[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF THE WITWATERSRAND]

The Reaction between β-Keto Esters and Arylamines in the Presence of Polyphosphoric Acid. I. Ethyl Benzoylacetate and Arylamines

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2-Phenyl-4-hydroxyquinolines may be obtained directly from ethyl benzoylacetate and arylamines using polyphosphoric acid. Under certain conditions a mixture of benzoylacetanilide and β-arylaminocinnamate (or anil) is obtained. It is also shown that while the β-arylaminocinnamates give the expected 4-hydroxyquinolines on cyclization when heated with polyphosphoric acid, the benzoylacetanilides tend to give mixtures of the isomeric 2-hydroxy- *and* 4-hydroxyquinolines.

As relatively small quantities of polyphosphoric acid (PPA) in the von Pechmann reaction were found to give satisfactory yields of hydroxycoumarins[1] it was decided to investigate the effect of this reagent in the synthesis of 2-hydroxy- and 4-hydroxyquinolines by the Conrad-Limpach[2] and Knorr[3] reactions from the respective acetanilides I and the β-arylaminocrotonates or cinnamates (anils) II obtained from the corresponding β-keto ester and arylamine.

The synthesis of 2-phenyl-4-hydroxyquinolines from ethyl benzoylacetate in this way has not been successful[4,5] because of the difficulty in obtaining the intermediate β-arylaminocinnamate or anil.

Although a direct synthesis of 2-alkyl- or 2-aryl-4-hydroxyquinolines from β-keto esters and arylamines has as yet not been reported, such a method for the synthesis of 2-phenyl-4-hydroxyquinolines has now been obtained by heating an excess of ethyl benzoylacetate and arylamine with polyphosphoric acid at 170°, the yields varying from 50 to 70%, traces of the isomeric 4-phenyl-2-hydroxyquinolines being formed.

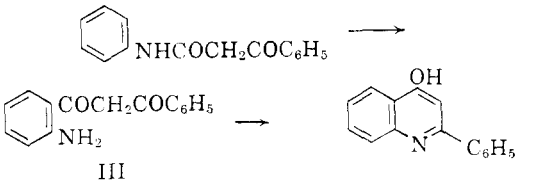
The ester and the amine on heating for one hour at 140° in the absence of polyphosphoric acid, gave the expected benzoylacetanilide as well as a small amount of the β-arylaminocinnamate. In the presence of polyphosphoric acid at the same temperature, the yield of β-arylaminocinnamate was increased to approximately 20% with a consequent decrease in the yield of benzoylacetanilide. This method of preparing the cinnamate is much more rapid than any other described in the literature.[6,7]

Very good yields of 2-phenyl-4-hydroxyquinolines and of 4-phenyl-2-hydroxyquinolines were obtained when the respective arylaminocinnamates and benzoylacetanilides were cyclized by heating the former with equal weights of polyphosphoric acid and the latter with ten times the weight of polyphosphoric acid.

In the case of some anilides, however, low yields of the phenylhydroxyquinoline were obtained due to the decomposition of the benzoylacetanilide by the polyphosphoric acid. A similar observation was noted by Stephenson[8] who used a very large excess of polyphosphoric acid.

When benzoylacetanilides were heated under similar conditions but using an equal weight of polyphosphoric acid, a small quantity of the 4-phenyl-2-hydroxyquinolone was obtained together with about a 20% yield of the isomeric 2-phenyl-4-hydroxyquinoline.

This would seem to be the first time that a mixture of the two isomeric hydroxyquinolines has been obtained in this reaction. The formation of the isomeric phenylhydroxyquinolines from a benzoylacetanilide may be explained on the assumption that the anilide undergoes a Fries type rearrangement under the influence of the polyphosphoric acid, into the *o*-amino-ω-benzoylacetophenone III which on dehydration would give the 4-hydroxyquinoline:



III

One of the interesting arylamines studied was *p*-nitroaniline. Attempts to prepare the corresponding β-arylaminocinnamate by previous investigators were unsuccessful and the preparation of 2-phenyl-6-nitro-4-hydroxyquinoline by the Conrad-Limpach method has not been reported. In some preliminary experiments carried out, it was shown that when *p*-nitroaniline and ethyl benzoylacetate were heated with polyphosphoric acid at 160° for twenty minutes 2-phenyl-6-nitro-4-hydroxyquinoline was isolated. Other nitroarylamines are being investigated.

(1) E. Barris and S. S. Israelstam, *J. S. Afr. Chem. I.*, **13**, 125 (1960).

(2) M. Conrad and L. Limpach, *Ber.*, **20**, 944 (1887).

(3) L. Knorr, *Ann.* **245**, 378 (1888); **236**, 83 (1886).

(4) S. A. Kulkarni, V. M. Thakor, and R. C. Shah: *J. Ind. Chem. Soc.*, **28**, 688 (1951).

(5) R. C. Elderfield, W. J. Gensler, T. H. Bembry, C. B. Cremer, D. J. Head, F. Brody, and R. Frohardt: *J. Am. Chem. Soc.*, **68**, 1272 (1946).

(6) C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948).

(7) R. V. Schock and H. J. Eichel, U. S. Pat. **2,785,165** (1957).

(8) E. F. M. Stephenson, *J. Chem. Soc.*, 2557 (1956).

The reaction of arylamines with other β-keto esters and with 1,3-diketones in the presence of polyphosphoric acid is also being studied, the results of which will be published later.

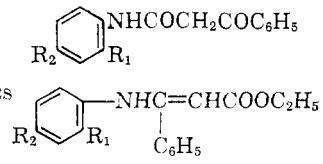
EXPERIMENTAL

Benzoylacetanilides and β-arylaminocinnamates. (a) *Heating without polyphosphoric acid.* A mixture of the arylamine (0.02 mole) and ethyl benzoylacetate (0.02 mole) was stirred and heated at 140–145° for 1 hr. during which period effervescence occurred. After cooling, the mixture was warmed with 10% sodium hydroxide and filtered. The alkaline filtrate on acidification with acetic acid yielded the benzoylacetanilide which was crystallized from dilute ethanol. The residue, a gummy-like material, after washing with water and triturating with 10% hydrochloric acid to remove unchanged amine, was dissolved in warm ethanol. On cooling, the crude β-arylaminocinnamate separated and was recrystallized from dilute ethanol (charcoal). All the benzoylacetanilides gave a purple coloration with alcoholic ferric chloride.

(b) *Heating with polyphosphoric acid.* A mixture of the arylamine (0.02 mole), ethyl benzoylacetate (0.02 mole) and polyphosphoric acid (1–2 g.) was stirred and heated at 140° for 1 hr. The product was treated as in (a).

The results are summarized in Table I.

TABLE I



I. BENZOYLACETANILIDES
II. β-ARYLAMINOCINNAMATES

Arylamine R_1	Arylamine R_2	Product	With PPA Yield, %	Without PPA Yield, %	M.P. Obs.	M.P. Lit.
H	H	I	19.1	63.0	107–108	107–108[6]
		II[a]	9.6	3.3	71–72	92–93[7]
CH_3	H	I	32.0	65.0	138–139	138–139[9]
		II	16.0	1.0	101–102	99–100[7]
H	CH_3	I	9.9	71.5	131–132	131–132[9]
		II	14.5	trace	69–70	71–72[7]
H	OCH_3	I[b]	11.3	75.5	121	127–128[9]
		II	12.1	1.0	113–114	111–113[7]
H	Cl	I	22.2	70.3	157–158	154–156[9]
		II	11.9	1.0	111–113	107–108[7]
CH_3	CH_3	I	11.65	34.6	156–157	157
		II[c]	25.0	9.0	87.5–88.5	
H	NO_2	I		38.0	175–180	179–180[9]

[a] Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.45; Found: C, 76.00; H, 6.52. [b] Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.6; Found: C, 71.24; H, 5.61. [c] Calcd. for $C_{19}H_{21}O_2N$: C, 77.25; H, 7.17; Found: C, 76.82; H, 7.15.

Cyclization of β-arylaminocinnamates to 2-phenyl-4-hydroxyquinolines with polyphosphoric acid. The arylaminocinnamate (0.5 g.) and polyphosphoric acid (0.5 g.) were stirred and heated at 170° for 15 min. and the solution, after effervescence had ceased, was treated with 10% sodium hydroxide to dissolve the 2-phenyl-4-hydroxyquinoline produced. The alkaline solution, after treatment with charcoal, when acidified with acetic acid deposited the almost pure quinoline in 80–90% yield. Using an excess of polyphosphoric acid—*e.g.*, 5.0 g.—did not produce a noticeably better yield. The pure compound was obtained by recrystallization from dilute ethanol. The isomeric 4-phenyl-2-hydroxyquinoline was not found in the reaction product.

The following quinolines were obtained by cyclizing the corresponding arylaminocinnamates: 2-phenyl-4-hydroxyquinoline (m.p. 254°; lit.[6] 253–254°); 2-phenyl-4-hydroxy-8-methylquinoline (m.p. 226–227°; lit. [10] 224–225°); 2-phenyl-4-hydroxy-6-methylquinoline (m.p. 296–297°; lit.[10] 294–295°); 2-phenyl-4-hydroxy-6-chloroquinoline (m.p. 351–352°; lit.[10] 350–351°).

Cyclization of benzoylacetanilides with polyphosphoric acid into (a) *4-phenyl-2-hydroxyquinolines.* A mixture of the anilide (0.5 g.) and polyphosphoric acid (5.0 g.) was stirred and heated at 140–150° for 15–20 min. The product was then treated with 10% sodium hydroxide to remove any alkali-soluble impurities and the residue of crude 4-phenyl-2-hydroxyquinolines crystallized from dilute ethanol.

The following quinolines were obtained by cyclizing the corresponding benzoylacetanilides: 4-phenyl-2-hydroxyquinoline (m.p. 257–258°; lit.[6] 253–256°); 4-phenyl-2-hydroxy-6-methylquinoline (m.p. 243–244°; lit.[11] 238°); 4-phenyl-2-hydroxy-8-methylquinoline (m.p. 221–222°; lit.[6] 216–217°); 4-phenyl-2-hydroxy-6,8-dimethylquinoline (m.p. 250–251°).

Anal. Calcd. for $C_{17}H_{15}ON$: C, 81.91; H, 6.07. Found: C, 82.60; H, 6.22.

Little, if any, 4-phenyl-2-hydroxyquinolines resulted from benzoylaceto-*p*-chloroanilide, benzoylaceto-*p*-anisidide, and benzoylaceto-*p*-nitroanilide, the anilides in these cases undergoing decomposition.

(b) *2-Phenyl-4-hydroxyquinolines.* A mixture of the pure anilide (0.5 g.) and polyphosphoric acid (1.0 g.) was heated and stirred for 20 min. at 140°. The resulting yellow viscous mass was warmed with 10% sodium hydroxide and the alkaline solution separated from a gummy residue which on suitable treatment yielded a small amount of the 4-phenyl-2-hydroxyquinoline. The alkaline solution on acidification with acetic acid precipitated the crude 2-phenyl-4-hydroxyquinoline in about 20% yield. The crude product was purified by redissolving in alkali, treating with charcoal and then acidifying. A mixed melting point of the recrystallized material (dilute ethanol) with an authentic specimen of the 2-phenyl-4-hydroxyquinoline showed no depression, but a distinct depression was obtained with the 4-phenyl-2-hydroxyquinoline.

The following quinolines were obtained when the corresponding benzoylacetanilides were treated in the above manner: 2-phenyl-4-hydroxyquinoline, 2-phenyl-4-hydroxy-8-methylquinoline, 2-phenyl-4-hydroxy-6-methylquinoline, 2-phenyl-4-hydroxy-6-chloroquinoline, 2-phenyl-4-hydroxy-6-methoxyquinoline (m.p. 306–307°; lit.[12] 308–310°), 2-phenyl-4-hydroxy-6,8-dimethylquinoline (m.p. 228°; lit.[12] 228–230°).

Heating 1.0 g. of benzoylacetanilide with only 0.2 g. of polyphosphoric acid did not result in any quinoline being formed. No effect was observed when either the 2-hydroxy- or 4-hydroxyquinolines were heated with polyphosphoric acid.

2-Phenyl-4-hydroxyquinolines from arylamines and β-keto esters with polyphosphoric acid. The mixture of arylamine (0.05 mole), β-keto ester (0.05 mole) and polyphosphoric

(9) G. H. Brown, J. Figueras, R. J. Geldhill, C. J. Kibler, S. M. McCrossen, S. M. Parmerter, P. W. Vittum, and A. Weissburger, *J. Am. Chem. Soc.*, **79**, 2919 (1957).

(10) B. P. Bangdiwala and C. M. Desai, *J. Ind. Chem. Soc.*, **31**, 43 (1954).

(11) E. Ritchie, *J. Proc. Roy. Soc., N.S. Wales*, **80**, 33 (1946).

(12) B. Staskun, *J. S. Afr. Chem. I.*, **9**, 89 (1956).

acid (20 g.) was stirred and heated at 140–150° for 1 hr. after which the viscous mass was treated with 20% hydrochloric acid to form the sparingly soluble hydrochloride of the quinoline which was then warmed with 10% sodium hydroxide, filtered from very small quantities of the 4-phenyl-2-hydroxyquinoline; the filtrate was treated with charcoal and then acidified with acetic acid. The 2-phenyl-4-hydroxyquinolines were deposited in 35–40% yields. However, by increasing the amount of ester to 0.1 mole the yields of the quinolines increased to 50–70%.

The following quinolines were obtained by this procedure: 2-phenyl-4-hydroxyquinoline, 2-phenyl-4-hydroxy-6-methylquinoline, 2-phenyl-4-hydroxy-8-methylquinoline, 2-phenyl-4-hydroxy-6-methoxyquinoline, 2-phenyl-4-hydroxy-6-chloroquinoline.

2-Phenyl-4-hydroxy-6-nitroquinoline. A mixture of *p*-nitroaniline (4.0 g.), ethyl benzoylacetate (6 g.), and polyphosphoric acid (10 g.) was stirred and heated at 160° for 20 min. The product was extracted with hot, dilute acetic acid (to remove unchanged amine), the residue warmed wth 10% sodium hydroxide, and the alkaline solution filtered off from a dark tarry product and acidified with acetic acid to yield 0.42 g. of a compound which, after purification by dissolvind in dilute sodium hydroxide, treatment with charcoal, ang reprecipitating with acetic acid, gave a pale-yellow amorphous powder, m.p. 328–330°.

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.76. Found: C, 67.96; H, 3.89.

On treatment with a mixture of phosphorus oxychloride and phosphorus pentachloride the hydroxyquinoline gave 2-phenyl-4-chloro-6-nitroquinoline, pale yellow needles, m.p. 168–169°.

Anal. Calcd. for $C_{15}H_9N_2O_2Cl$: 63.26; H, 3.16. Found: C, 63.48; H, 3.09.

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Pyrolysis of Esters. XIX. Synthesis of Racemic and Optically Active 3-Methyl-1-pentene[1-3]

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Racemic 3-methyl-1-pentene was synthesized in three steps from *sec*-butyl bromide in an over-all yield of 12%, with the pyrolysis of a butyrate as the final step. Optically active *d*-3-methyl-1-pentene, the simplest optically active olefin, with $[\alpha]_D^{25}$ +33.49°, was prepared in four steps in an over-all yield of 20% from active amyl alcohol, with the pyrolysis of the butyrate as the final step.

In an over-all program to determine the correlation between the chemical structure and physical properties of polymers, the effect of asymmetry in the side chain of an isotactic polyolefin has been of interest.[5] For this study racemic and optically active 3-methyl-1-pentene, the simplest optically active olefin, was desired. Although Schmitt and Boord[6] had previously prepared *d,l*-3-methyl-1-pentene in five steps from *sec*-butyl bromide and acetaldehyde in an over-all yield of 18%, it was thought that a three-step synthesis involving the pyrolysis of an ester would be more convenient. For this reason the Grignard reagent from racemic *sec*-butyl bromide was treated with ethylene oxide to give a 28% yield of *d,l*-3-methyl-*n*-amyl alcohol. When this alcohol was esterified with acetyl chloride and pyridine, an 80% yield of *d,l*-3-methyl-*n*-amyl acetate was obtained. However, vapor phase chromatography revealed that a very careful and tedious fractionation was required to remove the unchanged alcohol from the ester, since their boiling points are very close. For this reason the preparation of a higher boiling ester was found to be considerably more convenient. Thus, when the *d,l*-3-methyl-*n*-amyl alcohol was esterified with a mixture of butyric anhydride and sodium butyrate, a 78% yield of the corresponding butyrate was obtained in a relatively pure state by a simple distillation.

Pyrolyses of the esters were carried out under conditions that had been demonstrated not to cause rearrangement of double bonds in the preparation of isomers of aromatic hydrocarbons.[7] Thus, at 530° the *d,l*-3-methyl-*n*-amyl acetate gave a 72% yield of the racemic 3-methyl-1-pentene, while the corresponding *n*-butyrate gave a 54% yield. As this olefin was intended for use in polymerization, the emphasis throughout the synthesis was on purity of the product, which was conveniently followed with gas-phase chromatography. With the butyrate it was much easier to obtain a pure product.

(1) Previous paper in this series, *J. Am. Chem. Soc.*, **81**, 5397 (1959).

(2) Presented in part before the Division of Polymer Chemistry at the 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 1960.

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(4) Office of Naval Research Fellow, 1955–1957; Goodyear Tire and Rubber Fellow, 1957; and Dunlop Research Fellow, 1957–1958.

(5) W. J. Bailey and E. T. Yates, *J. Org. Chem.*, **25**, 1800 (1960).

(6) C. G. Schmitt and C. E. Boord, *J. Am. Chem. Soc.*, **54**, 751 (1932).

(7) W. J. Bailey and R. Barclay, Jr., *J. Am. Chem. Soc.*, **81**, 5393 (1959).