770. *The Pfitzinger Reaction of* p-*Hydroxypropiophenone and Similar Phenolic Ketones.*

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The Pfitzinger reaction of isatin with *p*-hydroxypropiophenone proved to be abnormally slow compared with that of *p*-methoxypropiophenone. The same observation was made with similar *p*- and, to a smaller extent, with *o*-hydroxyketones.

It has frequently been pointed out that the Pfitzinger reaction (*J. pr. Chem.*, 1897, **56**, 283) with alkyl aryl ketones proceeds smoothly except when steric hindrance is involved (Buu-Hoï, *J.*, 1946, 795; Buu-Hoi and Cagniant, *Bull. Soc. chim.*, 1946, **13**, 123, 134; *Rec. Trav. chim.*, 1943, **62**, 519, 713; 1945, **64**, 214; Buu-Hoï and Royer, *Bull. Soc. chim.*, 1946, **13**, 374; 1950, **17**, 489; *Rec. Trav. chim.*, 1951, **70**, 825; Mueller and Stobaugh, *J. Amer. Chem. Soc.*, 1950, **72**, 1598; Buu-Hoi, Royer, Xuong, and Jacquignon, *J. Org. Chem.*, 1953, **18**, 1209). Sterically unhindered propiophenones and butyrophenones, in particular, give high yields of the corresponding cinchoninic acids, within 12—24 hours at 85—90°. It has now been found that whilst *p*-methoxypropiophenone under those conditions gives 2-*p*-methoxyphenyl-3-methylcinchoninic acid in excellent yield, acceptable yields are obtained from *p*-hydroxypropiophenone only after at least 15 days' heating. This remarkable inertia was also encountered when 5-bromo- and 5-chloro-isatin were used, and with *p*-hydroxybutyrophenone; 3-substituted *p*-hydroxypropiophenones such as the 3-chloro- and the 3-bromo-derivatives showed the same inertia to a somewhat smaller extent. These observations were not associated with any chemical alteration of the reagents, as the unchanged isatin and ketone could generally be recovered on acidification; nor could they be explained by the mere presence of a phenolic group, as *o*-hydroxy-acetophenone, -propiophenone, and -butyrophenone reacted with isatin far more rapidly than did the *p*-isomers. At present, no clear explanation can be offered; it should, however, be mentioned that more enolizable hydroxy-ketones such as *p*-phenylacetylphenol were more reactive, and that both 2-*p*-hydroxyphenyl-3-phenyl- and 6-

bromo-2-*p*-hydroxyphenyl-3-phenyl-cinchoninic acid were obtained in 90% yield after 10 days' heating.

2-*p*-Hydroxyphenyl-3-methylcinchoninic acid has proved a satisfactory substitute for atophan, with lower toxicity; it was best prepared in bulk by demethylation of 2-*p*-methoxyphenyl-3-methylcinchoninic acid with pyridine hydrochloride. All the new cinchoninic acids were readily decarboxylated to the corresponding quinolines.

Experimental

2-p-*Methoxyphenyl-3-methylcinchoninic Acid.*—A mixture of isatin (10 g.), *p*-methoxypropiophenone (10 g.), potassium hydroxide (10 g. in 60 c.c. of water), and ethanol (100 c.c.) was gently refluxed for 18 hr.; most of the ethanol was distilled off *in vacuo*, and the residue diluted with water and acidified with acetic acid. The precipitated *acid* (92%) crystallised as colourless prisms, m. p. 301—302°, from ethanol (Found: C, 73·7; H, 5·3. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1%).

2-p-*Hydroxyphenyl-3-methylcinchoninic Acid.*—(*a*) A mixture of 2-*p*-methoxyphenyl-3-methylcinchoninic acid (5 g.) and redistilled pyridine hydrochloride (50 g.) was gently refluxed for 45 min.; after cooling and addition of water, the precipitate was purified by digestion with boiling acetic acid or recrystallisation from nitrobenzene, giving yellowish prisms (80%) of an *acid*, which did not melt below 350° and gave colourless, water-soluble potassium and sodium salts (Found: C, 73·0; H, 4·6. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7%).

(*b*) A solution of isatin (9·6 g.), *p*-hydroxypropiophenone (10 g.), and potassium hydroxide (10 g.) in water (60 c.c.) was heated at 85—90° for 20 days; the precipitate (15·5 g.) obtained on dilution with water and acidification with acetic acid was purified as above. No sizeable amount of this cinchoninic acid could be isolated after 18 hr.' heating, and the yield obtained after 3 days was less than 25%; isatin and *p*-hydroxypropiophenone were recovered in almost quantitative yield.

Other *acids* prepared are reported in Table 1. They were purified by recrystallisation from glacial acetic acid, except the last two substances in the Table, which required aqueous acetic

Table 1. *Substituted cinchoninic acids.*

Substituents	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H	Yield, %	Duration of heating (days)
6-Bromo-2-*p*-hydroxyphenyl-3-methyl-	$C_{17}H_{12}O_3NBr$	56·7	3·5	57·0	3·4	80	15
6-Chloro-2-*p*-hydroxyphenyl-3-methyl-	$C_{17}H_{12}O_3NCl$	65·0	4·0	65·1	3·8	88	15
2-(3-Chloro-4-hydroxyphenyl)-3-methyl-	$C_{17}H_{12}O_3NCl$	65·0	3·8	65·1	3·8	92	11
2-(3-Bromo-4-hydroxyphenyl)-3-methyl-	$C_{17}H_{12}O_3NBr$	56·8	3·4	57·0	3·4	72	11
2-*p*-Hydroxyphenyl-3-phenyl-	$C_{22}H_{15}O_3N$	77·3	4·6	77·4	4·4	90	10
6-Bromo-2-*p*-hydroxyphenyl-3-phenyl-	$C_{22}H_{14}O_3NBr$	62·6	3·5	62·9	3·3	92	10
3-Ethyl-2-*p*-hydroxyphenyl- [a]	$C_{18}H_{15}O_3N$	73·4	5·0	73·7	5·1	73	15
2-*o*-Hydroxyphenyl-3-methyl-	$C_{17}H_{13}O_3N$	72·9	4·6	73·1	4·7	92	5
3-Ethyl-2-*o*-hydroxyphenyl- [b]	$C_{18}H_{15}O_3N$	73·5	5·2	73·7	5·1	83	5

[a] [b] The picrates of the corresponding quinolines had m. p. (*a*) 198; (*b*) 188°.

Table 2. *Substituted quinolines.*

Substituents	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
2-*p*-Methoxyphenyl-3-methyl-	83°	$C_{17}H_{15}ON$	81·6	6·2	81·9	6·0
2-*p*-Hydroxyphenyl-3-methyl-	234	$C_{16}H_{13}ON$	81·5	5·5	81·7	5·5
6-Bromo-2-*p*-hydroxyphenyl-3-methyl-	225	$C_{16}H_{12}ONBr$	61·3	4·0	61·1	3·8
6-Chloro-2-*p*-hydroxyphenyl-3-methyl- [a]	202	$C_{16}H_{12}ONCl$	71·0	4·5	71·2	4·5
2-(3-Chloro-4-hydroxyphenyl)-3-methyl- [b]	206	$C_{16}H_{12}ONCl$	71·0	4·5	71·2	4·5
2-(3-Bromo-4-hydroxyphenyl)-3-methyl- [c]	218	$C_{16}H_{12}ONBr$	61·2	3·6	61·1	3·8
6-Bromo-2-*p*-hydroxyphenyl-3-phenyl- [d]	237	$C_{21}H_{14}ONBr$	—	—	—	—
2-*o*-Hydroxyphenyl-3-methyl-	119	$C_{16}H_{13}ON$	81·7	5·8	81·7	5·5
2-*o*-Methoxyphenyl-3-methyl [e]	Liquid	$C_{17}H_{15}ON$	—	—	—	—

[a] Picrate, m. p. 198°. [b] Picrate, m. p. 213°. [c] Picrate, m. p. 223—224°. [d] Found: N, 3·4. Reqd.: N, 3·7%. [e] Found: N, 5·5. Reqd.: N, 5·6%. Prepared from the preceding compound by methyl sulphate, it gave a picrate forming yellow prisms, m. p. 188°, from ethanol.

acid; they formed colourless or yellowish prisms, which did not melt below 320°. The *quinolines* reported in Table 2 were obtained by heating the acids *in vacuo* above the m. p. and were recrystallised from ethanol.

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