

140. The Preparation of *o*- and *p*-Nitroacetophenone.

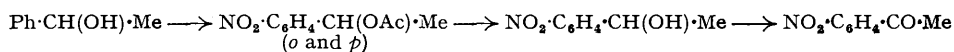
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Two convenient preparative procedures, starting from phenylmethylcarbinol and ethylbenzene respectively, are described.

THE principal product of the nitration of acetophenone is *m*-nitroacetophenone, which may readily be prepared in this way (Morgan and Moss, *J. Soc. Chem. Ind.*, 1923, **42**, 461r; Elson, Gibson, and Johnson, *J.*, 1930, 1128); much *o*-nitroacetophenone is also produced in the nitration but cannot be isolated from the reaction product in good yield or in a satisfactory state of purity. We have accordingly investigated other methods for preparing *o*- and *p*-nitroacetophenone.

Both compounds can be prepared by the classical acetoacetic ester synthesis from the corresponding nitrobenzoyl chlorides (Gevekoht, *Annalen*, 1883, **221**, 323; Needham and Perkin, *J.*, 1904, **85**, 148; Kermack and Smith, *ibid.*, 1929, 814). This method gives products of high purity and we have been able, by its use, to obtain *o*-nitroacetophenone for the first time as a solid, m. p. 24.5°; it is, however, not well suited for the preparation of even moderately large quantities and we have developed two other methods which are preferable in this respect.

The first of these methods starts from phenylmethylcarbinol:

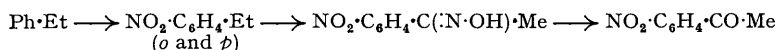


The nitration of phenylmethylcarbinol does not appear to have been studied previously; the procedure we

adopted was nitration with 1.1 mols. of fuming nitric acid in acetic anhydride solution (cf. the nitration of β -phenylethyl alcohol; Sabetay, Bléger, and de Lestrangé, *Bull. Soc. chim.*, 1931, **49**, 3). The nitration product contained approximately equal amounts of the *o*- and *p*-isomerides; despite the fact that the *p*-compound is a solid a satisfactory separation cannot be readily achieved at this stage. Accordingly, the mixed nitro-acetates, after removal of any solid *p*-isomer by filtration, were hydrolysed directly with aqueous alcoholic hydrochloric acid. The hydrolysis product was readily separated, by fractional distillation, into *o*- and *p*-nitrophenylmethylcarbinols, which were then oxidised with chromic acid to the nitroacetophenones. In this way an overall yield of 21% of pure *p*-nitroacetophenone and 23% of *o*-nitroacetophenone of 80% purity was obtained without difficulty from phenylmethylcarbinol. von Braun and Bartsch (*Ber.*, 1913, **46**, 3053) have previously described the *p*-intermediates; the physical properties of their products were, however, very different from ours (thus the *p*-nitroacetate was described as an oil whereas we obtained it as a solid, m. p. 55–56°) and it seems almost certain that they were mixtures.

Some preliminary experiments on the nitration of α -phenylethyl chloride were also carried out; the α -chlorine atom was readily displaced with the formation, among other products, of α -(4-nitrophenyl)ethyl nitrate.

The second method (cf. Reich and Nicolaeva, *Helv. Chim. Acta*, 1919, **2**, 86) proceeds from ethylbenzene, thus:



Nitration of ethylbenzene yields a fairly easily separable mixture of *o*- and *p*-nitroethylbenzenes (Beilstein and Kuhlberg, *Annalen*, 1870, **156**, 206; Schultz and Flachslander, *J. pr. Chem.*, 1902, **66**, 155; Cline and Reid, *J. Amer. Chem. Soc.*, 1927, **49**, 3150). The conversion of *o*-nitroethylbenzene into *o*-nitroacetophenone oxime with amyl nitrite and sodium ethoxide has been described in a patent (Höchst, D.R.-P. 109,663); in our hands the yields by this method were poor, but both *o*- and *p*-nitroethylbenzene were converted, in excellent yield, into the oximes by means of *tert*-butyl nitrite and sodium *tert*-butoxide. The oximes are readily hydrolysed by dilute sulphuric acid to the corresponding nitroacetophenones. By this route overall yields of 15% of pure *p*-nitroacetophenone and 20% of pure *o*-nitroacetophenone were obtained from ethylbenzene.

A number of other nitroacetophenone derivatives are described in the experimental section.

EXPERIMENTAL.

Nitration of Phenylmethylcarbinol.—Phenylmethylcarbinol (244 g.) was added, with periodic cooling, over 10 minutes to acetic anhydride (400 c.c.) containing sulphuric acid (2 c.c.). After being kept at room temperature for 15–30 minutes the acetic anhydride solution of phenylmethylcarbiny acetate was stirred mechanically while fuming nitric acid (94 c.c.; *d* 1.50) was added dropwise over 1½–2 hours, the temperature being kept below 20° by ice-cooling. After being stirred for a further 1–2 hours at 15–20°, the product was poured into ice and water (1000 c.c.). Next day the mixture was filtered and the solid and filtrate treated separately.

Crystallisation of the solid (average yield 34 g.; 8%) from light petroleum (b. p. 40–60°) yielded α -(4-nitrophenyl)ethyl acetate in colourless prisms, m. p. 55–56° (Found: C, 57.7; H, 5.4; N, 6.8. $\text{C}_{10}\text{H}_{11}\text{O}_4\text{N}$ requires C, 57.4; H, 5.3; N, 6.7%).

The oily mixture of nitrophenylethyl acetates was separated from the filtrate and washed; it was not found possible to obtain an adequate separation of the isomers by fractional distillation. Accordingly the mixture was hydrolysed by refluxing for 6 hours with alcohol (1000 c.c.) and concentrated hydrochloric acid (200 c.c.); the residue obtained by evaporation on a water-bath under reduced pressure was then carefully fractionated using a 20 cm. Vigreux column. The progress of the fractionation was followed by observation of the refractive index, the following relations holding:

$$\% \text{ } o\text{-isomer} = 9616(1.5621 - n_D^{20}); \quad n_D^{20} = n_D^{25} - 0.00103(20 - t).$$

For the preparation of the nitroacetophenones it is most convenient to collect a first fraction, b. p. 125–140°/2 mm., containing (mean of 4 runs) 86% of *o*-nitrophenylmethylcarbinol (average yield 108 g.; 32%), a middle fraction, b. p. 140–145°/2 mm. (49% of *o*-isomer; average yield 27 g. = 8%), and an end fraction, b. p. 145–155°/2 mm. (88% *p*-isomer; average yield 75.5 g. = 23%); the pure isomers can be obtained by further fractionation of the head and tail fractions.

Pure *o*-nitrophenylmethylcarbinol so prepared was a viscous yellow oil with a marked sweet taste, b. p. 131–132°/3 mm., 124–126°/1.5 mm., n_D^{20} 1.5517 (Found: C, 56.8; H, 5.7; N, 8.35. $\text{C}_8\text{H}_9\text{O}_2\text{N}$ requires C, 57.5; H, 5.4; N, 8.4%); the *p*-nitrobenzoate crystallised from alcohol in pale yellow needles, m. p. 145–146° (Found: C, 56.9; H, 3.95. $\text{C}_{15}\text{H}_{12}\text{O}_6\text{N}_2$ requires C, 57.0; H, 3.8%).

Pure *p*-nitrophenylmethylcarbinol, obtained by hydrolysis of the crystalline acetate, was a sweet-tasting viscous yellow oil, b. p. 161–163°/4 mm., n_D^{20} 1.5621 (Found: C, 56.8; H, 5.4; N, 8.6%); the *p*-nitrobenzoate crystallised from alcohol in colourless leaflets, m. p. 138° (Found: C, 56.95; H, 3.9%).

Oxidation of Nitrophenylmethylcarbinols.—(a) *o*-Nitroacetophenone. *o*-Nitrophenylmethylcarbinol (86%; 108 g.) was added during 10 minutes to a stirred solution of sodium dichromate (190 g.) in water (475 c.c.) and sulphuric acid (95 c.c.), previously heated to 60°. After the internal temperature, which rose to 95°, had again fallen to 60° (about 15 minutes) the mixture was stirred at 60° for a further 3 hours and then poured into ice and water (1000 c.c.). The product was extracted with benzene and the extract washed with 10% sodium carbonate solution, dried, and distilled, *o*-nitroacetophenone being collected at 134–135°/4 mm., 146–148°/7 mm. The composition of the product can be determined by measurement of the refractive index; the following relations hold:

$$\% \text{ } o\text{-isomer} = 5181(1.5497 - n_D^{20}); \quad n_D^{20} = n_D^{25} - 0.00055(20 - t).$$

The average yield of *o*-nitroacetophenone from three such runs was 92 g. (85%); the product contained 80% of the *o*-isomer.

(b) *p*-Nitroacetophenone. *p*-Nitrophenylmethylcarbinol (87%; 69 g.) was oxidised as described for the *o*-isomer; the solid product (62.6 g.) was crystallised from methanol, yielding 44.5 g. (65%) of pure *p*-nitroacetophenone, m. p. 79–80°.

Nitration of α -Phenylethyl Chloride.— α -Phenylethyl chloride (40 g.; Norris, Watt, and Thomas, *J. Amer. Chem. Soc.*,

1916, **38**, 1078) was added dropwise with mechanical stirring over 5 hours to fuming nitric acid (200 c.c.; d 1.50), the temperature being kept below -10° ; chlorine was freely evolved during the later part of the process. The product was poured into water and the resulting paste filtered off and pressed well. Crystallisation of the solid (25.7 g.; 45%) from alcohol yielded α -(4-nitrophenyl)ethyl nitrate in almost colourless rectangular leaflets, m. p. 50° (Found: C, 45.9; H, 4.0; N, 13.2. $C_8H_8O_5N_2$ requires C, 45.3; H, 3.8; N, 13.2%); the position of the nuclear nitro-group was established by oxidation to *p*-nitrobenzoic acid.

Nitration of Ethylbenzene (cf. Cline and Reid, *J. Amer. Chem. Soc.*, 1927, **49**, 3150).—Ethylbenzene (867 g.) was treated with stirring with a mixture of nitric (436 c.c.; d 1.459) and sulphuric (436 c.c.; d 1.84) acids, the temperature being kept at $25-30^{\circ}$ by external cooling; the reaction mixture was then heated on the water-bath for 2 hours. The nitration product was separated from the cooled mixture, washed with sodium carbonate, dried, and fractionally distilled under reduced pressure through a long column. The course of the fractionation was followed by observation of the refractive index, the following relations holding:

$$\% \text{ } o\text{-isomer} = 14080(1.5459 - n_D^{15}) ; n_D^{15} = n_D^{\ddagger} - 0.00052(15 - t).$$

Two fractionations gave 485 g. (39%) of *o*-nitroethylbenzene, b. p. $87-89^{\circ}/4$ mm., n_D^{15} 1.5388, 130 g. of an intermediate mixture, and 471 g. (38%) of *p*-nitroethylbenzene, b. p. $102-104^{\circ}/4$ mm., n_D^{15} 1.5459. The distillation residue yielded 7 g. of 2 : 4-dinitroethylbenzene, b. p. $148-150^{\circ}/8$ mm.

Oximation of Nitroethylbenzene.—Sodium *tert*.-butoxide was prepared by dissolving sodium wire (25 g.) in dry *tert*.-butyl alcohol (1000 c.c.) on the water-bath and distilling off 300 c.c. of butyl alcohol after the reaction was complete; the product was cooled to room temperature and treated with a mixture of *o*-nitroethylbenzene (151 g.) and *tert*.-butyl nitrite (110 g.; b. p. $65-66^{\circ}$; prepared in 62% yield by the method described for *n*-butyl nitrite by Noyes, *Org. Synth.*, 1936, **16**, 7). After being kept overnight the mixture was heated to 50° on the water-bath and then steam-distilled to remove *tert*.-butyl alcohol; the steam distillate consists largely of a constant-boiling mixture of water and the alcohol and can be used for the preparation of more nitrite. The residue from the steam distillation was cooled and extracted with chloroform; the chloroform extract was shaken with 10% sodium hydroxide. This alkaline washing was added to the aqueous layer from the chloroform extraction and the whole treated with carbon dioxide until precipitation was complete. The precipitated oxime was filtered off and dried in a vacuum desiccator; m. p. $113-114^{\circ}$, yield 80 g. (73.5% allowing for 91 g. of redistilled *o*-nitroethylbenzene obtained by distillation of the washed chloroform extract); *o*-nitroacetophenone oxime recrystallised from methanol had m. p. 117° (Höchst, D.R.P. 109,663, give m. p. 115°).

p-Nitroacetophenone oxime, m. p. 174° after crystallisation from methanol (Posner, *Annalen*, 1912, **389**, 42, gives m. p. $172-173^{\circ}$), was similarly obtained in 67% yield from *p*-nitroethylbenzene. The reaction does not proceed so smoothly with 2 : 4-dinitroethylbenzene which gives only 27% of 2 : 4-dinitroacetophenone oxime, m. p. 121° from 90% alcohol (Reich and Nicolaeva, *Helv. Chim. Acta*, 1919, **2**, 86, give m. p. 124°).

Hydrolysis of Oximes.—Crude *o*-nitroacetophenone oxime (76 g.), water (100 c.c.), and sulphuric acid (50 c.c.) were refluxed, with stirring, for 3 hours. The cooled reaction product was extracted with chloroform, washed with dilute sodium hydroxide solution, dried, and distilled, yielding 50 g. (72%) of pure *o*-nitroacetophenone, b. p. $129^{\circ}/3$ mm., m. p. 23° ; 9 g. of unreacted oxime were recovered from the alkali washings.

p-Nitroacetophenone oxime was similarly hydrolysed in 60% yield to *p*-nitroacetophenone, b. p. $138^{\circ}/1.5$ mm., m. p. 80° from methanol (Drewsen, *Annalen*, 1882, **212**, 60, gives m. p. $80-81^{\circ}$), and 2 : 4-dinitroacetophenone oxime in 30% yield to 2 : 4-dinitroacetophenone, b. p. $192^{\circ}/7$ mm., m. p. $41-42^{\circ}$ from methanol (Found: C, 45.7; H, 2.9. $C_8H_6O_5N_2$ requires C, 45.7; H, 2.9%).

Bromination of 2 : 4-dinitroacetophenone (2.5 g.) in acetic acid with bromine (1.6 g.) gave ω -bromo-2 : 4-dinitroacetophenone, m. p. $90-91^{\circ}$ after crystallisation from methanol (Found: C, 33.6; H, 1.7. $C_8H_5O_5N_2Br$ requires C, 33.25; H, 1.7%).

Derivatives of *o*-Nitroacetophenone.—*o*-Nitroacetophenone, prepared by the acetoacetic ester synthesis from *o*-nitrobenzoyl chloride, solidified on keeping at -70° for some hours. The crystalline product, m. p. 24.5° , was used for the preparation of the following derivatives.

The oxime, prepared in pyridine and twice crystallised from aqueous alcohol, had m. p. 117° . The *semicarbazone* crystallises from dilute acetic acid, m. p. $208-210^{\circ}$ (Found: C, 49.0; H, 5.0; N, 25.2. $C_9H_{10}O_5N_4$ requires C, 48.6; H, 4.5; N, 25.2%), and the 2 : 4-dinitrophenylhydrazone from glacial acetic acid, m. p. $168-170^{\circ}$ (Found: C, 49.0; H, 3.3. $C_{14}H_{11}O_6N_5$ requires C, 48.8; H, 3.2%).

All analyses were micro-analyses carried out by Mr. G. Ingram.

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