[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Certain α-Amino Acid Esters from Malonic Ester[1]

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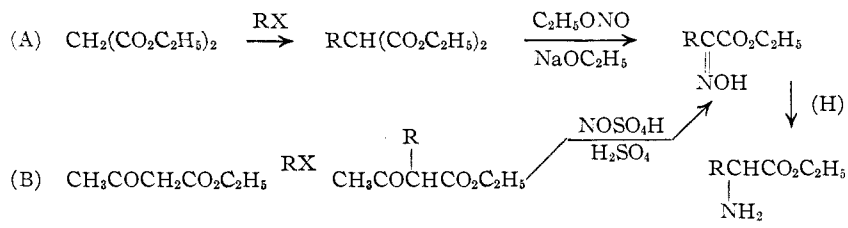
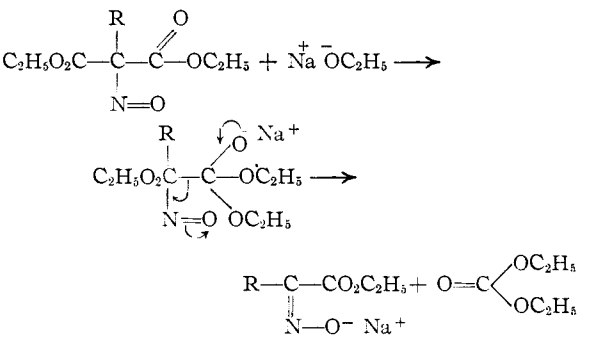
Esters of α-amino acids have usually been prepared from the corresponding α-amino acids, which have generally been synthesized from malonic,[2] acetoacetic[3] or cyanoacetic[4] ester. However, the esters may be synthesized directly from malonic or acetoacetic ester without first preparing the amino acids. Two methods, (A) and (B), in which this is done are represented below.[5]



Method (B) has been described by Bouveault and Locquin,[6] and Hamlin and Hartung,[3] although yields are not reported for the last step. These workers developed the method primarily for the preparation of amino acids which they obtained by the hydrolysis of the oximino ester and reduction of the resulting oximino acid.[7] Method (A) has been indicated by Fischer and Weigert[8] for the preparation of the ethyl ester of lysine, although they did not isolate the ester; apparently no other cases have been reported.

In the present investigation Method (A) has been found satisfactory for the synthesis of the ethyl ester of norleucine, phenylalanine and of N^{δ},N^{δ}-diethylornithine in which R is *n*-butyl, benzyl and γ-diethylaminopropyl, respectively. Although the first two esters could probably be prepared equally well by method (B), the γ-diethylaminopropyl ester has been obtained in considerably lower yield by this method.[9] Because of the presence of the basic diethylamino group, the oximino ester was difficult to isolate from the acidic medium used in Method (B)[10] and it could be obtained from the alkylated acetoacetic ester in only 26% yield.[9] In contrast to this, the oximino ester was readily isolated from the basic medium used in Method (A), it being obtained from the alkylated malonic ester in 94% yield. Method (A) has also been superior to the well-known method of Redemann and Dunn,[2b] an adaption of which failed to produce even the amino acid in which R is diethylaminopropyl.

The conversion of the alkylated malonic ester to the oximino ester, represented in Method (A), presumably involves first the formation of the nitroso derivative which is cleaved by the sodium ethoxide to form the sodium salt of the oximino ester and diethyl carbonate. Actually, diethyl carbonate has been isolated in the preparation of the ethyl ester of norleucine. The mechanism of the cleavage may be represented as



The ethyl ester of norleucine, prepared by Method (A), has been hydrolyzed in 91% yield to norleucine. In one experiment with diethyl *n*-butylmalonate, the resulting oximino ester (without being isolated) was hydrolyzed to the oximino acid in an over-all yield of 90%.

(1) The work described in this paper was supported by grants from the Duke University Research Council and from the Committee on Medical Research of the Office of Scientific Research and Development.

(2) (a) Sörensen, *Compt. rend. trav. lab., Carlsberg*, **6**, 1-60 (1903); *Z. phys. Chem.*, **44**, 448-460 (1905); (b) Redemann and Dunn, *J. Biol. Chem.*, **130**, 341 (1939); Painter, THIS JOURNAL, **62**, 232 (1940); (c) Albertson, Archer and Suter, *ibid.*, **67**, 36 (1945); Albertson and Archer, *ibid.*, **67**, 308 (1945); **67**, 2043 (1945); Albertson, *ibid.*, **68**, 450 (1946); Snyder, Shekleton and Lewis, *ibid.*, **67**, 310 (1945); Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945); Goldsmith and Tishler, *ibid.*, **68**, 144 (1946).

(3) Hamlin and Hartung, *J. Biol. Chem.*, **145**, 349 (1942).

(4) Albertson, THIS JOURNAL, **68**, 450 (1946); Albertson and Tullar, *ibid.*, **67**, 502 (1945).

(5) These methods are convenient not only because they avoid the formation of the amino acid but also, by introducing the amino group after alkylation, they avoid the necessity of preparing the acyl derivative of the amino ester, which appears to be required in several of the common methods (ref. 2) in order to minimize N-alkylation. See Putochin, *Ber.*, **56**, 2213 (1923); Keimatsu and Kato, *J. Pharm. Soc. Japan*, **49**, 731 (1929); Locquin and Cerchez, *Bull. soc. chim.*, [4] **47**, 1386 (1930).

(6) Bouveault and Locquin, *Bull. soc. chim.*, [3] **31**, 1055 (1904).

(7) A recent development of this method of preparing the oximino acids without isolating the intermediate esters will be described in a forthcoming paper by Barry and Hartung (private communication from Dr. Hartung).

(8) Fischer and Weigert, *Ber.*, **35**, 3772 (1902).

(9) Breslow, Walker, Yost, Shivers and Hauser, THIS JOURNAL, **68**, 100 (1946).

(10) We have attempted to avoid this difficulty by alkylating acetoacetic ester with trimethylene chlorobromide with the hope that the resulting γ-chloropropyl acetoacetic ester might be nitrosated and cleaved to the oxime (see ref. 9) and the diethylamino group then introduced; however, the alkylated product underwent cyclization to form 2-methyl-3-carbethoxy-5,6-dihydropyran. See Anderson, Crawford and Sherrill, THIS JOURNAL, **68**, 1294 (1946).

Experimental

Conversion of Alkylated Malonic Esters to α-Oximino Acid Esters.—In a typical experiment, 64.9 g. (0.3 mole) of diethyl *n*-butylmalonate[11] was placed in a 500-ml. flask equipped with a mercury-sealed stirrer, dropping funnel and an ice-water cooled condenser having a drying tube. The flask was immersed in an ice-bath and 33.8 g. (0.4 mole) of ethyl nitrite[12] was added to the stirred solution, the temperature of which was maintained at about 0°. The mixture was then cooled to −10° in an ice–salt bath and 0.3 mole of sodium ethoxide (prepared from 6.9 g. of sodium) in 138 ml. of absolute ethanol was added slowly with stirring. The flask was stoppered tightly and kept in a freezing unit of a refrigerator at −10° for twelve hours. The mixture was poured into an evaporating dish which was kept in a vacuum desiccator over concentrated sulfuric acid until the alcohol had evaporated. (The alcohol may be removed rapidly with equally good results by gently heating the mixture on a steam-bath under reduced pressure.) To the residue was added an equal volume of ice-water and the aqueous solution was extracted with ether.[13] While cooling in an ice-bath the aqueous solution was made acidic (*p*H 5) with cold concentrated hydrochloric acid. (During the neutralization ice was added directly to the aqueous solution.) The α-oximino ester, which precipitated as a yellow oil, was taken up in ether and the aqueous layer extracted several times with ether. The combined ether solution was dried over drierite and the solvent distilled leaving 42.8 g. (83%) of ethyl α-oximino caproate as a light yellow solid, m. p. 49–53°. Recrystallization from petroleum ether (30–60°) gave 41.4 g. (80%) of a white product, melting at 53–55° (reported m. p. 57 or 42°).[14]

Diethyl benzylmalonate[15] (50 g., 0.20 mole) was treated with 22.5 g. (0.30 mole) of ethyl nitrite and 0.2 mole of sodium ethoxide in 92 ml. of absolute ethanol. Crude ethyl α-oximino-β-phenylpropionate (40 g., 97%) was isolated as a light yellow solid, melting at 54–57°. Recrystallization from ligroin (90–120°) gave a white product (92%) melting at 56–58° (reported m. p. 57–58°).[16]

Diethyl γ-diethylaminopropylmalonate[17] (82.01 g., 0.3 mole) was treated with 33.8 g. (0.45 mole) of ethyl nitrite and 0.3 mole of sodium ethoxide in 138 ml. of absolute ethanol. After the neutralization and extractions with ether, the solvent was distilled from the dried ether solution and the residue heated on a steam-bath under reduced pressure (5 mm.) for forty-five minutes. Crude ethyl α-oximino-δ-diethylaminovalerate (65.3 g., 94%) was obtained as a reddish-brown oil.

Reduction of α-Oximino Esters to α-Amino Esters.—*In* a typical experiment, 51.0 g. (0.3 mole) of ethyl α-oximinocaproate was dissolved in 850 ml. of ethanol and reduced with Raney nickel at high pressure at 70–75°. The catalyst was filtered off, the solvent distilled under reduced pressure and the residue fractionated. No forerun was obtained and 40.9 g. (86%) of colorless ethyl ester of norleucine was collected, boiling at 87–88° at 11 mm. (reported b. p. 90–91° at 11 mm.).[18]

Ethyl α-oximino-β-phenylpropionate (16.8 g., 0.81 mole) in 850 ml. of ethanol was reduced to the ethyl ester of phenylalanine, which was obtained as a colorless liquid boiling at 141–142° at 10 mm. (reported b. p. 143° at 10 mm.)[19]; yield, 8.3 g. (53%).

Crude ethyl α-oximino-δ-diethylaminovalerate (62.0 g., 0.27 mole) in 850 ml. of ethanol was reduced to the ethyl ester of N^{δ},N^{δ}-diethylornithine, which was obtained as a colorless liquid boiling at 108–110° at 2 mm. (reported b. p. 120–123° at 6 mm.)[9]; yield, 29.5 g. (51%). The picrolonate melted at 185° in agreement with that reported previously.[9]

Norleucine.—The ethyl ester (5.0 g., 0.031 mole) was dissolved in 25 ml. of concentrated hydrochloric acid and the mixture refluxed for three hours. Excess solvent was evaporated over a steam-bath and the residue dissolved in a minimum of water. The solution was heated to boiling and concentrated ammonium hydroxide added until the solution reached a *p*H of 6. Three volumes of alcohol were added to the aqueous solution and the mixture allowed to chill overnight. Norleucine precipitated as a white powder; yield, 3.7 g. (91%); benzoyl derivative melted at 133° (reported m. p. 134°).[20]

α-Oximino Caproic Acid.—Diethyl *n*-butylmalonate (0.3 mole) was nitrosated and cleaved as described above. After removing the alcohol, the residue was treated with an equal volume of ice water and the mixture extracted with ether. The ether solution was extracted with 10% sodium hydroxide and the combined aqueous solution refluxed for ten minutes. The cooled solution was acidified with cold concentrated hydrochloric acid and the light yellow α-oximinocaproic acid (96%) filtered off. Recrystallization from benzene gave a product (90%) melting at 136° (reported m. p. 137°[3] or 132°[14b]).

Summary

1. The direct synthesis of the ethyl esters of norleucine, phenylalanine and N^{δ},N^{δ}-diethylornithine from malonic ester is described and compared with certain other methods.

2. The method has been used also to prepare norleucine and the corresponding α-oximino acid.

3. The mechanism of cleavage of nitrosated alkyl malonic esters by sodium ethoxide to form α-oximino esters is presented.

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(11) An 85% yield of this compound, b. p. 128–132° at 20 mm. was obtained by the procedure given in "Organic Syntheses," Coll. Vol. I (1941), p. 250.

(12) Gaseous ethyl nitrite, prepared essentially as described in "Organic Syntheses" (Coll. Vol. II (1943), p. 204), was condensed, stored and used in these experiments. Purified commercial butyl nitrite was used in an experiment with diethyl *n*-butylmalonate but the resulting ethyl α-oximino-*n*-caproate was quite impure.

(13) From the ether solution after drying and removing the solvent there was obtained 9.4 g. (27%) of ethyl carbonate, b. p. 124–127°.

(14) (a) Kondo, *Biol. Zentr.*, **38**, 408 (1912); (b) Hicks, *J. Chem. Soc.*, 113, 556 (1918).

(15) This compound was prepared in 80% yield by alkylation of sodio-malonic ester with benyzl phenyl dimethyl ammonium chloride as described by Snyder, Smith and Stuart, THIS JOURNAL, **66**, 200 (1944), or in 60% yield by alkylation of sodio-malonic ester with benzyl chloride in absolute ethanol or dioxane.

(16) Dieckmann and Groeneveld, *Ber.*, **33**, 600 (1900).

(17) Obtained in 60–70% yields from sodio-malonic ester and γ-diethylaminopropyl chloride in dioxane as described by Breslow, Walker, Yost and Hauser, THIS JOURNAL, **67**, 1473 (1945); Magidson and Strukov, *Arch. Pharm.*, **271**, 569–580 (1933).

(18) Fischer, *Ber.*, **34**, 450 (1901).

(19) Fischer, *ibid.*, **38**, 2919 (1905).

(20) Fischer, *ibid.*, **33**, 2382 (1900).