The Conversion of Benzoylacetanilides into 2- and 4-Hydroxyquinolines

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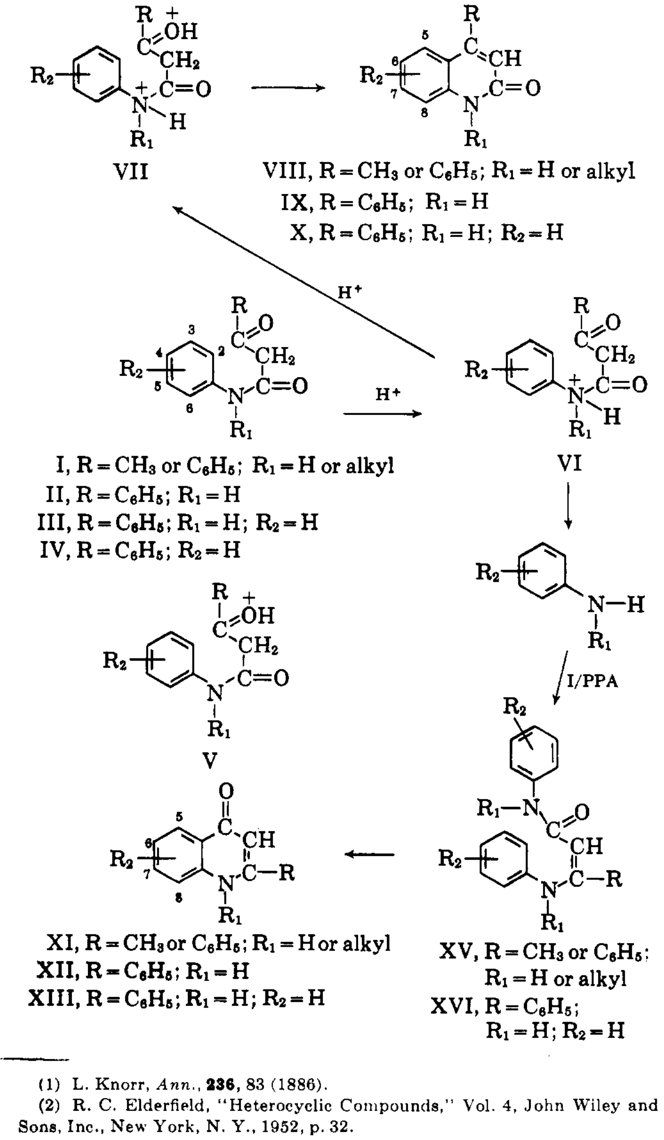
Relatively small proportions of polyphosphoric acid or anhydrous aluminum chloride convert benzoylacetanilides (II) to the corresponding 4-hydroxyquinolines (XII), while with excess of reagent the expected 2-hydroxyquinolines (IX) are furnished. A scheme to account for these results and for the action of acids on the anilide generally is discussed.

The cyclization of a substituted anilide (I) to the 2-hydroxyquinoline (VIII) is effected usually with concentrated sulfuric acid,[1-4] and it is believed generally that the product results from the ring closure of a monoprotonated entity such as V. This view of the mechanism now requires modification since it has been found that the reaction course may be altered by varying the acid–anilide ratio. A relatively small amount of acid merely hydrolyzes the anilide (I, R = C_6H_5) at 130–140° to the arylamine and acetophenone, and negligible 2-hydroxyquinoline results; utilization of a higher proportion of acid in the reaction, however, leads to the Knorr product in good yield.



It is now suggested that the anilide (I) on treatment with a limited amount of reagent is transformed to the monoprotonated form (VI), the amide function alone being affected.[5] On warming, VI is unable to cyclize, and undergoes fission at the susceptible amide link (*cf.* Duffy and Leisten[6]) producing arylamine and eventually also, acetophenone.[7] With a larger proportion of acid, the weakly basic carbonyl group in VI is likewise affected, furnishing a diprotonated anilide (VII). A subsequent electrophilic attack on the neighboring aromatic nucleus by the protonated carbonyl group in VII, the positive charge of which tends to hinder the competing ionization process at the amide bond, leads eventually to the 2-hydroxyquinoline (VIII).[8] The nature and position of the substituents in I will necessarily influence the electronic effects operating in VI and VII and consequently also the competing heterolytic and cyclization processes. It is reported,[3,9] for example, that the nitro- and chloroacetoacetanilides (I, R = CH_3; R_1 = H; R_2 = NO_2 or Cl) are appreciably decomposed to arylamine even in an excess of concentrated sulfuric acid. Moreover, cyclization to the quinoline proceeds more readily with acetoacetanilides (I, R = CH_3; R_1 = H) than with the corresponding benzoylacetanilides (II) under similar conditions (*cf.* Knorr[10]).

The acid strength of the reagent needs to be considered in the Knorr reaction: an excess of glacial acetic acid and even a mixture of concentrated sulfuric acid and glacial acetic acid were ineffective at 90° in transforming benzoylaceto-*o*-toluidide (II, R_2 = 2-CH_3) to the 2-hydroxyquinoline. The acetic acid and the acetic acidium ion[11] (in the latter solution) were incapable, presumably, unlike concentrated sulfuric acid or 74% sulfuric acid,[12] of protonating the carbonyl group in VI and forming VII.

It was recently reported[13] that, while an excess of

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[1] L. Knorr, *Ann.*, **236**, 83 (1886).

[2] R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 32.

[3] J. Joubert, M.S. thesis, Witwatersrand University, 1960.

[4] C. F. Koelsch and J. W. Britain, *J. Org. Chem.*, **24**, 1551 (1959).

[5] It is now generally agreed [A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961)] that amides are predominantly protonated at the oxygen atom. The fission process may possibly involve this form of the protonated amide; alternatively, the N-protonated form (VI) could arise from the former *via* a tautomeric change.

[6] J. A. Duffy and J. A. Leisten, *Nature*, **178**, 1242 (1956).

[7] Koelsch and Britain[4] isolated acetophenone from the reaction mixtures of N-alkylbenzoylacetanilides and concentrated sulfuric acid at 60–90°, and the ketone was assumed to arise during the subsequent working up procedures. It is possible, however, for the acetophenone to have been produced during the reaction proper.

[8] The conversion of anils into quinolines by means of concentrated sulfuric acid is believed to proceed by cyclization of the diprotonated anils [T. G. Bonner and M. Barnard, *J. Chem. Soc.*, 4181 (1958)].

[9] J. L. C. Marais and O. G. Backeberg, *ibid.*, 2207 (1950).

[10] L. Knorr, *Ann.*, **245**, 372 (1888).

[11] R. J. Gillespie and J. A. Leisten, *Quart. Rev.* (London), 40 (1954).

[12] A. L. Searles and R. J. Kelly, *J. Am. Chem. Soc.*, **77**, 6075 (1955).

[13] B. Staskun and S. S. Israelstam, *J. Org. Chem.*, **26**, 3191 (1961). In the Experimental section, the weight of anilide (II) taken for reaction with PPA (1 g.) at 140° for 20 min. to form 4-hydroxyquinoline (XII) was 1 g. and not 0.5 g. as reported.

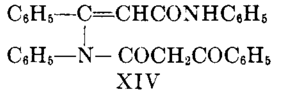
TABLE I

ACTION OF POLYPHOSPHORIC ACID ON BENZOYLACETANILIDES

Anilide^{a} (1 g.)	PPA, g.	Reaction time, min.	Temp., °C.	2-Hydroxy-quinoline, g.^{b}	4-Hydroxyquinoline, g.^{b}
III	0.5	20	140	Nil^{c}	0.16 (+0.2, recovered anilide)
	+0.5, sirupy phosphoric acid			Nil	0.09
	0.8			Nil^{c}	0.22–0.24
	1			Negligible^{c}	0.22–0.24
		30	145–150	Negligible^{c}	0.24
		40	110–120	Negligible^{c}	0.20 (+0.16, recovered anilide)
		12	180	Negligible^{c}	0.18
	+0.5, aniline	30	145–150	Negligible	0.1 g. (+0.2, recovered anilide)
	+0.5, ethyl benzoylacetate	20	140	Negligible^{c}	0.34–0.40
	+0.5, acetophenone				0.15
	+1, benzanilide^{d}				0.24
	+1, β-phenylpropionanilide^{d}				0.22
	1.5			*ca.* 0.2^{e}	0.15–0.18
	+1, ethyl benzoylacetate			Nil	0.34
	2	30	145–150	*ca.* 0.4^{e}	0.07
	+0.5, aniline			Negligible	0.42
	2.5			0.53	0.02
	4			0.63	Negligible
	+0.5, aniline			0.15	0.15
II, R_2 = 2-CH_3	1	30	145–150	Negligible	0.14^{f}
	+0.5, ethyl benzoylacetate				0.30
	+0.5, acetophenone				0.10
II, R_2 = 4-CH_3	1	30	145–150	Negligible	0.13^{g}
	+0.5, ethyl benzoylacetate				0.23
II, R_2 = 4-NO_2	1	20	140	Negligible	0.10–0.14^{h}
	+0.5, ethyl benzoylacetate				0.19

[a] Ref. 13. [b] Crude yields reported; the melting point of the product was taken and, after recrystallization from dilute ethanol, its identity was confirmed by melting point and mixture melting point with authentic sample.[13,22] [c] The alkali-insoluble material isolated from the reaction mixture consisted of substance B (see Experimental), m.p. 200–201°, and contained little if any 4-phenyl-2-hydroxyquinoline (X). [d] Recovered unchanged. [e] Contaminated with substance B, m.p. 200–201°. [f] XII, R_2 = 8-CH_3, m.p. 226–227°. [g] XII, R_2 = 6-CH_3, m.p. 296–297°. [h] XII, R_2 = 6-NO_2; pale yellow tiny needles from glacial acetic acid, m.p. 378–380° (copper block) (incorrectly reported[13] as 328–330°); soluble in dilute alkali to give an orange solution. The infrared spectrum was identical with that of the sample prepared from ethyl benzoylacetate, *p*-nitroaniline, and PPA.[13]

polyphosphoric acid (PPA) converts the anilide (II) to the expected 2-hydroxyquinoline (IX) in good yield, utilization of a smaller proportion of reagent furnishes the isomeric 4-hydroxyquinoline (XII). Further study has shown that the yield of 2-phenyl-4-hydroxyquinoline (XIII) from benzoylacetanilide (III) at 140° varies considerably with the PPA-anilide ratio. The optimum yield (~24%) was obtained when treating III with an equal weight of acid, while with both lesser and greater weights of the latter the production of XIII was decreased (Table I). An ω-(*p*-aminobenzoyl)acetophenone, which might have been expected as a by-product on the basis of a Fries-type rearrangement,[13] was not isolated.[14] Benzanilide (and β-phenylpropionanilide) had no significant effect on the optimum yield (Table I), thus making an entity such as XIV improbable as the precursor of XIII.[15] When mixed with ethyl benzoylacetate, however, III was transformed into XIII in increased (35–40%) yield; since acetophenone was without a similar effect, the improvement could not be attributed to the solvent action of the ester on the reactants. The anilide (III) on warming with an equal weight of sirupy phosphoric acid at 140° merely was hydrolyzed to aniline and acetophenone, while, with a larger quantity of acid, it was converted to the 2-hydroxyquinoline (X). Poor yields of XIII resulted when employing PPA diluted with sirupy phosphoric acid.



$$\begin{array}{l} C_6H_5\text{—}C{=}CHCONHC_6H_5 \\ \qquad\quad | \\ C_6H_5\text{—}N\text{—}COCH_2COC_6H_5 \end{array}$$

XIV

The results, collectively, make improbable a purely intramolecular reaction mechanism[13] and may be ac-

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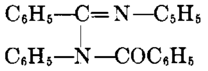
[14] A fair amount (about 10% yield) of an alkali- and acid-insoluble substance (B), m.p. 200-201°, was isolated (see Experimental).

[15] Benzanilide is not affected by PPA at 140°; at a higher temperature (180°), however, excess reagent converts it to 4-aminobenzophenone while utilization of an equal weight of reagent furnishes N,N′-diphenylbenzamidine as will be reported at a later date. Formation of the latter base most likely involves self-condensation of benzanilide to an intermediate of type



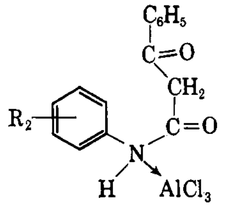
$$\begin{array}{l} C_6H_5\text{—}C{=}N\text{—}C_5H_5 \\ \qquad\quad | \\ C_6H_5\text{—}N\text{—}COC_6H_5 \end{array}$$

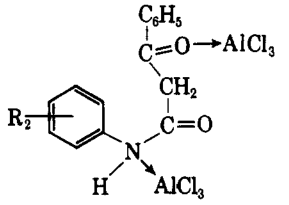
and the possibility of a similar self-condensation of III to XIV occurring, therefore, was considered and subsequently rejected.

counted for as follows. With an excess of PPA, the anilide (III) is extensively diprotonated, thus allowing for its appreciable conversion to the 2-hydroxyquinoline (X). A small proportion of acid, however, forms the monoprotonated VI solely and this hydrolyzes to aniline under the reaction conditions prevailing. The latter now condenses with unchanged III to give an acrylanilide (XVI)[16] which then cyclizes to the 4-hydroxyquinoline (XIII).[17] When ethyl benzoylacetate is also present, ethyl β-phenylaminocinnamate likewise results[13] and the over-all yield of XIII is consequently increased. Support for the view that XVI is in fact formed was obtained by rearranging III with PPA in the presence of aniline when the yield of XIII relative to X was enhanced (Table I). Increased proportions of PPA, however, brought about preferential cyclization of III to X. The observation that XIII is formed on warming N-ethylbenzoylacetanilide (IV, $R_1 = C_2H_5$) with aniline in the presence of PPA is explicable in terms of the suggested acrylanilide-type intermediate (XV).

Although not isolated from the reaction mixtures of III and PPA, β-phenylamino-β-phenylacrylanilide (XVI) was prepared by warming III with aniline in the presence of a small amount of PPA.[18] Its structure was confirmed by (i) acid hydrolysis to III, (ii) thermal cyclization in liquid paraffin to 2-phenyl-4-hydroxyquinoline (XIII), and (iii) conversion to 4-phenyl-2-hydroxyquinoline (X) with 74% sulfuric acid (involving preliminary *in situ* hydrolysis of XVI to III and subsequent ring closure of the latter). On warming with an equal weight of PPA, XVI was quantitatively converted to XIII, making feasible its proposed role of precursor.[19]

The critical effect of the anilide–reagent ratio on the course of the Knorr reaction was observed also when using a Lewis-type acid, *viz.*, anhydrous aluminum chloride. The behavior of I with this reagent previously has not been reported. Treatment of II with an equimolar proportion of aluminum chloride for 1 hr. at 200° brought about its conversion to 4-hydroxyquinoline (XII) in 20–46% yields; little if any of the isomeric 2-hydroxyquinoline (IX) was formed. Arylamine (detected as a sublimate of the hydrochloride) was produced during the reaction, and it is, therefore, possible for XII to have arisen *via* an acrylanilide intermediate (XV). An alternative Fries-type process,[13] nevertheless, also merits consideration and further work to help decide the issue is in progress. A preliminary step in the reaction sequence leading to XII (and arylamine) may well be heterolysis at the amide link in an initially formed anilide–aluminum chloride complex such as XVII.


XVII


XVIII

An increased molar proportion (3:1) of aluminum chloride, however, converted II solely to the 2-hydroxyquinoline (IX), in high yield. A doubly coordinated complex such as XVIII, analogous in structure and behavior to VII, may be involved in this instance.

In the absence of reagent, II was decomposed by dry hydrogen chloride at 200° furnishing arylamine, acetophenone, a trace (3%) of 4-hydroxyquinoline (XII), and negligible 2-hydroxyquinoline (IX). It may be supposed that the hydrogen chloride converts II to VI which then rapidly decomposes to arylamine under the conditions prevailing so that negligible VII is made available for cyclization to the Knorr quinoline. During the process some XV may arise and so account for the XII obtained. The effect on anilides (I) of various acidic reagents is being studied further.

Experimental[20]

The Action of Concentrated Sulfuric Acid on Anilides (I).—Benzoylacetanilide (III, 1 g.) was warmed with the acid (0.7 g., *d* 1.84, 98%) on the water bath (about 90°) for 1 hr. with occasional stirring, and the viscous solution was treated with water. The precipitated material was removed and separated into crude alkali-soluble anilide (0.68 g.) and alkali-insoluble 4-phenyl-2-hydroxyquinoline (X, 0.05 g., colorless crystals from dilute ethanol, m.p. and m.m.p. 256–257° with authentic sample[13]) by means of dilute sodium hydroxide. Benzoylacet-*o*-toluidide (II, $R_2 = CH_3$), acetoacet-*o*-toluidide (I, $R = CH_3$; $R_1 = H$; $R_2 = 2\text{-}CH_3$; 2 g.), and the alkali-insoluble N-methylbenzoylacetanilide (IV, $R_1 = CH_3$), when similarly treated and suitably worked up, likewise yielded unchanged anilide (0.75 g., *ca.* 0.5 g., 0.75 g., respectively) and negligible Knorr product. With an increased reaction time (4.5 hr.), the yield of X was improved (0.26 g.). A smaller weight of acid (0.5 g.) was even less effective as a catalyst.

Compound III (1 g.), on warming with the acid (0.7 g.) at 130–140° for 10–15 min., was decomposed rapidly. The green viscous mixture was treated with dilute sulfuric acid, and a small amount (0.16 g.) of insoluble X was removed. The ether-extracted filtrate when made alkaline furnished aniline while the ethereal layer on evaporation yielded crude acetophenone (characterized as its 2,4-dinitrophenylhydrazone, m.p. 237°). Acetoacet-*o*-toluidide (2 g.) and N-methylbenzoylacetanilide were likewise hydrolyzed to the respective amines and ketones at 130–140°, negligible Knorr quinoline being isolated in each case.

Utilization of increased acid (2 g.) in the reaction with III (1 g.) at ±90° for 1 hr. led to enhanced conversion to X (0.30 g.); some III (0.32 g.) was recovered. Substantially higher yields (60–70%) of Knorr product were obtained from acetoacet-*o*-toluidide (2 g.), benzoylacet-*o*-toluidide, and N-methylbenzoylacetanilide under similar conditions.[21a]

Reaction of III (1 g.) with acid (2 g.) at 130–140° for 10–15 min., followed by addition of water to the mixture, deposited X (0.37 g.) and negligible unchanged III. In like manner acetoacet-*o*-toluidide (2 g.) gave 4,8-dimethyl-2-hydroxyquinoline (1.1 g., colorless crystals from dilute ethanol, m.p. 228–229°, lit.[3]

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(16) The acrylanilide (XVI) has been proposed as an intermediate (not isolated) in the formation of the anil of benzoylmalonic acid dianilide from acetophenone anil and phenyl isocyanate [J. Moszew, A. Inasinski, K. Kubiczek, and J. Zawrzykraj, *Chem. Abstr.*, **55**, 15383 (1961)]; also ref. 19.

(17) It is possible also that XIII may result by cyclization of a β-phenylaminocinnamate formed from the aniline and an ester such as $C_6H_5COCH_2CO_2PO(OH)_2$ (furnished by PPA hydrolysis of III). It is suggested, however, that the predominating reaction of the latter ester would be a rapid preferential decomposition to acetophenone, and that XVI is the chief precursor.

(18) The preparation of XVI from aniline and methyl benzoylacetate has been reported by L. Knorr[10] who gives its melting point as 133°.

(19) J. Moszew (Abstracts of Congress Lectures and Scientific Papers presented at the XIXth Conference of the IUPAC, July, 1963, p. 38) has reported on the quinoline cyclization of anil-anilides of β-keto esters by H_2SO_4 and PPA which proceed according to the Conrad-Limpach scheme.

(20) Melting points are uncorrected and infrared spectra were measured on a Perkin-Elmer Infracord Model 137 spectrophotometer.

(21) (a) Treatment of benzoylaceto-*o*-toluidide (II, $R_2 = 2\text{-}CH_3$, 1 g.) with a relatively larger amount of acid (3 ml.) at 90° for 1 hr. gave the 2-hydroxyquinoline in poor yield (0.25 g.). It is supposed that some of the product remains in aqueous solution as the soluble sulfonated base (*cf.* J. Joubert[3]). (b) The British Drug Houses Ltd.

m.p. 217–218°), and N-methylbenzoylacetanilide yielded 1-methyl-4-phenyl-2-quinolone (VIII, R = C_6H_5; R_1 = CH_3; R_2 = H; 0.72 g.; colorless needles from dilute ethanol, m.p. 143–144°, lit.[4] m.p. 141–142°; no coloration with alcoholic ferric chloride; NH stretching absent, amide–CO stretching at 6.05 μ).

Action on Benzoylacet-*o*-toluidide of Concentrated Sulfuric Acid–Glacial Acetic Acid.—A solution of the anilide (II, R_2 = 2-CH_3; 1 g.) in glacial acetic acid (10 ml.) was warmed at about 90° for 1 hr.; treatment with water precipitated unchanged anilide (0.90 g.) and negligible Knorr product. Use of a mixture of glacial acetic acid (7 ml.) and concentrated sulfuric acid (3 ml.) as solvent in the reaction led to a trace of 4-phenyl-8-methyl-2-hydroxyquinoline (IX, R_2 = 8-CH_3; 0.02 g.; colorless crystals from dilute ethanol, m.p. and m.m.p. 220–221° with authentic specimen[13]) and unchanged anilide (0.86 g.).

Action on Benzoylacetanilide (III) of *o*-Phosphoric Acid Alone, and in the Presence of Phosphorus Pentoxide. A.—The anilide (1 g.) and sirupy H_3PO_4 (0.75 g., *d* 1.75, 88–93%) were reacted at 140–150° for 15 min.; the mixture was then made alkaline and extracted with ether; acidification of the aqueous layer with glacial acetic acid deposited unchanged III (0.12 g.), while the ethereal layer was found to contain aniline and acetophenone. On addition of ethyl benzoylacetate (0.5 g.) and P_2O_5 (0.8 g.) to the reaction mixture prior to the treatment with alkali and continuation of the heating at 140–150° for a further 25 min., there resulted 0.24 g. of crude (m.p. 220–230°) 2-phenyl-4-hydroxyquinoline (XIII, colorless needles from ethanol, m.p. and m.m.p. 254–255°).

B.—A mixture of acid (0.7 g.) and P_2O_5 (1.2 g.) was warmed at 140° for 10 min. and III (1.5 g.) then was added. Further heating at 140° for 20 min. produced 0.42 g. of crude XIII. In the absence of the pentoxide, warming of the acid (0.7 g.) and III (1.5 g.) at 140° for 30 min. led to hydrolysis to aniline and acetophenone, 0.3 g. anilide being recovered.

Relatively small amounts of H_3PO_4 at 140° similarly hydrolyzed benzoylacet-*p*-toluidide (II, R_2 = 4-CH_3) to *p*-toluidine and acetophenone. Use of 4 g. of acid with 0.4 g. of anilide at 140° for 20 min. furnished 4-phenyl-6-methyl-2-hydroxyquinoline (0.15 g., crude m.p. 240–243°) as well as *p*-toluidine and acetophenone.

Action of PPA on Benzoylacetanilide (III).—A mixture of the anilide (5 g.) and PPA (5 g., B.D.H.[21b] "tetraphosphoric acid," approx. 80% P_2O_5) was heated with manual stirring at 140–150° for 30 min.; the yellow viscous mass frothed considerably during the course of the reaction and the odor of acetophenone was detected. The orange product was warmed with 2 *N* sodium hydroxide and some brown, gummy alkali-insoluble material (A) was removed. Acidification of the alkaline filtrate (treated with charcoal) with glacial acetic acid deposited the crude 2-phenyl-4-hydroxyquinoline (XIII, 1.13 g.; 24%; m.p. 205–245°; negligible purple color with alcoholic $FeCl_3$; colorless woolly needles from dilute ethanol, m.p. and m.m.p. 254–255°; with authentic sample[13,22] infrared spectrum identical with that of 2-phenyl-4-hydroxyquinoline[13,22]).

The alkali-insoluble A was warmed with 95% ethanol and the sparingly-soluble product B (0.4–0.5 g.) was removed. The ethanolic filtrate on treatment with water deposited material from which was isolated a small amount (*ca.* 0.05 g.) of alkali-insoluble 4-phenyl-2-hydroxyquinoline (X). Substance B was recrystallized from glacial acetic acid containing traces of water and was obtained as colorless, tiny crystals, m.p. 200–201°, insoluble in dilute acid and alkali and in ether, sparingly soluble in hot 95% ethanol, soluble in hot methanol and in glacial acetic acid. The methanolic solution gave no coloration with $FeCl_3$. On heating with soda-lime, B furnished acetophenone. Hydrolysis with *ca.* 70% sulfuric acid yielded acetophenone and a nitrogen-free substance, m.p. 139–140°. The infrared spectrum of B differed from that of 4-phenyl-2-hydroxyquinoline and showed a NH stretching band at 3.2 and strong CO absorption at 6.0 μ. The possibility of B being a β-O-substituted cinnamanilide derivative is being considered.

The XIII obtained from equal weights of PPA and III was contaminated with negligible unchanged anilide (as indicated by the melting point range of the crude product and by the relative absence of a purple coloration with alcoholic ferric chloride). However, on employment of a smaller proportion of reagent (Table I), a mixture of quinoline and anilide resulted. The amount of the former component was determined by refluxing the weighed, crude, alkali-soluble product with dilute (1:1) sulfuric acid (which hydrolyzed III), and subsequently precipitating the unaffected XIII with ammonium hydroxide.

Reaction in the Presence of Ethyl Benzoylacetate (or Aniline).—The anilide (II), ester (or aniline), and PPA after warming (Table I) was treated with dilute sodium hydroxide, and the alkaline mixture either was extracted with ether (to remove acetophenone, etc.) or filtered. Acidification of the alkaline aqueous layer or filtrate deposited the 4-hydroxyquinoline (XII) contaminated with negligible anilide. During the course of the reaction, the ethyl benzoylacetate appeared to hydrolyze to acetophenone.

2-Phenyl-4-hydroxyquinoline from N-Ethylbenzoylacetanilide (IV, R_1 = C_2H_5), Aniline, and PPA.—After warming of the anilide (1.5 g.), aniline (0.5 g.), and PPA (1.5 g.) at 145–150° for 40 min., the mixture was made alkaline and was extracted with ether; the aqueous layer (charcoal) on acidification with glacial acetic acid precipitated the crude quinoline (XIII, 0.4 g.). Recrystallization from dilute ethanol yielded colorless needles, m.p. and m.m.p. (with 2-phenyl-4-hydroxyquinoline[13]) 254–255°. In the absence of aniline, the anilide underwent hydrolysis to N-ethylaniline and little if any 1-ethyl-2-phenyl-4-quinolone (XI, R = C_6H_5; R_1 = C_2H_5; R_2 = H) was formed.

β-Phenylamino-β-phenylacrylanilide (XVI).—Benzoylacetanilide (2 g.), aniline (0.9 g.), and PPA (1 g.) were stirred together at 140–150° for 15 min.; the yellow, viscous, semisolid mass was warmed (*ca.* 50°) with 2 *N* sodium hydroxide, and the alkali-insoluble material was removed (the filtrate on acidification with glacial acetic acid deposited some unchanged III) and triturated with cold 2 *N* hydrochloric acid (to remove aniline). the acid-insoluble residue was dissolved in warm, slightly alkaline 95% ethanol, and the filtered solution was treated with water and chilled when 0.7–0.8 g. of crude product separated; pale yellow needles from dilute ethanol had m.p. 117–118°, lit.[10] m.p. 133°.

Anal. Calcd. for $C_{21}H_{18}N_2O$: N, 8.92. Found: N, 9.07.

The substance was insoluble in dilute acid and alkali and gave no immediate coloration with alcoholic $FeCl_3$; a purple color developed gradually as hydrolysis to III occurred. The infrared spectrum showed NH stretching at 3.15 and amide-CO stretching at 6.2 μ.

Hydrolysis to Benzoylacetanilide.—The acrylanilide (XVI, 0.2 g.) was dissolved in dilute ethanol containing a few drops of concentrated hydrochloric acid and the solution was warmed (*ca.* 50°) for 10 min. Water was added and precipitated crude III, m.p. 105–108°; when recrystallized from dilute ethanol it had m.p. and m.m.p. 107–108° and gave an immediate purple coloration with $FeCl_3$.

Conversion to 2-Phenyl-4-hydroxyquinoline. A.—The acrylanilide (XVI, 0.15 g.) in *ca.* 6 ml. of medicinal liquid paraffin was heated at 240–250° for 15 min. Ether was added to the cooled viscous mass, and the crude quinoline (m.p. 245–255°) was removed. This was dissolved in 2 *N* sodium hydroxide, the solution was treated with charcoal, and the practically pure substance (m.p. and m.m.p. 254–255° with authentic sample[13]) precipitated with glacial acetic acid.

B.—PPA (0.4 g.) and acrylanilide (0.4 g.) were warmed together at 140–145° for 20 min. during which period only slight effervescence occurred (*cf.* with the anilides II which froth considerably). The mixture was treated with 2 *N* sodium hydroxide, negligible alkali-insoluble impurity was removed, the filtrate was treated with charcoal, and XIII (0.22 g., m.p. 240–255°) precipitated with glacial acetic acid. Recrystallization from dilute ethanol furnished colorless woolly needles, m.p. and m.m.p. 254–255°.

Conversion to 4-Phenyl-2-hydroxyquinoline.—XVI (0.2 g.) was warmed with *ca.* 3 ml. of 74% sulfuric acid (2 ml. of concentrated acid + 1 ml. of water) on the water bath (about 90°) for 80 min. Water was added and the precipitate was removed, washed, and dried. The product, which melted over a range and gave a purple coloration with $FeCl_3$, was separated into benzoylacetanilide (III) and alkali-insoluble X (m.p. 253–257°) by means of 2 *N* sodium hydroxide; colorless crystals formed from dilute ethanol with m.p. and m.m.p. (with authentic sample[13]) 256–257°. Benzoylacetanilide (0.2 g.) when similarly treated led also to a mixture of unchanged III and X.

Action on Benzoylacetanilides of Aluminum Chloride to Form (A) 4-Hydroxyquinolines.—The procedure is illustrated using benzoylacet-*p*-toluidide (II, R_2 = 4-CH_3). The anilide (2 g.,

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(22) B. Staskun, *J. S. African Chem. Inst.*, **9**, 89 (1956).

TABLE II

ACTION OF ANHYDROUS ALUMINUM CHLORIDE ON BENZOYLACETANILIDES AT 200° FOR 1 HR.

Anilide[a] (2 g.)	Aluminum chloride, g.	Mole reagent per mole anilide	% yield[b] 2-Hydroxyquinoline	% yield[b] 4-Hydroxyquinoline	Recovered anilide,[b] g.
III	1.1	1.0	Negligible	35[c]	Negligible
	2.4	2.2	30[d]	Negligible	0.3
	2.6	2.4	35	Negligible	0.15
II, R_2 = 2-CH_3	1.1	1.0	Negligible	25[e]	Negligible
	3.0	3.0	90[f]	Negligible	
II, R_2 = 4-CH_3	1.1	1.0	Negligible	46[g]	Negligible
	2.2	2.1	40[h]	Negligible	0.4
	3.3	3.2	91	Negligible	
II, R_2 = 2,4-diCH_3	1.0	1.0	Negligible	20[i]	Negligible
	3.1	3.0	90[j]	Negligible	
II, R_2 = 4-NO_2	1.0	1.1	Decomposition products		0.15
	3.0	3.2			
IV, R_1 = CH_3[k]	1.1	1.0	Negligible	Negligible	0.33
	3.4	3.3	67[l]	Negligible	

[a] Ref. 13. [b] See footnote *b* in Table I. [c] XIII, m.p. 254–255°. [d] X, m.p. 256–257°. [e] XII, R_2 = 8-CH_3, m.p. 226–227°. [f] IX R_2 = 8-CH_3, m.p. 220–221°. [g] XII, R_2 = 6-CH_3, m.p. 296–297°. [h] IX, R_2 = 6-CH_3, m.p. 243–244°. [i] XII, R_2 = 6,8-diCH_3, m.p. 228–229°. [j] IX, R_2 = 6,8-diCH_3, m.p. 250–251°. [k] M.p. 97–98°, lit.[4] m.p. 97–98°. [l] M.p. 143–144°, lit.[4] m.p. 141–142°.

0.008 mole) and powdered anhydrous aluminum chloride (1.1 g., 0.008 mole), after intimate mixing in a mortar (undue exposure to the atmosphere being avoided), was transferred to a 50-ml. round-bottomed flask fitted with an air condenser carrying a cotton-wool plug and then warmed at 160–180° for several minutes when preliminary fuming occurred. The mixture was then kept at about 200° for 1 hr. during which period hydrogen chloride was evolved and a small amount (0.05–0.1 g.) of *p*-toluidine hydrochloride (m.p. 230–238°) sublimed onto the walls of the flask. The dark red viscous product was dissolved in the minimum volume of hot 95% ethanol, the solution was treated with 2 *N* hydrochloric acid, the mixture was chilled, and the sparingly soluble quinoline hydrochloride was removed. (The yellow acid filtrate, when made alkaline, furnished a little *p*-toluidine.) The crude hydrochloride was warmed with 2 *N* sodium hydroxide, negligible alkali-insoluble material was removed, and the warm filtrate (charcoal) containing the somewhat sparingly soluble sodium salt of the 4-hydroxyquinoline was acidified with glacial acetic acid when the crude 2-phenyl-6-methyl-4-hydroxyquinoline (XII, R_2 = 6-CH_3) was deposited (0.87 g., 46%, m.p. 275–285°). Recrystallization from 50% acetic acid furnished colorless crystals, m.p. and m.m.p. (with authentic specimen[13,22]) 296–297°. The results using other anilides are collected in Table II.

(B) **2-Hydroxyquinolines.**—The procedure using benzoylacet-*p*-toluidide is typical. The anilide (2 g., 0.008 mole) and aluminum chloride (3.3 g., 0.025 mole) reacted at 200° for 1 hr. as above; hydrogen chloride was evolved readily, but little if any *p*-toluidine hydrochloride sublimated. The crude sparingly soluble quinoline hydrochloride was isolated as before and warmed with 2 *N* sodium hydroxide, and the insoluble 4-phenyl-6-methyl-2-hydroxyquinoline (IX, R_2 = 6-CH_3) was washed (with dilute acetic acid) and dried (1.6 g., m.p. 225–235°). The alkaline filtrate on acidification with glacial acetic acid deposited a small amount of crude carbostyril (IX, R_2 = 6-CH_3, 0.1 g., m.p. 175–210°); 2-phenyl-6-methyl-4-hydroxyquinoline was absent. The combined product (1.7 g., 91%), when recrystallized from dilute ethanol, gave colorless woolly needles, m.p. and m.m.p. (with authentic specimen[13]) 243–244°. Table II lists the details and results using other anilides.

Action of Hydrogen Chloride on Benzoylacet-*p*-toluidide (II, R_2 = 4-CH_3).—Dry hydrogen chloride was passed over 2 g. of recrystallized and dried anilide (contained in a 50-ml. roundbottomed flask and protected from atmospheric moisture) at 200° for 1 hr. A reaction occurred and a pale yellow oil and *p*-toluidine hydrochloride collected slowly on the upper portion of the flask during the passage of the gas. The dark red viscous residue was extracted with 2 *N* sodium hydroxide, and the alkali-insoluble material (0.5 g.; m.p. 170–190°; needles from dilute acetic acid, m.p. 230–235°; mixture melting point with IX, R_2 = 6-CH_3, was depressed; infrared spectra were dissimilar) was removed. The alkaline filtrate (charcoal) on acidification with glacial acetic acid deposited XII (R_2 = 6-CH_3, 0.06 g., m.p. 280–290°). Recrystallization from dilute ethanol gave colorless crystals, m.p. and m.m.p. 296–297° with authentic sample.[22] Benzoylacetanilide (III) and benzoylacet-*o*-toluidide (II, R_2 = 2-CH_3) likewise furnished traces (about 3%) of the respective 4-hydroxyquinolines and little if any of the 2-hydroxyquinolines.