Synthetic Studies of the Derivatives of Nitroacetic Acid. I. The Preparation of Nitroacetic Ester and the Synthesis of α, β-Unsaturated α-Nitrocarboxylic Esters

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(Received April 30, 1963)

The Steinkopf method[1] for the preparation of nitroacetic ester has been modified, and it has been found that, when dipotassium nitroacetate is esterified with ethanol and hydrogen chloride in the presence of a dehydrating agent such as magnesium sulfate, the yield of ethyl nitroacetate is greatly raised, to 78%, probably because the decomposition of nitroacetic acid by the Nef reaction[2] is prevented by the dehydrating agent.

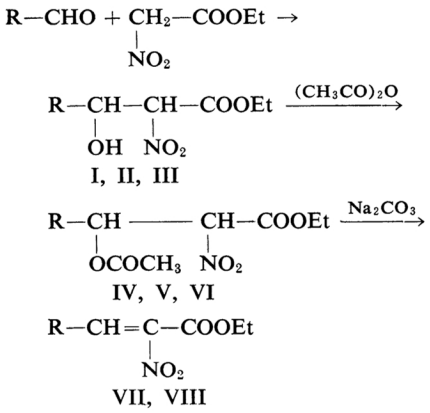
α, β-Unsaturated α-nitroesters have been prepared by the reactions shown in Chart 1.

This is a general synthesis of α, β-unsaturated α-nitroesters. Although the literature contains some examples[3] of the preparation of α, β-unsaturated α-nitroesters, esters of the sort form a relatively unknown class of compounds and are expected to be extraordinary reactive.

1) W. Steinkopf, *Ann.*, **434**, 21 (1923).
2) J. U. Nef, ibid., **280**, 263 (1894); W. E. Noland, *Chem. Revs.*, **55**, 137 (1955).
3) H. B. Hill and O. E. Black, *Am. Chem. J.*, **32**, 232 (1904); L. Bouveault and A. Wahl, *Compt. rend.*, **131**, 687 (1900); P. Friedländer, J. Mähly and M. Lazarus, *Ann.*, **229**, 203 (1885); A. Dornow and H. Menzel, ibid., **580**, 43 (1952).

TABLE I. β-ACETOXY-α-NITROESTERS AND α,β-UNSATURATED α-NITROESTERS

Compound	B. p., °C/mmHg	n_D^{20}	Formula	Analysis Found C, %	Found H, %	Found N, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Yield %
IV	84~92/0.2	1.4360	$C_8H_{13}O_6N$	44.26	5.68	6.86	43.83	5.98	6.39	52.9
V	98.5~107/0.04~0.05	1.440	$C_{10}H_{17}O_6N$	48.22	6.63	6.19	48.58	6.93	5.67	88.5
VI	118~120/0.04	1.4498	$C_{11}H_{17}O_8N$	45.39	5.91	4.78	45.36	5.85	4.80	65
VII	72~75/3	1.4535	$C_6H_9O_4N$	45.72	5.38	8.21	45.28	5.66	8.80	62.5
VIII	72.5~79.5/0.7	1.4548	$C_8H_{13}O_4N$	50.44	6.82	7.74	51.33	7.00	7.48	80
IX	125~130/0.2	1.4788	$C_9H_{13}O_6N$	—	—	6.12	—	—	6.06	29.8



(I, IV, VII: R=CH_3; II, V, VIII: R=n-C_3H_7; III, VI: R=EtOOC—CH_2)

Chart 1

Ethyl β-hydroxy-α-nitrocarboxylates (I and II) were prepared by the general method used by Rodionov and Belikov.[4]

The condensation of sodium ethyl formylacetate with ethyl nitroacetate in aqueous sodium carbonate gave diethyl β-hydroxy-α-nitroglutarate (III), which is a potential intermediate to β-hydroxyglutamic acid.

The acetylation of ethyl β-hydroxy-α-nitrobutyrate (I) with acetic anhydride in the presence of a small quantity of sulfuric acid gave ethyl β-acetoxy-α-nitrobutyrate (IV). Ethyl β-acetoxy-α-nitrocaproate (V) and diethyl β-acetoxy-α-nitroglutarate (VI) were prepared from ethyl β-hydroxy-α-nitrocaproate (II) and diethyl β-hydroxy-α-nitroglutarate (III) by an analogous procedure.

The treatment of the ethyl β-acetoxy-α-nitrocarboxyrates with anhydrous sodium carbonate in benzene at room temperature resulted in deacetylation and dehydration, giving ethyl α,β-unsaturated α-nitrocarboxylates; ethyl α-nitrocrotonate (VII) and ethyl 2-nitro-2-hexenoate (VIII) have been obtained by this procedure from IV and V respectively (Table I).

TABLE II. INFRARED SPECTRA OF α,β-UNSATURATED α-NITROESTERS (liquid, cm^{-1})

Compound	Ester CO	C=C	C—NO_2
VII	1742	1667	1542, 1346
VIII	1742	1660	1544, 1347
IX*	1750	1659	1588, 1310

* Carbon tetrachloride

The treatment of diethyl β-acetoxy-α-nitroglutarate (VI) with sodium carbonate by the procedure described above failed to produce the corresponding α,β-unsaturated α-nitroester. The condensation of sodium ethyl formylacetate[5] (1.0 mol.) with ethyl nitroacetate (2.0 mol.) in the presence of an amine such as n-butylamine or diethylamine (1.0 mol.) gave diethyl α-nitroglutaconate (IX) by the reactions shown in Chart 2.

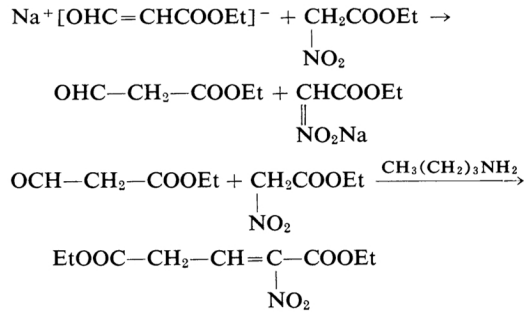


Chart 2

Experimental

Ethyl Nitroacetate.—A mixture of powdered dipotassium nitroacetate (50 g., 0.27 mol.) and anhydrous magnesium sulfate (10 g.) in absolute ethanol (300 g.) was stirred and cooled −8~−10°C, and dry hydrogen chloride was passed into the mixture. After the mixture absorbed 42 g. (1.15 mol.) of hydrogen chloride, the mixture was stirred

4) K. M. Rodionov and V. M. Belikov, *Chem. Abstr.*, **49**, 1550 (1955). The preparation of ethyl β-hydroxy-α-nitrobutyrate (I) and of ethyl β-hydroxy-α-nitrovalerate is described.

5) M. Cogan, *Bull. soc. chim. France*, [5] **8**, 125 (1941); S. M. McElvain and R. L. Clake, *J. Am. Chem. Soc.*, **69**, 2657 (1947); W. Deuschell, *Helv. Chim. Acta*, **35**, 1587 (1952).

for an additional hour and allowed to stand overnight at room temperature. The inorganic salt which separated was removed by filtration, and the ethanol was evaporated under reduced pressure at about 30°C. The residue was dissolved in benzene (100 ml.), and the solution was washed with a small quantity of a 5% sodium carbonate solution to neutralize the reaction product. After drying with anhydrous magnesium sulfate, followed by the evaporation of the solvent, the product was distilled under reduced pressure to give ethyl nitroacetate, b. p. 102~105°C/23 mmHg, yield 30.2 g. (78.2%).

Ethyl β-Hydroxy-α-nitrocaproate (II).—A solution of anhydrous sodium acetate (0.107 g.) in water (1.1 ml.) was added to a solution of *n*-butyraldehyde (8.48 g., 0.118 mol.) in ethanol (11.3 ml.) at below 10°C. To this solution ethyl nitroacetate was added drop by drop (14.1 g., 0.118 mol.), while the temperature was maintained at 8~14°C. Stirring was continued for 3.5 hr. to give a clear, pale-yellow solution. After the removal of the solvent under reduced pressure, the residue was dissolved in ether (200 ml.) and the solution was acidified with 10% hydrochloric acid and washed with a small quantity of water. The ethereal solution was dried with anhydrous magnesium sulfate and evaporated. The resulting residue was distilled under reduced pressure to ethyl β-hydroxy-α-nitrocaproate, b. p. 102~114°C/3 mmHg, n_D^{20} 1.4479, yield 14 g. (64.2%).

Found: C, 46.76; H, 7.45; N, 7.26. Calcd. for $C_8H_{15}O_5N$: C, 46.80; H, 7.37; N, 6.83%.

Diethyl β-Hydroxy-α-nitroglutarate (III).—Ethyl nitroacetate (7.5 g. 0.054 mol.) was added to a solution of concentrated hydrochloric acid (4.5 ml.) in water (7 ml.) below −10°C. Into this mixture was added sodium ethyl formylacetate (7.2 g., 0.05 mol.) rapidly under vigorous stirring. The solution was strongly acidic. Then a 5% aqueous sodium carbonate (about 45 ml.) which had been cooled to about 5°C was added to the reaction mixture to make pH 7.2~7.6, and the mixture was stirred at about 0°C for 1 hr. After the mixture had been made acidic (pH 1~2) by the addition of concentrated hydrochloric acid (about 4.5 ml.) under cooling in an ice-bath, the mixture was extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate, and then the solvent was removed by evaporation, giving a yellow sirup. This product was subjected to fractional distillation under reduced pressure in the usual way. After small fore-runs of unchanged ethyl nitroacetate and triethyl trimesate, diethyl β-hydroxy-α-nitroglutarate distilled at 120~123°C/0.08 mmHg, n_D^{20} 1.4616; yield 3.5 g. (26%); infrared spectrum (liquid): 3480 (OH), 1750 (ester CO), 1565 and 1375 cm^{-1} (C-NO_2).

Found: C, 44.87; H, 5.63; N, 5.71. Calcd. for $C_9H_{15}O_7N$: C, 43.37; H, 6.07; N, 5.62%.

The agreement between the found and calculated values of analysis was not very good, probably because the sample was accompanied with a trace of triethyl trimesate, the removal of which by distillation was difficult. However, acetylation gave an analytically pure sample of the acetate of III, as will be described below.

Ethyl β-Acetoxy-α-nitrobutyrate (IV).—A mixture of ethyl β-hydroxy-α-nitrobutyrate (I) (9.0 g., 0.05 mol.), acetic anhydride (5.7 g., 0.056 mol.) and concentrated sulfuric acid (0.04 ml.) was stirred at 60°C for 30 min. After the removal of acetic acid and acetic anhydride by distillation under reduced pressure, the residue was subjected to fractional distillation to give the title compound; yield, 5.9 g.

Ethyl α-Nitrocrotonate (VII).—To a solution of ethyl-β-acetoxy-α-nitrobutyrate (IV) (5.0 g. 0.023 mol.) in dry benzene (2.5 ml.) anhydrous sodium carbonate (1.21 g., 0.0114 mol.) was added; the mixture was stirred at about 60°C for about 5 min. until the evolution of carbon dioxide ceased. When the temperature of the mixture had fallen to room temperature, additional dry benzene was added and the mixture was stirred. The benzene-layer was dried with anhydrous sodium sulfate, and the solvent was removed by distillation. The residue was fractionated under reduced pressure to give a colorless oil, b. p. 72~76°C/3 mmHg, yield 2.27 g. Repeated distillation gave an analytically pure sample of ethyl α-nitrocrotonate.

Diethyl α-Nitroglutaconate (IX).—To a mixture of sodium ethyl formylacetate (6.0 g., 0.04 mol.) and ethyl nitroacetate (11.6 g., 0.086 mol.) in absolute ethanol, *n*-butylamine (3.2 g., 0.04 mol.) was added, and the mixture was refluxed on a water bath for 8 hr. After the mixture had stood overnight at room temperature, the precipitate of sodium ethyl nitroacetate was removed by filtration and the reddish brown filtrate was concentrated by evaporation. To the concentrate dry benzene (90 ml.) was added to precipitate additional sodium ethyl nitroacetate, this was removed again by filtration. After cooling to about 10°C, the benzene solution was washed with a small quantity of 20% acetic acid and with water. The benzene solution was dried over anhydrous sodium sulfate overnight, and filtered, and the solvent was removed, going an oily residue. This residue was fractionated under reduced pressure to give a crude product of diethyl α-nitroglutaconate; b. p. 144~158°C/0.1~0.5 mmHg, yield 3.0 g. (29.8%). When the product was allowed to stand, a small quantity of crystalline triethyl trimesate separated. After removal of this trimesate, the oily product was repeatedly fractionated.

The authors are indebted to Mr. Saburo Nakada of this Laboratory for his microanalysis.

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