77. *The Fries Rearrangement. Part IV.* Study of the Reversibility of the Reaction.*

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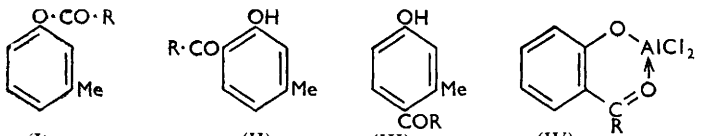
Contrary to the results obtained by Rosenmund and Schnurr [1] *p*-hydroxy-ketones do not undergo the reverse Fries reaction, to give the corresponding esters, when treated with (+)-camphorsulphonic acid or similar reagents. While most of the original ketone is recovered, some scission takes place to the phenolic and acyl components; the components can then react, to give the *o*-hydroxy-ketone and in certain cases even acylate the hydroxyl group in the initial *p*-hydroxy-ketone.

It is generally accepted that, in the Fries rearrangement of phenol esters (cf. I) to hydroxy-ketones, formation of the *ortho*-isomer (II) tends to be favoured at high temperatures and that of the *para*-isomer (III) at low temperatures. It has therefore been suggested [2] that *para*-substitution, which is considered to be the more rapid reaction, is a reversible process, and that the ester re-formed in this way can then isomerise to the *o*-hydroxy-ketone, which is more stable owing to chelation with the catalyst, as indicated in (IV). The evidence on which these conclusions are based is, however, somewhat conflicting, and it has been shown that *o*-hydroxy-ketones are often formed at low temperatures, examples being provided in the transposition of phenyl [3] and *p*-tolyl [4] acetate and of *m*-tolyl propionate [5] and benzoate.[6,7] Moreover, migration to the *para*-position has also been observed at high temperatures. *e.g.*, for phenyl acetate [3] and phenyl [7] and *o*-tolyl benzoate.[1,8]



(I) (II) (III) (IV)

The chief experimental evidence in support of the reversibility of the tries reaction is due to Rosenmund and Schnurr, who claimed that a number of *p*-hydroxy ketones, including those derived from *m*-tolyl acetate, benzoate, and phenylacetate, and from thymyl and carvacryl acetate, can be converted, often in quantitative yield, into the initial esters by heating them with camphorsulphonic or sulphuric acid or a similar reagent. More recently Miguel, Müller, and Buu-Hoï [9] stated that many aliphatic esters of *m*-cresol were obtained in moderate yields by boiling the corresponding *p*-hydroxy-ketones with hydrochloric or hydrobromic acid.

The mechanism proposed for the Fries transposition in the present series of papers is based on the irreversibility of the *para*-isomerisation under the conditions examined and the results presented here are in agreement with this view. A quantitative study of the action of camphorsulphonic acid on the hydroxy-ketones cited by Rosenmund and Schnurr, under similar experimental conditions, shows that while most of the initial material is recovered some is split into its phenolic and acyl components. When concentrated

* Part III, *J.*, 1957, 3016.

[1] Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56.
[2] Cf. Wheland, "Advanced Organic Chemistry," Wiley and Sons, New York, 1951, p. 565; Fieser and Fieser, "Organic Chemistry," Harrap and Co., Ltd., London, 1953, p. 676; Fuson, "Advanced Organic Chemistry," Wiley and Sons, New York, 1950, p. 346.
[3] Szekeres and Karsey, *Gazzetta*, 1947, **77**, 471.
[4] Cullinane and Edwards, *J.*, 1957, 3016.
[5] Baltzly and Bass, *J. Amer. Chem. Soc.*, 1933, **55**, 471; Coulthard, Marshall, and Pyman, *J.*, 1930, 280.
[6] Cox, *J. Amer. Chem. Soc.*, 1927, **49**, 1028.
[7] Unpublished results.
[8] Cox, *J. Amer. Chem. Soc.*, 1930, **52**, 352.
[9] Miguel, Müller, and Buu-Hoï, *Bull. Soc. chim. France*, 1956, 633.

sulphuric acid is substituted for the camphorsulphonic acid the decomposition is more extensive and nearly 60% of the cresol is obtained. Not more than a trace of the isomeric ester is formed in any of these reactions.

When the *p*-hydroxy-ketones were treated with hydrochloric acid, as in the method of Miguel *et al.*[9] (although they did not provide experimental details), the original ketone was almost entirely cleaved, to give the phenol: again we obtained none of the corresponding ester.

The acyl component resulting from scission of the *p*-hydroxy-ketone may be expected to attach itself to some extent to the *ortho*-position relative to the hydroxyl group by normal substitution, and we observed that small quantities of the *ortho*-isomer were obtained in some experiments. Moreover, acylation of the hydroxyl group should also be feasible and we found that small amounts of acylated *p*-hydroxy-ketones were sometimes formed.

According to Rosenmund and Schnurr the reversal does not take place if there is no alkyl group substituted in the *ortho*-position to the acyl substituent and our experiments with 4-hydroxy-3-methylacetophenone confirm this.

Experimental

Action of (+)-*Camphor*-10-*sulphonic Acid on* 4-*Hydroxy*-2-*methylacetophenone*.—The ketone was first obtained [10] by the action of acetyl chloride on *m*-cresol in contact with zinc chloride. We prepared it in 66% yield by heating *m*-tolyl acetate (0·1 mole, 15·0 g.) and anhydrous aluminium chloride (0·22 mole, 29·4 g.) in nitrobenzene (150 c.c.) for 24 hr. at 25°. The product was decomposed by ice and hydrochloric acid, the hydroxy-ketone extracted from the organic layer with 2N-sodium hydroxide, the extract acidified, and any of the *ortho*-isomer and *m*-cresol removed by distillation with steam, leaving the *p*-hydroxy-ketone [1,7,11] behind. This was filtered off and recrystallised from boiling water, as needles, m. p. 127°. The portion remaining in solution was converted into its 2 : 4-*dinitrophenylhydrazone*, which separated from aqueous alcohol in orange-red needles, m. p. 216° (Found: C, 54·5; H, 4·2; N, 17·0. $C_{15}H_{14}O_5N_4$ requires C, 54·5; H, 4·3; N, 17·0%).

(*a*) 4-Hydroxy-2-methylacetophenone (3 g.) and camphorsulphonic acid (0·006 g.) were heated at 150° for 30 min. under reflux, with exclusion of moisture. After being cooled, the mixture which had an odour of acetic acid, became solid. It was dissolved in ether and extracted with 2N-sodium hydroxide. Traces of ether were removed by warming and the solution was then cooled, acidified with concentrated hydrochloric acid, and distilled with steam. After the addition of a little hydrochloric acid a slight excess of 2 : 4-dinitrophenylhydrazine reagent (containing 4 g. per 100 c.c. of concentrated sulphuric acid) was introduced and the whole set aside for 12 hr. The precipitated 2 : 4-*dinitrophenylhydrazone* of the *o*-hydroxy-ketone was washed successively with dilute hydrochloric acid and water and dried to constant weight at 110°. Recrystallisation from ethyl acetate yielded red prisms, m. p. 244° (Found: C, 53·9; H, 4·2; N, 16·9%). The filtrate from the hydrazone was cooled in ice, and excess of bromine water (10 g. of bromine and 15 g. of potassium bromide per 100 c.c. of water) was added gradually. After 1 hr. in the cold the 2 : 4 : 6-tribromo-*m*-cresol, m. p. 84°, was collected, washed with water, and dried. The residue from the steam-distillation, which contained the *para*-isomer, was filtered while hot through glass wool, and the residue extracted with boiling water, leaving a trace only of insoluble material. The product separated from the filtrate on cooling and was dried to constant weight. The small amount in solution was analysed by conversion into its 2 : 4-dinitrophenylhydrazone.

The results obtained were: recovered 4-hydroxy-2-methylacetophenone 91; 2-hydroxy-4-methylacetophenone 2; *m*-cresol 5·5%. No *m*-tolyl acetate was formed. In a similar experiment Rosenmund and Schnurr claimed a quantitative yield of this ester.

(*b*) The above experiment was repeated except that 0·03 g. of camphorsulphonic acid was used, with the following results: recovered 4-hydroxy-2-methylacetophenone 89; 2-hydroxy-4-methylacetophenone 1; *m*-cresol 8%.

(*c*) When concentrated sulphuric acid (0·1 g.) was substituted for camphorsulphonic acid

[10] Eijkman, *Chem. Weekblad*, 1904, **1**, 453.
[11] Baltzly, Ide, and Phillips, *J. Amer. Chem. Soc.*, 1955, **77**, 2522.

and the mixture was heated for 30 min. at 180° a smell of acetic acid and considerable darkening were observed. The sole products obtained were: 4-hydroxy-2-methylacetophenone 37; 2-hydroxy-4-methylacetophenone 4; *m*-cresol 59%.

Action of (+)-*Camphor*-10-*sulphonic Acid on* 4-*Hydroxy*-2-*methylbenzophenone*.—(*a*) To anhydrous aluminium chloride (0·22 mole, 29·4 g.) in nitrobenzene (100 c.c.) at 0° *m*-tolyl benzoate (0·1 mole, 21·2 g.) in the same volume of nitrobenzene was added gradually, with stirring. The whole was heated at 60° for 13 hr., with stirring, then cooled in ice-water and treated with cold concentrated hydrochloric acid. The aqueous portion was extracted with ether, and the solution added to the nitrobenzene layer, which was next shaken with 10% sodium hydrogen carbonate solution (to dissolve the benzoic acid which was then precipitated by hydrochloric acid, dried, and weighed). Extraction of the organic layer with 2N-sodium hydroxide took up the *o*- and *p*-hydroxy-ketone and *m*-cresol, and acidification followed by steam-distillation removed the cresol and *o*-hydroxy-ketone which are volatile. The *o*-hydroxy-ketone separated on cooling, and was filtered off after being kept in the cold for 12 hr. Recrystallisation from alcohol and water gave pale yellow lustrous needles, m. p. 63°, as given by Baltzly *et al.*[11] The ketone remaining in solution was converted into the 2 : 4-*dinitrophenylhydrazone*, orange-red prisms (from ethyl acetate), m. p. 236° (Found: C, 60·6; H, 4·0; N, 14·2. $C_{20}H_{16}O_5N_4$ requires C, 61·2; H, 4·1; N, 14·3%). From the filtrate the *m*-cresol was precipitated in the usual way as the tribromo-derivative. The *p*-hydroxy-ketone,[11] which was present in the residue from the steam-distillation, was isolated by extraction with boiling water. It was deposited from aqueous alcohol in needles, m. p. 129°. The small amount in solution was converted into its 2 : 4-*dinitrophenylhydrazone*, red needles (from benzene), m. p. 224° (Found: C, 61·2; H, 4·0; N, 14·2%). From the organic layer, which contained any of the original *m*-tolyl benzoate and ketone esters, the ether was removed and the esters were hydrolysed for 8 hr. with boiling 6N-sodium hydroxide. When the nitrobenzene had been distilled with steam the residue was acidified and extracted with ether. Shaking with 10% sodium hydrogen carbonate solution took up the benzoic acid which was precipitated by hydrochloric acid. The ether solution, which now contained *m*-cresol (formed from the original ester) and the *o*- and *p*-hydroxy-ketone (formed from the ketone esters), was extracted with 2N-sodium hydroxide, and the products were analysed as described above.

Taking into account the small quantity of benzoic acid in solution, obtained by reference to solubility tables, we found: 4-hydroxy-2-methylbenzophenone 50·7; 2-hydroxy-4-methylbenzophenone 15·4; *m*-cresol 19·3; 4-benzoyl-3-methylphenyl benzoate 4·2; 2-benzoyl-5-methylphenyl benzoate 2·9; benzoic acid 25·0%; resin 0·3 g.

The benzoic acid formed was composed of that produced by the scission of the original *m*-tolyl benzoate (equivalent to the *m*-cresol), as well as that resulting from the hydrolysis of the other esters present in the products. The ketone esters were estimated by the analysis of their hydrolysis products only.

(*b*) Repetition of the experiment recorded by Rosenmund and Schnurr, in which *m*-tolyl benzoate (5 g.) and aluminium chloride (5 g.) were heated in nitrobenzene (30 g.) for 5 hr. at 60°, and in which they claimed as sole product (60%) the *p*-hydroxy-ketone, gave the following results: 4-hydroxy-2-methylbenzophenone 46·9; 2-hydroxy-4-methylbenzophenone, 9·2; *m*-cresol 25·4; 2-benzoyl-5-methylphenyl benzoate, 3·6; *m*-tolyl benzoate recovered 11·6; and benzoic acid 41%.

4-Hydroxy-2-methylbenzophenone (3 g.) and camphorsulphonic acid (0·03 g.) were heated at 150° for 30 min., then at 200° for 4 hr. N-Sodium hydroxide was added and dissolved all except a small quantity of solid. This was washed with more alkali and recrystallised from aqueous alcohol, giving colourless needles, m. p. 105°, of the benzoyl derivative [12] of the original hydroxy-ketone, identified by admixture with a specimen prepared from 4-hydroxy-2-methylbenzophenone. The alkaline filtrate was worked up in the usual way. The products were 4-hydroxy-2-methylbenzophenone (85·3%) and its benzoyl derivative (2·9%) together with *m*-cresol (5·7%) and a little resin (0·16 g.). No *m*-tolyl benzoate was formed, although this was the only product claimed by Rosenmund and Schnurr.

Action of (+)-*Camphor*-10-*sulphonic Acid on Benzyl* 4-*Hydroxy*-2-*methylphenyl Ketone*.—This compound was prepared by Blau [13] by treating a mixture of phenylacetic acid and *m*-cresol with zinc chloride. In our preparation powdered aluminium chloride (0·3 mole, 41 g.)

[12] Bartolotti, *Gazzetta*, 1900, **30**, 224.
[13] Blau, *Monatsh.*, 1905, **26**, 1149.

was added gradually to phenylacetyl chloride (0·13 mole, 20 g.) and *m*-cresol (0·13 mole, 14 g.) in nitrobenzene (100 c.c.), and the whole heated on a boiling-water bath for 30 min. The products, obtained by the usual method, consisted of the *p*-hydroxy-ketone (25·9%), needles (from aqueous alcohol), m. p. 142°, and *m*-cresol (9·2%), with some tar (6·3 g.).

The phenylacetyl-*m*-cresol (3 g.) was heated at 170° for 15 min. with camphorsulphonic acid (0·05 g.). The product had an odour of phenylacetic acid. When 0·5N-sodium hydroxide was added and the whole kept at 0° for 12 hr. a small amount of sticky solid remained undissolved; this was evidently mainly the phenylacetyl ketone ester since it gave the *p*-hydroxy-ketone (2·2%) on hydrolysis with alkali. The other products were the original ketone (87·3%) and *m*-cresol (4·1%). Unlike Rosenmund and Schnurr we obtained no *m*-tolyl phenylacetate.

Action of (+)-*Camphor*-10-*sulphonic Acid on* 4-*Hydroxy*-2-*methyl* 5-iso*propylacetophenone*.—The starting material was prepared by Rosenmund and Schnurr's method from thymol and acetyl chloride, in 97% yield, as needles (from aqueous alcohol), m. p. 125°. The 2 : 4-*dinitrophenylhydrazone* consisted of red needles (from alcohol), m. p. 189° (Found: C, 57·6; H, 5·4; N, 15·0. $C_{18}H_{20}O_5N_4$ requires C, 58·1; H, 5·4; N, 15·0%). No thymyl acetate was formed in the reaction.

The hydroxy-ketone (5 g.) was heated for 1 hr. at 180° with camphorsulphonic acid (0·05 g.). The mixture darkened somewhat and an odour of acetic acid was observed. The product, when cool, was treated with 0·5N-sodium hydroxide, a small quantity of sticky solid remaining undissolved; from this was obtained 1·6% of 4-*acetoxy*-2-*methyl*-5-iso*propylacetophenone*, needles (from aqueous alcohol), m. p. 49° (Found: C, 71·6; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). From the alkali-soluble portion thymol was isolated by taking advantage of its volatility in steam (the *p*-hydroxy-ketone was also slightly volatile; the amount in the steam-distillate was ascertained by precipitation as the 2 : 4-dinitrophenylhydrazone). In addition to the ketone ester there were obtained 75·1% of the initial ketone and 15·4% of thymol, but no thymyl acetate.

Action of (+)-*Camphor*-10-*sulphonic Acid on* 4-*Hydroxy*-5-*methyl*-2-iso*propylacetophenone*.—This compound was prepared by treating carvacrol (0·1 mole) and acetyl chloride (0·1 mole) in nitrobenzene (100 c.c.) with aluminium chloride (0·25 mole) at 25° for 24 hr. Of the products obtained the *p*-hydroxy-ketone (71%) was soluble in sodium hydroxide solution; the carvacryl acetate (16%) was hydrolysed, and the resulting carvacrol distilled with steam. The small quantity (2%) of acetoxy-ketone was estimated by hydrolysis. Although this ketone is slightly volatile in steam it is much less so than the carvacrol. Some tar (0·8 g.) was also produced. Recrystallisation of the main product from aqueous alcohol gave colourless needles, m. p. 101°. Rosenmund and Schnurr claimed a 90% yield of this substance and gave m. p. 120°, but John and Beetz [14] point out that the carvacrol used by the former authors was contaminated with thymol.

4-Hydroxy-5-methyl-2-*iso*propylacetophenone (3 g.) was heated with camphorsulphonic acid (0·03 g.) for 30 min. at 180°. Addition of 0·5N-sodium hydroxide to the cooled product left a small quantity of a sticky solid undissolved; this was mostly the ketone ester, for hydrolysis with 2N-sodium hydroxide yielded 4·9% of the hydroxy-ketone. The alkali-soluble portion contained the recovered ketone (69%) and carvacrol (21%).

Action of (+)-*Camphor*-10-*sulphonic Acid on* 4-*Hydroxy*-3-*methylacetophenone*.—The hydroxy-ketone 11, 15 (3 g.) was heated for 30 min. at 150° with camphorsulphonic acid (0·03 g.). The product dissolved completely in 2N-sodium hydroxide. The yield of recovered ketone was 90·8%, and a little resin (0·2 g.) was also formed. No *o*-hydroxy-ketone, *o*-cresol, or *o*-tolyl acetate was formed.

Action of Hydrochloric Acid on 4-*Hydroxy*-2-*methylacetophenone*.—The ketone (5 g.) was boiled under reflux for 14 hr. with concentrated hydrochloric acid (50 c.c.). The product had an odour of acetic acid. Excess of N-sodium hydroxide was introduced with cooling and the whole shaken with benzene; no *m*-tolyl acetate was present in this layer. Traces of benzene were removed by heat from the aqueous portion which was then cooled, acidified with concentrated hydrochloric acid, and distilled with steam. The distillate contained a small quantity (0·4%) of 2-hydroxy-4-methylacetophenone (analysed by conversion into its 2 : 4-dinitrophenylhydrazone) and *m*-cresol (90·7%). Only 0·7% of the original hydroxy-ketone was recovered; it was estimated in the same way as its isomeric ketone.

[14] John and Beetz, *J. prakt. Chem.*, 1935, **143**, 342.
[15] Cullinane, Evans, and Lloyd, *J.*, 1956, 2222.

Action of Concentrated Hydrochloric Acid on 4-Hydroxy-2-methylpropiophenone.—Propionyl chloride (0·3 mole, 27·8 g.), *m*-cresol (0·3 mole, 32·4 g.), aluminium chloride (0·66 mole, 88·0 g.), and nitrobenzene (300 c.c.) were stirred for 42 hr. at 15°. Working up in the usual way gave the *p*-hydroxy-ketone [5,9] (38·5%), m. p. 118°.

The above ketone (5 g.) was boiled under reflux for 14 hr. with concentrated hydrochloric acid (50 c.c.), and the products were extracted by a similar method to that described above. *m*-Cresol (94·9%) and the original ketone (2·1%) were the only compounds isolated. Miguel *et al.*[9], in a similar experiment, claimed a 39% yield of *m*-tolyl propionate.

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