684. *Ethyl* p-*Nitrobenzoylethoxaloacetate.*

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Ethyl *p*-nitrobenzoylethoxaloacetate (V) has been prepared from *p*-nitrobenzoyl chloride and ethyl ethoxaloacetate. Its hydrolytic transformations have been studied and its conversion into *p*-nitrophenacyl bromide (III) and *p*-nitroacetophenone achieved.

Conversion of *p*-nitrobenzoic acid (I) into *p*-nitroacetophenone (IX) may be effected through intermediates of the β-keto-ester type. Thus *p*-nitroacetophenone is obtained (i) by hydrolytic decarboxylation of ethyl *p*-nitrobenzoylmalonate (VIII; R′ = R″ = CO_2Et), prepared from *p*-nitrobenzoyl chloride and ethyl sodio-[1] or ethoxymagnesio-malonate,[2] or (ii) by reaction[3] of ethyl *p*-nitrobenzoylacetoacetate[3] (VIII; R′ = Ac, R″ = CO_2Et) with 30% sulphuric acid.[4] A third route, which forms the subject of the present communication, lies in the use of ethyl ethoxaloacetate, an intermediate rarely employed hitherto for ketone synthesis.[5] It offers advantages over ethyl malonate and ethyl acetoacetate, however, in that the intermediate *p*-nitrobenzoylethoxaloacetate (V) may be converted directly, not only into the acetophenone (IX), but also into the valuable intermediate (III) as indicated below.

Preliminary experiments showed that condensation of *p*-nitrobenzoyl chloride with ethyl sodioethoxaloacetate, followed by hydrolysis of the total product with sulphuric acid–acetic acid, led to *p*-nitrobenzoic acid (I), *p*-nitroacetophenone (IX), and compound A, $C_{22}H_{18}O_{11}N_2$, of which only the second was required. Examination of the products of condensation before hydrolysis revealed the complex nature of the initial condensation. Thus compound A was also obtained from those condensations of *p*-nitrobenzoyl chloride and ethyl sodioethoxaloacetate that yielded the intermediate ethyl *p*-nitrobenzoylethoxaloacetate (V) in poor yield. Occasional experiments giving the intermediate (V) in relatively good yield, in contrast, furnished small quantities of an isomeric compound B. We were obliged, consequently, to study the initial condensation in greater detail. The work was simplified by the observation that the intermediate (V) (essentially pure) was completely extracted from the reaction products by sodium hydrogen carbonate solution. In this way the yield of this intermediate was found to be governed largely by the purity of the *p*-nitrobenzoyl chloride, prepared in this instance by heating *p*-nitrobenzoic acid with thionyl chloride and a little pyridine. Even slight contamination of the acid chloride with pyridine (hydrochloride) drastically lowered the yield of the intermediate (V) with concomitant increase in the quantity of compound A. Traces of undesirable impurities were, however, readily removed by shaking the *p*-nitrobenzoyl chloride solution, before use, with alumina or activated charcoal. A similar, but less marked, deleterious effect was produced by traces of hydroxylic solvents in the reaction medium. Rapid mixing of the components proved desirable. By paying careful attention to detail, the yield of the intermediate (V) was ultimately raised to 70%.

Hydrolysis of this diester (V) with sulphuric–acetic acid gave a 1 : 2 mixture of *p*-nitrobenzoic acid and *p*-nitroacetophenone. As only the latter was required, this stage was further studied.

Hydrolysis with very dilute hydrochloric acid gave ethyl *p*-nitrobenzoylacetate (VI) and *p*-nitrobenzoylpyruvate (II), whose constitutions were confirmed by direct comparison with an authentic specimen[3] in the case of the former and by alternative synthesis[6] of the latter from *p*-nitroacetophenone and ethyl oxalate. The nitrobenzoylacetate could not be reconverted into the diester (V), nor could the latter be prepared from the sodium salt of the pyruvate (I) and ethyl chloroformate. Vigorous hydrolysis of the

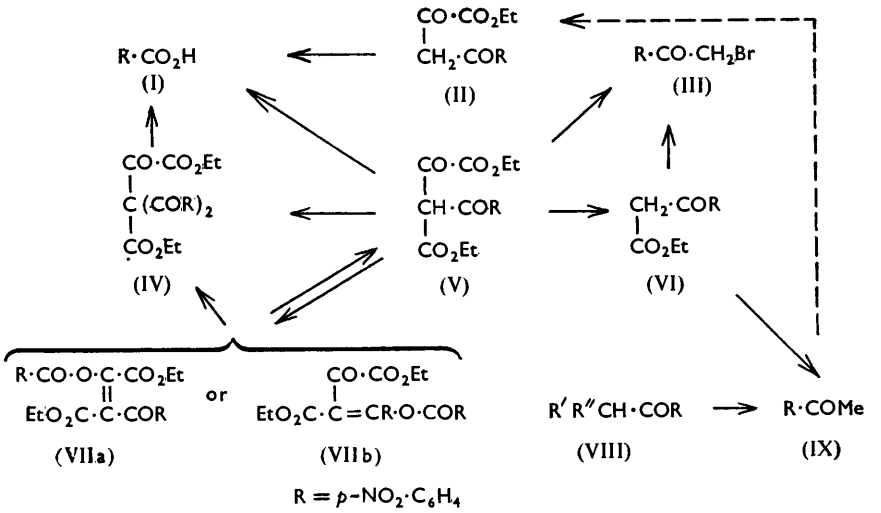
[1] Jackson and Whitmore, *J. Amer. Chem. Soc.*, 1915, **37**, 1929.
[2] Long and Troutman, *ibid.*, 1949, **71**, 2474.
[3] Bülow and Hailer, *Ber.*, 1902, **35**, 931.
[4] Gevekodt, *Annalen*, 1883, **221**, 335.
[5] See, however, Nef, *ibid.*, 1893, **276**, 22.
[6] Cf. *Org. Synth.*, **6**, p. 40, for method used.

p-nitrobenzoyl acetate (VI) with sulphuric–acetic acid furnished *p*-nitroacetophenone (IX) in almost quantitative yield: the pyruvate (II), in contrast, gave solely *p*-nitrobenzoic acid (I) under these experimental conditions.

Ethanolysis of the diester (V), or alternatively its hydrolysis with glacial acetic acid at 95°, gave a high yield of the *p*-nitrobenzoylacetate (VI). Conversion of the diester (V) to *p*-nitroacetophenone (IX) with minimal formation of by-products is thereby achieved.

The marked reactivity of the diester (V) has been additionally utilised in developing a new route to *p*-nitrophenacyl bromide (III). Bromination in acetic acid, followed by dilution with water and heating, gave the phenacyl bromide (III) directly and in high yield. The benzoylacetate (VI) was likewise converted into the bromide (III) with negligible formation of *p*-nitrobenzoic acid. The pyruvate (II), in contrast, gave only *p*-nitrobenzoic acid on similar treatment.

The empirical formulæ of compounds A and B corresponded to that of an ethyl di-*p*-nitrobenzoylethoxaloacetate. Compound B differed from A in its readier hydrolysis (see below) and characteristically in its being irreversibly transformed into its isomer by



such reagents as hot aqueous acetic acid, potassium carbonate suspended in ethyl acetate, catalytic quantities of a tertiary base in a non-polar solvent, and partly even in hot ethanol. It was also more readily soluble than compound A in hydroxylic solvents. These differences recall the contrasting properties of ethyl *O*- and *C*-acetylacetoacetate, the former being transformed into the latter by alkaline reagents such as potassium carbonate suspended in ethyl acetate.[7] The structures ethyl αα-di-*p*-nitrobenzoyl-α-ethoxaloacetate (IV) and the *O*-acyl-ester (VIIa or b) * are consequently assigned to compounds A and B respectively, though attempts to confirm them by synthesis were not wholly successful. Presumptive evidence in favour of the assigned formulations, however, is furnished by the observations that (i) compound B is formed in high yield by condensing the sodium salt of the diester (V) with *p*-nitrobenzoyl chloride in a non-polar solvent, (ii) the presence of an unsaturated linkage (infrared spectrum) in compound B, and (iii) the preparation of the ester (IV) in low yield (15%) by direct condensation of the intermediate (V) with *p*-nitrobenzoyl chloride in a non-polar solvent and in high yield when equimolar proportions of these components were mixed in an inert solvent in the presence of a molar equivalent of a tertiary base. The reactions, however, lack diagnostic significance.[8]

* The latter was kindly suggested by a referee.

[7] Claisen and Zedel, *Annalen*, 1893, **277**, 175; Claisen and Hoas, *Ber.*, 1900, **33**, 3780.

[8] See, for example, James, *Annalen*, 1884, **226**, 211; Michael, *Ber.*, 1905, **38**, 2088; Mirgasson, *Bull. Soc. chim. France*, 1886, **45**, 716.

Prolonged ethanolysis of compound B with 95% ethanol gave *p*-nitrobenzoic acid (I) as the major product, together with small quantities of compound A (IV). Careful hydrolysis with a molar equivalent of ethanolic potassium hydroxide gave three products, (I), (IV), and (V). Compound A (IV), in contrast, was largely unaffected by prolonged heating with ethanol: it slowly gave *p*-nitroacetophenone and *p*-nitrobenzoic acid (I) in the proportion of 1 : 2 on vigorous hydrolysis with sulphuric–acetic acid. Concentrated sulphuric acid converted it into ethyl *p*-nitrobenzoylacetate (VI) with larger quantities of *p*-nitrobenzoic acid.

Experimental

Ethyl p-*Nitrobenzoylethoxaloacetate* (V).—(*a*) *p*-Nitrobenzoyl chloride (18·5 g.) (preferably distilled; alternatively the solution of the crude acid chloride may be shaken for a few minutes with alumina before use) in dichloroethylene (50 ml.) was added rapidly at room temperature to technical ethyl sodioethoxaloacetate (21 g., 1 mol.) in dichloroethylene (100 ml.). After 20 minutes' shaking at <30° (cooling), the mixture was extracted twice with 3% sodium hydrogen carbonate solution (150 and 100 ml.). Acidification (Congo-red) of the combined extracts with 5% hydrochloric acid gave *ethyl* p-*nitrobenzoylethoxaloacetate* (V) (50%), large pale yellow rhombs, m. p. 80—82° (Found: C, 53·4; H, 4·6; N, 4·6. $C_{15}H_{15}O_8N$ requires C, 53·4; H, 4·4; N, 4·2%), after crystallisation from benzene–light petroleum (b. p. 40—60°).

(*b*) By using 2 mols. of ethyl sodioethoxaloacetate, the yield of product (V) was raised to 65—70%.

Ethyl α-p-*Nitrobenzoyl*-α′-p-*nitrobenzoyloxyfumarate* (VIIa) *or* α-*Ethoxalo*-β-p-*nitrophenyl*-β-p-*nitrobenzoyloxyacrylate* (VIIb).—(*a*) The dichloroethylene liquors from experiment (*a*) (above) were washed with water and evaporated to dryness under reduced pressure and the residue slowly crystallised from benzene–light petroleum (b. p. 40—60°), to give the *ester* (VIIa or b) (5—6 g.), feathery needles, m. p. 108—110° (Found: C, 54·2; H, 3·7; N, 5·6. $C_{22}H_{18}O_{11}N_2$ requires C, 54·3; H, 3·7; N, 5·7%).

(*b*) The ester (V) (17 g.) in dichloroethylene (100 ml.) was treated with stirring with sodium ethoxide (1·2 g. of sodium in 35 ml. of ethanol). After 10—15 min. the mixture was carefully taken to dryness under reduced pressure and dichloroethylene (100 ml.) was added, followed by *p*-nitrobenzoyl chloride (9·25 g. in 75 ml. of dichloroethylene). Stirring was continued for a further 30 min. Precipitated sodium chloride was removed, and the filtrate washed with cold 3% sodium hydrogen carbonate solution (200 ml.) and then water, dried, and evaporated under reduced pressure. The residue in ethanol (*ca.* 80 ml.) was filtered to remove *p*-nitrobenzoic anhydride (*ca.* 1 g.; m. p. 190°) and set aside, giving compound B, m. p. 109—110° (Found: C, 54·4; H, 3·5; N, 5·3%), not depressed in admixture with a sample obtained as in (*a*).

Ethyl αα-*Di*-p-*nitrobenzoyl*-α-*ethoxaloacetate* (IV).—(*a*) Crude *p*-nitrobenzoyl chloride (18·5 g.) in dichloroethylene (50 ml.) was added rapidly at room temperature to ethyl sodioethoxaloacetate (21 g.) in dichloroethylene (100 ml.). After 15 minutes' shaking the solvents were removed under reduced pressure and the residue hydrolysed for *ca.* 3 hr. with hot acetic acid (30 ml.), water (10 ml.), and concentrated sulphuric acid (6 ml.). The mixture was poured into water (200 ml.), extracted with chloroform and filtered to remove *p*-nitrobenzoic acid (I), the chloroform removed, and the residue crystallised from ethanol (charcoal), to give *ethyl* αα-*di*-p-*nitrobenzoyl*-α-*ethoxaloacetate*, pale yellow needles, m. p. 145—146° (Found: C, 54·4; H, 3·4; N, 5·3. $C_{22}H_{18}O_{11}N_2$ requires C, 54·3; H, 3·7; N, 5·7%).

(*b*) Compound B (12 g.) in dichloroethylene containing 3 drops of piperidine was heated under reflux for 1 hr. The product, from ethanol–ethyl acetate, furnished the *CC*-diacyl derivative (IV), m. p. 144—145° (Found: C, 54·7; H, 3·4; N, 5·5%) not depressed in admixture with a sample prepared as in (*a*).

(*c*) The diester (V) (10 g.) in dichloroethylene (50 ml.) was treated with *p*-nitrobenzoyl chloride (5·4 g.). After 2 hr., the mixture was washed with 3% sodium hydrogen carbonate solution and then water, dried, and evaporated and the residue crystallised from ethanol, giving the diacyl derivative (IV), m. p. 144—145° alone or in admixture with an authentic specimen.

(*d*) The diester (V) (34 g.) in dichloroethylene (100 ml.) was mixed with *p*-nitrobenzyl chloride (18·5 g.), followed immediately by pyridine (7·8 g.). The temperature of the mixture rose to 40° and a little pyridine hydrochloride separated. Working up as in (*c*) furnished the product (IV), m. p. and mixed m. p. 144—146°.

Acid Hydrolysis of Ethyl αα-*Di*-p-*nitrobenzoyl*-α-*ethoxaloacetate* (IV).—This ester (20 g.) and

concentrated sulphuric acid (25 ml.) were left at room temperature for 1 hr.; carbon dioxide was evolved. The mixture was poured into water (500 ml.) and mixed with chloroform (150 ml.); *p*-nitrobenzoic acid (9 g.) separated and was removed (a further 2 g. were extracted from the chloroform solution with aqueous sodium hydrogen carbonate). The chloroform was then removed and the residue taken up in benzene (10 ml.) and light petroleum (15 ml.) (b. p. 40—60°); the solution was filtered and evaporated and the residue crystallised from ethanol, giving ethyl *p*-nitrobenzoylacetate, yellow needles, m. p. 79—80° (Found: C, 56·0; H, 4·3; N, 5·5. Calc. for $C_{11}H_{11}O_5N$: C, 55·7; H, 4·6; N, 5·9%).

Hydrolysis of Ethyl α-p-*Nitrobenzoylethoxaloacetate* (V).—(*a*) This ester (50 g.) was heated with sulphuric–acetic acid–water (5 : 3 : 1 v/v; 100 ml.) at 95—100° with stirring for 1½ hr. Ethyl acetate slowly distilled off. The mixture was poured into water (500 ml.) and extracted with chloroform (2 × 100 ml.), and *p*-nitrobenzoic acid (7 g.) was filtered off. The chloroform extracts yielded *p*-nitroacetophenone (IX) (14 g.), m p and mixed m. p. 80°.

(*b*) The ester (V) (10 g.) in water (140 ml.) and hydrochloric acid (10 ml.) was stirred at 80—83° for ½ hr., then extracted with chloroform and the extract shaken with concentrated aqueous sodium hydrogen carbonate solution (2 × 50 ml.) to remove unchanged material (1·2 g.). Removal of chloroform, followed by crystallisation from ethanol, furnished ethyl *p*-nitrobenzoylacetate (VI) (4·4 g.), yellow needles, m. p. and mixed m. p. 79—80° (Found: C, 55·6; H, 4·4; N, 6·1. Calc. for $C_{11}H_{11}O_5N$: C, 55·7; H, 4·6; N, 5·9%).

(*c*) The mixture as in (*b*) was heated under reflux for 30 min. and the product isolated with chloroform. The non-aqueous fraction was shaken with sodium hydrogen carbonate solution and filtered from yellow solids. The latter were acidified, to give *ethyl* p-*nitrobenzoylpyruvate* (II) (1·75 g.), m. p. 116—117° after crystallisation from ethanol (Found: C, 54·4; H, 4·3; N, 5·2. $C_{12}H_{11}O_6N$ requires C, 54·4; H, 4·2; N, 5·3%). The chloroform liquors yielded ethyl *p*-nitrobenzoylacetate (VI) (2·5 g.).

(*d*) Ethyl *p*-nitrobenzoylacetate (VI), pale yellow needles, m. p. and mixed m. p. 78—79°, was obtained by heating the ester (V) (25 g.) in ethanol (60 ml.) for 1 hr. and then allowing the solution to cool.

Hydrolysis of the *p*-nitrobenzoylacetate with sulphuric–acetic acid–water as above gave *p*-nitroacetophenone in 90% yield.

(*e*) Heating the diester (V) (50 g.) with ethanol (100 ml.) for 1 hr., followed by removal of solvent under reduced pressure and acid hydrolysis as above, gave *p*-nitroacetophenone in 90% yield.

(*f*) The diester (V) (10 g.) was heated with glacial acetic acid (40 ml.) for 2 hr. at 95°. Pouring the mixture into water then gave ethyl *p*-nitrobenzoylacetate (93%), m. p. 79—80° after crystallisation from ethanol.

(*g*) The diester (V) (10 g.) was heated with glacial acetic acid (40 ml.) for 2 hr. at 95°, then sulphuric acid (15 g.) in water (20 ml.) was added and heating continued for a further 3 hr. Precipitation with water (200 ml.) and isolation with chloroform gave *p*-nitroacetophenone (85%), m. p. 80° (from ethanol).

Ethyl p-*Nitrobenzoylpyruvate* (II).—Ethyl oxalate (75 g.), mixed with *p*-nitroacetophenone (82·5 g.), was added at 20° to a stirred solution of sodium ethoxide (from 12·5 g. of sodium in 280 ml. of ethanol) during 1½ hr. Stirring was continued for a further 1 hr., then the mixture was poured into water (500 ml.) and immediately acidified to Congo-red, and the product was isolated with chloroform, to give the pyruvate (II) (70 g.), pale yellow needles, m. p. 115—116° (Found: C, 54·6; H, 3·8; N, 5·0%), not depressed in admixture with a sample prepared from the ester (V) as above.

Hydrolysis of the pyruvate with sulphuric–acetic acid–water gave *p*-nitrobenzoic acid in 90% yield.

p-*Nitrophenacyl Bromide* (III).—The diester (V) (20 g.) in acetic acid (45 ml.) was treated with bromine (9·3 g.) in one portion. After stirring to ensure homogeneity, the mixture was heated to 95—100° and there maintained for 10 min. Water (7·5 ml.) was added and heating continued for a further 1—1½ hr. Water (20 ml.) was then added and the mixture allowed to cool. *p*-Nitrophenacyl bromide (11 g.) separated and formed straw-coloured needles, m. p. and mixed m. p. 98—99° (Found: C, 39·6; H, 2·5; N, 5·4. Calc. for $C_8H_6O_3NBr$: C, 39·3; H, 2·5; N, 5·7%), from light petroleum (b. p. 40—60°).

Ethyl *p*-nitrobenzoylacetate (VI) (23·7 g.) similarly gave the bromide (80%), m. p. and mixed m. p. 98—99° (Found: C, 39·5; H, 2·7; N, 5·3%).

Ethyl *p*-nitrobenzoylpyruvate gave *p*-nitrobenzoic acid on similar treatment.

Ethanolysis of Compound B.—The compound (10 g.) in 95% ethanol (50 ml.) was heated

under reflux for 4 hr., then allowed to cool, and the *CC*-diacyl compound (IV) (3 g.) removed by filtration. Removal of solvent under reduced pressure and treatment of the residue with chloroform gave *p*-nitrobenzoic acid (1·5 g.), which was filtered off. Removal of solvent and crystallisation from ethanol (5 ml.) at 0° gave ethyl *p*-nitrobenzoylacetate (VI) (1·0—1·5 g.), m. p. 79—80°.

Alkaline Hydrolysis of Compound B.—The compound (2 g.) was added to potassium hydroxide (250 mg.) in 95% ethanol (15 ml.), and the solution immediately refluxed for 2—3 min., poured into water (80 ml.), acidified to Congo-red, and extracted with chloroform (2 × 10 ml.). The combined extracts were washed with water and extracted with 3% sodium hydrogen carbonate solution (2 × 25 ml.), which was then acidified to Congo-red. The precipitated solids (800 mg.) were collected and separated by chloroform treatment into *p*-nitrobenzoic acid (350 mg.) and a soluble fraction which gave ethyl α-*p*-nitrobenzoylethoxaloacetate (V), m. p. and mixed m. p. 80—82°. The original chloroform extracts, after evaporation and trituration of the residue with ethanol (10 ml.), gave the *CC*-diacyl compound (IV) (250 mg.), m. p. and mixed m. p. 144—145°.

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