THE FRIES REARRANGEMENT OF PHENYL ISOBUTYRATE[1]

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ABSTRACT

Phenyl isobutyrate has been found to undergo a normal Fries rearrangement with anhydrous aluminum chloride at 140°C. to give a mixture of 2-hydroxy- (40%) and 4-hydroxy-isobutyrophenone (11%). When the reaction was carried out in nitrobenzene solution at room temperature the 4-isomer was formed in 86% yield. Methylation of these compounds furnished 2- and 4-methoxy-isobutyrophenone, identical with the compounds obtained by direct acylation of anisole. Reduction of the hydroxy-isobutyrophenones, which were also prepared by direct acylation of phenol, afforded an alternative route to the isobutylphenols. The orientation of each methoxy ketone was verified by oxidation to the corresponding acid.

INTRODUCTION

The literature pertaining to the Fries rearrangment has been well documented (3, 4) but these reviews make no mention of the reaction having been applied to esters of phenol in which the acyl group has a branched carbon chain. Since 2-isobutylphenol and 4-isobutylphenol were required as part of a program investigating herbicidal activity of dinitrophenols, their preparation was considered by subjecting phenyl isobutyrate to a Fries rearrangement and reducing the hydroxy ketones thus formed according to the method of Clemmensen (5) as modified by Martin (10).

Examination of the literature revealed very little information on 2-hydroxy- or 2-methoxy-isobutyrophenone, although the corresponding 4-isomers, being readily accessible by direct acylation, have been more fully described. In the course of a series of experiments on the reaction between ferric chloride and phenols, Huber and Brunner (8) found that anhydrous ferric chloride converted phenyl isobutyrate into a mixture of 2- and 4-hydroxy-isobutyrophenone. No yield was quoted for the 2-isomer, which was identified as the oxime, and the 4-isomer was obtained in 16% yield but no derivatives were prepared; the latter was oxidized to 4-hydroxybenzoic acid thus determining the orientation. The work of these authors appears to be the only reference to 2-hydroxy-isobutyrophenone. The results described in the present paper show that when phenyl isobutyrate is reacted with anhydrous aluminum chloride at 140–150°C. for one hour 2-hydroxy-isobutyrophenone is formed in 40% yield and the 4-isomer in 11% yield. These results and the constants of the two isomers agree well with those quoted by Huber and Brunner (8). We have also found that when phenyl isobutyrate is reacted with aluminum chloride in nitrobenzene solution at room temperature 4-hydroxy-isobutyrophenone is formed in 86% yield (1). Both isomers on reduction by Clemmensen's method give the corresponding isobutylphenol, identical with authentic specimens prepared by an alternative route (6).

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The only reference to 2-methoxy-isobutyrophenone is in a paper by Vavon and Décombe (13) in which they report the preparation of this compound by reaction of the Grignard reagent of 2-bromoanisole with isobutyryl chloride. They describe the compound as a solid melting at 96–98°C. but were unable to form an oxime. We have prepared 2-methoxy-isobutyrophenone by two methods. In one case the hydroxy ketone obtained from the Fries rearrangement of phenyl isobutyrate was methylated with dimethyl sulphate and in the other case anisole was acylated directly with isobutyryl chloride. The 2-methoxy-isobutyrophenone, prepared by either route, has so far remained as an oil, but readily formed a crystalline 2,4-dinitrophenylhydrazone and a crystalline oxime. Portions of the 2- and 4-methoxy-isobutyrophenones were oxidized with alkaline permanganate to 2-methoxybenzoic and anisic acids, thus confirming the orientation of the substituents. In view of recent work (7) on the anomalous reactivity of 2-methoxyphenylmagnesium halides there must be some doubt whether the compound isolated by Vavon and Décombe was 2-methoxy-isobutyrophenone, owing to the lack of supporting evidence.

EXPERIMENTAL*

Phenyl Isobutyrate

Isobutyryl chloride (106 gm., 1.0 mole), prepared from redistilled thionyl chloride and isobutyric acid in 95% yield by a standard procedure (9), was gradually added at room temperature to phenol (104 gm., 1.1 moles) when hydrogen chloride was vigorously evolved. The crude ester, obtained by distillation, was cooled to 0°C., repeatedly washed with ice-cold potassium hydroxide solution (1 *N*), and dried over solid potassium hydroxide, the flask being constantly immersed in an ice bath. Fractionation gave phenyl isobutyrate (161 gm., 81%) as a clear liquid boiling at 211°C. and having n^{25}, 1.4919. Literature (2), 112°C. (25.5 mm.).

High Temperature Fries Rearrangement of Phenyl Isobutyrate

Anhydrous aluminum chloride (21.5 gm., 0.16 mole) was placed in a 500 ml. flask and heated to 70°C. Phenyl isobutyrate (20 gm., 0.10 mole) was added in small portions over a period of 10 to 15 min. with stirring. A vigorous evolution of hydrogen chloride occurred and the temperature rose to about 100°C. When the addition of ester was complete the temperature was rapidly raised to 140–150°C. and maintained between these limits for one hour. The reaction mixture was cooled to room temperature and the glassy solid decomposed by the addition of hydrochloric acid (100 ml., 6 *N*). After the solution was heated for five minutes on the steam cone in order to complete the hydrolysis, the viscous red oil was separated and washed with warm hydrochloric acid (30 ml., 6 *N*) and two portions of warm water. Distillation of the oil *in vacuo* yielded two fractions which were separately redistilled.

Fraction 1, identified as 2-hydroxy-isobutyrophenone, distilled as a clear liquid (8.0 gm., 40%) boiling at 68°C. (0.4 mm.) and having n^{25}, 1.5367. Literature (8) 110°C. (10 mm.). *2,4-Dinitrophenylhydrazone*, m.p. 186°C.

**All melting and boiling points are uncorrected.*

(decomp.). Anal. calc. for $C_{16}H_{16}O_5N_4$: N, 16.2%. Found: N, 16.3%. *Semicarbazone*, m.p. 178°C. Anal. calc. for $C_{11}H_{15}O_2N_3$: N, 19.0%. Found: N, 19.1%. *Oxime*, m.p. 126°C.; literature (8), m.p. 129°C. Anal. calc. for $C_{10}H_{13}O_2N$: N, 7.8%. Found: N, 7.9%.

Fraction 2, identified as 4-hydroxy-isobutyrophenone, distilled as an oil (2.2 gm., 11%) boiling at 128°C. (0.1 mm.). On standing the oil solidified and recrystallization from ether – petroleum ether gave the pure compound m.p. 54°C. Literature (8), m.p. 56°C. *2,4-Dinitrophenylhydrazone*, m.p. 166°C. (decomp.). Anal. calc. for $C_{16}H_{16}O_5N_4$: N, 16.2%. Found: N, 16.2%. *Semicarbazone*, m.p. 199°C. Anal. calc. for $C_{11}H_{15}O_2N_3$: N, 19.0%. Found: N, 19.1%. *Oxime*, m.p. 159°C. Anal. calc. for $C_{10}H_{13}O_2N$: N, 7.8%. Found: N, 7.7%.

Low Temperature Fries Rearrangement of Phenyl Isobutyrate

Phenyl isobutyrate (11 gm., 0.07 mole) was added in small portions at room temperature to a solution of anhydrous aluminum chloride (11 gm., 0.09 mole) in nitrobenzene (50 ml.). The reaction was allowed to proceed at 25°C. for 40 hr. and then the solution was poured on to ice and hydrochloric acid. When hydrolysis was complete the mixture was extracted with ether and the ethereal solution extracted with potassium hydroxide solution (1 *N*). The alkaline solution was acidified and re-extracted with ether. Removal of the solvent and distillation *in vacuo* yielded 4-hydroxy-isobutyrophenone (9.5 gm., 86%) boiling at 133°C. (0.5 mm.) and m.p. 54°C. on recrystallization from ether – petroleum ether (1).

The following crystalline derivatives were found not to depress the melting point of the same derivatives obtained from fraction 2 obtained in the high temperature rearrangement: 2,4-dinitrophenylhydrazone, m.p. 166°C. (decomp.); oxime, m.p. 159°C.; semicarbazone, m.p. 199°C.

Acylation of Phenol with Isobutyryl Chloride

Anhydrous aluminum chloride (13.3 gm., 0.1 mole) and a solution of phenol (4.7 gm., 0.05 mole) in nitrobenzene (50 ml.) were placed in a flask fitted with a mechanical stirrer and a reflux condenser. Isobutyryl chloride (5.3 gm., 0.05 mole) was gradually added with vigorous stirring and the solution heated on the steam cone for one half-hour with continuous stirring. The cooled solution was poured on to cracked ice and hydrochloric acid. Distillation of the resulting oil yielded two fractions which were separately redistilled.

Fraction 1 was identified as 2-hydroxy-isobutyrophenone (0.5 gm., 7%) which distilled as an oil boiling at 67°C. (0.7 mm.) and having n^{25}, 1.5355. 2,4-Dinitrophenylhydrazone m.p. 186°C. (decomp.).

Fraction 2 was identified as 4-hydroxy-isobutyrophenone (6 gm., 73%), which distilled at 135°C. (0.7 mm.) and on recrystallization melted at 54°C. 2,4-Dinitrophenylhydrazone m.p. 166°C. (decomp.).

2- and 4-Methoxy-isobutyrophenone

Dimethyl sulphate (3.2 gm.) was added to a solution of 2-hydroxy-isobutyrophenone (2.5 gm.) in water (50 ml.) containing potassium hydroxide (1.2 gm.). The solution was warmed to 50°C. and stirred for six hours. The oil which separated was extracted with ether and the ethereal solution was washed with aqueous alkali and with water. Removal of the ether and distillation yielded *2-methoxy-isobutyrophenone* (2.2 gm., 90%) boiling at 71°C. (0.3 mm.) and n^{25}, 1.5229. The oil showed no tendency to crystallize. Literature (13), m.p. 97–98°C. *2,4-Dinitrophenylhydrazone*, m.p. 136°C. Anal. calc. for $C_{17}H_{18}O_5N_4$: N, 15.6%. Found: N, 15.7%. *Oxime*, m.p. 105°C. Anal. calc. for $C_{11}H_{15}O_2N$: N, 7.2%. Found: N, 7.2%.

4-Methoxy-isobutyrophenone, prepared in a similar way, was obtained in 90% yield as an oil, b.p. 89°C. (0.3 mm.) and n^{25}, 1.5340. Literature, b.p. 82.7°C. (0.01 mm.) (11), n^{20}, 1.5363 (12). 2,4-*Dinitrophenylhydrazone*, m.p. 117°C. Anal. calc. for $C_{17}H_{18}O_5N_4$: N, 15.6%. Found: N, 15.6%. Semicarbazone, m.p. 181°C. Literature (11), m.p. 183–184°C. Anal. calc. for $C_{12}H_{17}O_2N_3$: N, 17.9%. Found: N, 17.9%. *Oxime*, m.p. 86°C. Literature (12) quotes the oxime as an oil. Anal. calc. for $C_{11}H_{15}O_2N$: N, 7.2%. Found: N, 7.2%.

Preparation of 2-Methoxybenzoic Acid and Anisic Acid

2-Methoxy-isobutyrophenone (2.0 gm., 0.01 mole) was added to a solution of anhydrous sodium carbonate (1.5 gm., 0.014 mole) and potassium permanganate (3.2 gm., 0.02 mole) in water (60 ml.) and the solution refluxed until oily drops were no longer observed in the condenser (about four hours). The cooled solution was filtered from precipitated manganese dioxide, the filtrate acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with water, dried with magnesium sulphate, and evaporated. The resulting solid, recrystallized from carbon tetrachloride, had m.p. 100°C. alone or when mixed with an authentic sample of 2-methoxybenzoic acid.

4-Methoxy-isobutyrophenone was oxidized in a similar manner and the acid obtained, recrystallized from water, had m.p. 184°C. alone or when mixed with an authentic sample of anisic acid.

Acylation of Anisole with Isobutyryl Chloride

Isobutyryl chloride (20 gm., 0.18 mole) was added with stirring over one half-hour to a mixture of anhydrous aluminum chloride (33 gm., 0.25 mole) and anisole (21 gm., 0.18 mole) in carbon disulphide (200 ml.). The solution was refluxed for one hour with stirring. The cooled reaction mixture was poured onto ice and hydrochloric acid and the aqueous layer extracted with ether. The oil resulting from the evaporation of the combined solvent extractions yielded two fractions on distillation and each was separately redistilled.

Fraction 1 gave 2-methoxy-isobutyrophenone (1 gm., 3%) as a liquid boiling at 75°C. (0.3 mm.) and having n^{25}, 1.5229. 2,4-Dinitrophenylhydrazone, m.p. 135°C.

Fraction 2 gave 4-methoxy-isobutyrophenone (19 gm., 60%) as a liquid boiling at 89°C. (0.3 mm.) and having n^{25}, 1.5341. 2,4-Dinitrophenylhydrazone, m.p. 115°C.

2-Isobutylphenol

2-Hydroxy-isobutyrophenone (2 gm.) was refluxed with a mixture of zinc amalgam (5 gm.), concentrated hydrochloric acid (8 ml.), and glacial acetic acid (8 ml.) until a negative test was obtained with 2,4-dinitrophenylhydrazine (about seven hours). 2-Isobutylphenol was obtained in 55% yield as an oil boiling at 62°C. (0.7 mm.). 3,5-Dinitrobenzoate m.p. and mixed m.p. 83°C. (6).

4-Isobutylphenol

4-Hydroxy-isobutyrophenone (2 gm.) was reduced as above and 4-isobutylphenol was obtained in 83% yield as an oil boiling at 82°C. (0.7 mm.). The oil solidified on standing and recrystallization gave the pure phenol m.p. and mixed m.p. 52°C. (1).

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