[22] These difficulties have been circumvented by use of catalytic hydrogenation,[21,23,24] or by use of the higher melting methyl esters.[22] In the present work, the reaction of zinc and formic acid with the addition compound IV, rather than impure oxime III, and avoidance of vacuum distillation have given pure I in 87% yield. A lower yield of I was obtained upon prolonged exposure to boiling formic acid, possibly because of transesterification, and also when I was separated from zinc formate at room temperature, probably because of occlusion.

Diethyl acetamidomalonate (II) has been obtained from the oxime III by reductive acetylation, usually without isolation of the intermediate diethyl aminomalonate; the reducing agents included aluminum amalgam,[3,4,13,15,25,26] zinc and acetic acid,[27–29] hydrogen (catalytic),[6,13,14,19,20,24,30–33] or hydrogen sulfide.[34,35] The use of impure III may have been partly responsible for the wide variation in the reported yields of II (40–90%). In the present work, treatment of the addition compound IV in a mixture of acetic acid and acetic anhydride with zinc has consistently provided II in quantitative yield.

The addition compound IV should prove suitable as an intermediate in the preparation of other diethyl acylamidomalonates.

## EXPERIMENTAL

*Diethyl oximinomalonate-sodium acetate complex* (IV). A solution of 160.2 g. (1.0 mole) of redistilled diethyl malonate (b.p.$_{11}$ 87°, uncorrected) in 175 ml. (3.0 moles) of glacial acetic acid was stirred *vigorously* at 0–5° while a solution of 207.0 g. (3.0 moles) of sodium nitrite in 250 ml. of water was added dropwise during 3–4 hr. The ice bath was removed and the mixture was stirred vigorously for 20 hr. more. The nitrosation was carried out in a three-necked flask with appropriate fittings and a small vent to permit escape of nitric oxide; the system was otherwise sealed to prevent ingress of air. The reaction mixture was extracted with a 400-ml., and then three 100-ml. portions of dichloromethane. The combined dichloromethane extracts were dried over anhydrous sodium sulfate and treated with charcoal; the filtrate was concentrated *in vacuo* at 60° or less until the residual yellow oil crystallized. The residue was dissolved in 500 ml. of warm dichloromethane; the solution was shaken with Celite and 40 g. of anhydrous sodium acetate for 15 min. and filtered. Sodium acetate reacts with any free oxime III in the solution and ensures maximum recovery of the addition compound IV. Sodium acetate also eliminates residual acetic acid, which impedes crystallization of IV, as solvates which are insoluble in dichloromethane. The filtrate was concentrated *in vacuo* at 60° or less to 400 ml. and petroleum ether (b.p. 30–60°) was added until the solution was faintly cloudy (500–600 ml.). The mixture was allowed to stand at room temperature for an hour and, after thorough mixing to promote crystallization, was refrigerated overnight. IV (194.2 g., 90% yield) was recovered as colorless blunt needles, m.p. 87–88°.[36] A second crop of 7.08 g. (3% yield), m.p. 83–85°, was obtained by concentrating the filtrate and crystallizing the residue from dichloromethane–petroleum ether.

The total yield of IV decreased to 80% when the reaction mixture was stirred for only 4 hr. after addition of the sodium nitrite solution. The total yield was 85–87% when practical grade diethyl malonate was used without redistillation and with stirring for 18–24 hr. When the reaction mixture was extracted with diethyl ether instead of dichloromethane, the oxime III containing acetic acid and small amounts of unreacted diethyl malonate was obtained in place of IV.

For analysis, IV was recrystallized from dichloromethane–petroleum ether (b.p. 30–60°), m.p. 87–88°.

*Anal.*[37] Calcd. for $C_{23}H_{36}N_3O_{17}Na$: C, 42.53; H, 5.59; N, 6.47; Na, 3.55. Found: C, 42.95; H, 5.45; N, 6.27; Na, 3.45.

*Characterization of diethyl oximinomalonate-sodium acetate complex* (IV). *A. Recovery of sodium acetate.* A suspension of 40.00 g. (0.0616 mole) of IV in 800 ml. of anhydrous ether was simmered for 10 min., cooled, and filtered. The filter cake was washed thoroughly with anhydrous ether and dried at 0.1 mm. and 60° over phosphorus pentoxide and potassium hydroxide to yield 6.01 g. of impure sodium acetate, m.p. 324–326° (darkened above 310°). This material was simmered with 50 ml. of dichloromethane, the suspension was filtered, and the filter cake was washed thoroughly with dichloromethane. The resulting white powder was dried *in vacuo;* 5.03 g. (99% yield), m.p. 327–329°

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(28) M. Tishler and E. E. Howe, U. S. Patent **2,521,809** [*Chem. Abstr.*, **45**, 644 (1951)].

(29) S. Tatsuoka, T. Kinoshita, and R. Nakamori, *J. Pharm. Soc. Japan*, **71**, 702 (1951) [*Chem. Abstr.*, **46**, 1978 (1952)]; Japan Patent **4472** (1952) [*Chem. Abstr.*, **48**, 8256 (1954)].

(30) P. A. Levene and A. Schormüller, *J. Biol. Chem.*, **106**, 595 (1934).

(31) P. Mastagli and M. Métayer, *Bull. soc. chim. France*, 1091 (1948) [*Chem. Abstr.*, **43**, 5738 (1949)].

(32) S. I. Lur'e, G. A. Ravdel, and E. S. Chaman, *Zhur. Obshchei Khim.*, **22**, 2011 (1952) [*Chem. Abstr.*, **47**, 8649 (1953)].

(33) S. Murahashi and S. Horie, Japan Patent **4871** (1952) [*Chem. Abstr.*, **48**, 8818 (1954)].

(34) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 345 (1914).

(35) R. Schwarz and K. Capek, *Monatsh.*, **84**, 595 (1953).

(36) Melting points are corrected and were taken in open capillary tubes.

(37) Analyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(colorless melt), not depressed upon admixture with authentic sodium acetate (m.p. 328–330°).

*B. Recovery of diethyl sodio-oximinomalonate (acid salt)* (V). The dichloromethane filtrate and wash from the sodium acetate (section *A*) was concentrated to dryness *in vacuo*. The residue (0.90 g.) was crystallized from 10 ml. of dichloromethane by addition of 20 ml. of petroleum ether (b.p. 30–60°) to give 0.82 g. of cream-colored powder, m.p. 141° (dec.). Following recrystallization from dichloromethane–petroleum ether, faintly yellow rosettes of stout needles were obtained, m.p. 141° (dec.), not depressed upon admixture with authentic V (section E).

*Anal.* Calcd. for $C_{14}H_{21}N_2O_{10}Na$: C, 42.00; H, 5.29; N, 7.00: Na, 5.75. Found: C, 42.55; H, 4.88; N, 6.80; Na, 5.62.

*C. Recovery of diethyl oximinomalonate* (III). The ether filtrate and wash from the sodium acetate (section A) was washed successively with 50 ml. of 1*N* sodium bicarbonate and three 50-ml. portions of water, treated with charcoal, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to dryness *in vacuo* at 60° or less to give 34.00 g. (97% yield) of III as a pale yellow, thick oil. III was colorless when concentration was effected without external heating, but darkened to orange-brown if heated at 100° *in vacuo* for 15 min.

*D. Reconstitution of addition compound* IV *from oxime* III. To a solution of 33.30 g. (0.1760 mole) of III (section C) in 200 ml. of dichloromethane was added 10.00 g. of anhydrous sodium acetate. The mixture was simmered for 10 min., cooled, and filtered. The filter cake was washed thoroughly with dichloromethane and dried *in vacuo* at 60° and 0.1 mm.; 5.08 g. of sodium acetate was recovered, m.p. 328–330°. The filtrate was concentrated to dryness *in vacuo* to give 37.97 g. of IV as a yellow oil which crystallized on cooling. The weight of the combined sodium acetate, averaged from the weight increase sustained in converting III to IV and from the weight of sodium acetate recovered, is 4.80 g.; the calculated value for IV is 4.82 g. The residue was crystallized from dichloromethane–petroleum ether to give two crops of IV; 36.37 g., m.p. 87–88°, and 0.89 g., m.p. 85–86° (total yield 98%).

*E. Diethyl sodio-oximinomalonate (acid salt)* (V) *from oxime* III. To a solution of 18.57 g. (0.098 mole) of III (section C) in 100 ml. of absolute ethanol was added 98 ml. of 0.5*N* sodium ethoxide in absolute ethanol. The yellow solution was concentrated to dryness *in vacuo*. The residue was concentrated to dryness with two successive 100-ml. volumes of dichloromethane, and then crystallized from dichloromethane–petroleum ether (1:2) to give 18.95 g. (97% yield) of V, m.p. 143° (dec.). Faintly yellow rosettes of stout needles were obtained by recrystallization from the same solvent mixture, m.p. 141° (dec.).

*F. Conversion of acid salt* V *to addition compound* IV. To a solution of 6.01 g. (0.015 mole) of V in 100 ml. of dichloromethane was added 0.90 ml. (0.015 mole) of glacial acetic acid; the yellow color of V disappeared and sodium acetate precipitated. The mixture was treated with charcoal and Celite, and the filtrate was concentrated to dryness *in vacuo*. The residual oil was crystallized from dichloromethane–petroleum ether to give 6.05 g. (93% yield) of IV, m.p. 87–88°.

*Diethyl formamidomalonate* (I). A solution of 90.94 g. (0.140 mole) of addition compound IV in 600 ml. of 88% formic acid, initially at 80°, was stirred vigorously, and 80 g. of zinc dust was added in small portions during 30 min. at such a rate that the temperature was maintained at 95–103°. The reaction was not easily controlled if carried out below 95°. The mixture was filtered through a preheated sintered glass filter immediately after addition of the final portion of zinc, and the filter cake was washed thoroughly with boiling formic acid. The filtrate was concentrated *in vacuo* at 70° or less until distillation of formic acid ceased. The residual oily crystals were shaken with a mixture of 300 ml. of dichloromethane and 300 ml. of water containing 75 g. of sodium chloride; the aqueous phase was reextracted with three successive 50-ml. volumes of dichloromethane. The combined dichloromethane extracts were shaken with increasing increments (50–100 ml.) of 1*N* sodium bicarbonate until the *p*H of the bicarbonate phase was 7.0–7.2; 12–25 g. of sodium chloride was then added and the bicarbonate phase was reextracted with three more 50-ml. volumes of dichloromethane. The combined dichloromethane extracts were treated with charcoal, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residual oil was dissolved in 250 ml. of anhydrous ether and petroleum ether (b.p. 30–60°) was added until the solution was faintly cloudy (100–125 ml.). Following refrigeration, 69.56 g. (82% yield) of I was recovered as long colorless needles, m.p. 51–53° (lit.[21] m.p. 50–52°). A second crop of 4.46 g. (5% yield), m.p. 50–52°, was obtained by concentrating the filtrate and crystallizing the residual oil from ether–petroleum ether. I was also obtained as dense prismoids, m.p. 52–53°, when an ether solution was shaken immediately after addition of petroleum ether. The melting point of each form was raised to 53–54° by recrystallization from ether–petroleum ether.

*Diethyl acetamidomalonate* (II). A solution of 90.94 g. (0.140 mole) of addition compound IV in a mixture of 200 ml. of glacial acetic acid and 300 ml. of acetic anhydride, initially at 80°, was stirred vigorously, and 80 g. of zinc dust was added in small portions during 40 min. at such a rate that the temperature was maintained at 110–115°. The reaction was not readily controlled if carried out below 110°. The mixture was filtered through a preheated sintered glass funnel, and the filter cake was washed thoroughly with boiling acetic acid. The filtrate was concentrated *in vacuo* until distillation of acetic acid ceased. The crystalline residue[38] was treated with dichloromethane, sodium chloride solution, and sodium bicarbonate solution, and the combined dichloromethane extracts were treated with charcoal, dried, and concentrated in the manner described for I (preceding section). The residual solid was dissolved in 100 ml. of boiling ethyl acetate and 400 ml. of hot cyclohexane was added. Following refrigeration, 89.00 g. (98% yield) of II was recovered as large colorless dendritic crystals, m.p. 96–97°, unchanged by recrystallization from ethyl acetate–cyclohexane (lit.[28] m.p. 95–97°). A second crop of 1.71 g. (2% yield), m.p. 93–95°, was obtained by concentrating the filtrate and crystallizing the residue from ethyl acetate–cyclohexane.

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(38) The direct recovery of II by recrystallization of a similar residue from isopropyl alcohol has been reported in a recent patent.[30] The presence of a substantial amount of zinc acetate in II prepared in this manner can be demonstrated by dissolving the material in dichloromethane or benzene.