effect and the delocalization effect of the 2-phenyl substituent are acting in the same direction. In the cation series, on the other hand, it is consistent with observation, that overlap of the 2-phenyl group with the imidazole or benzimidazole moiety results in the polar inductive and the resonance effect acting in opposite directions. In the cation, delocalization of the 2-phenyl group appears to favor an increase in the electron density at the point of dissociation accompanied by a stabilizing spreading out of the positive charge. It may also be that the polar inductive effect of the 2-phenyl group is not as effective in the cation series as in the neutral molecule series because the electrons associated with the nitrogen atoms are held more tightly in the cation than they are in the anion. This suggestion is related to the saturation effect.[10]

In both the neutral molecule and the cation dissociation equilibria the 4(or 5)-phenyl group parallels in direction the role of the 2-phenyl group. Variations in magnitude result in 2-phenylimidazole being a stronger acid and a stronger base (a weaker cationic acid) than 4(or 5)-phenylimidazole.

For 2,4(or 2,5)-diphenylimidazole small negative deviations from additivity of the phenyl groups are observed: 0.3 pK unit for the neutral molecule dissociation and 0.1 pK unit for the cation dissociation. For 4,5-diphenylimidazole, where the phenyl groups are on adjacent carbons and thereby restricted from assuming the coplanar conformation necessary for a maximum delocalization effect, we find larger negative deviations from additivity of the 4(or 5)-phenyl groups: 0.5 pK unit in the neutral molecule dissociation and 0.9 pK unit in the cation dissociation.

In the neutral molecule dissociation we expect the delocalization effect to be acid strengthening and therefore steric inhibition of resonance should decrease the effectiveness of the phenyl groups. The negative deviation from additivity is 0.2 pK unit greater in the 4,5-diphenylimidazole neutral molecule dissociation than in the corresponding sterically uninhibited 2,4(or 2,5)-diphenylimidazole dissociation. The difference is quite small but in the anticipated direction. In the cation dissociation we expect the delocalization effect to be acid weakening and, therefore, steric inhibition of resonance should increase the effectiveness of the phenyl groups. However, since we find that the negative deviation from additivity is greater by 0.8 pK unit in the 4,5-diphenylimidazole than in the sterically uninhibited 2,4(or 2,5)-diphenylimidazole cation dissociation, acid strengthening steric inhibition of resonance is not evidenced. A possible explanation for the masking of the steric inhibition of resonance is that the main tautomer of 4(or 5)-phenylimidazole is 4-phenylimidazole. Were this the case, the second phenyl entering the 5 position would be expected by its polar inductive effect to be more acid strengthening than the first phenyl in the neutral molecule dissociation and less acid strengthening in the cation dissociation. Thus in the neutral molecule dissociation of 4,5-diphenylimidazole the greater polar inductive effect of the second phenyl would counteract the expected acid weakening steric inhibition of resonance and in the cation dissociation the lesser polar inductive effect of the second phenyl would counteract the anticipated but not manifested acid strengthening steric inhibition of resonance.

Acknowledgment. We wish to acknowledge the support of the National Science Foundation and the Research Corporation. We are indebted to Michael Barfield for determining the effect of ionic strength on the hydrolysis constant of 2,4(or 2,5)-diphenylimidazole.

SAN DIEGO, CALIF.

(10) G. E. K. Branch and M. Calvin, *The Theory of Organic Chemistry*, Prentice-Hall, New York, 1941, pp. 205, 218.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF WITWATERSRAND]

A New Synthesis of 2-Aryl-3-acetyl-4-hydroxyquinolines Using Polyphosphoric Acid

B. STASKUN

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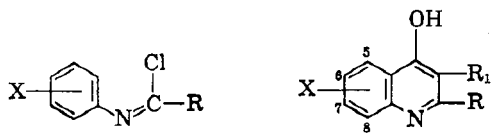
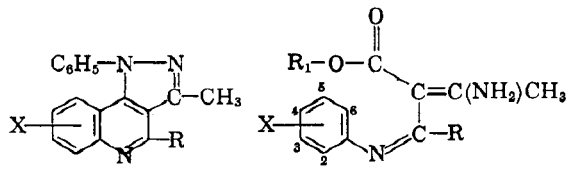
β-Amino-α-(*N*-arylimidoyl) crotonates are converted into 2-aryl-3-acetyl-4-hydroxyquinolines on treatment with polyphosphoric acid at 170°. The infrared spectra of the compounds and other evidence is presented in support of their formulation.

A general and unambiguous synthesis of the 2-aryl-3-acetyl-4-hydroxyquinolines (II) has until now not been available and these substances are relatively unknown and inaccessible. The preparative methods of Shah *et al.*, which involve the condensation of imidoyl chlorides (I) with ethyl sodioacetoacetate[1,2] and of arylamines with ethyl benzoylacetoacetate[3] respectively, have been found[4,5] not

always to yield the desired product since either of the isomeric quinolines (II or III) or a mixture of the two may result. The work of Singh and Nair[4] further suggests that several of the compounds originally formulated as 2-aryl-3-acetyl-4-hydroxyquinolines (II) by Shah, *et al.*[1,2] may well have been the isomeric bases (III).

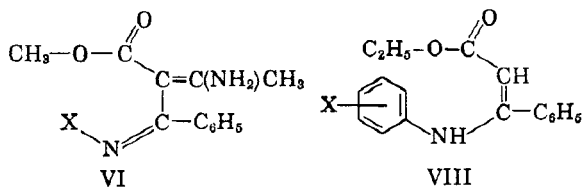


I. R = aryl
II. R_1 = $COCH_3$; R = aryl
III. R_1 = aroyl; R = CH_3
IV. R_1 = H; R = aryl
VII. R_1 = $C(:NH)CH_3$; R = aryl
X. R_1 = $C(:NNHC_6H_5)CH_3$; R = aryl
XI. R_1 = $C(:NOH)CH_3$; R = C_6H_5; X = H



IX. R = aryl

V. R_1 = CH_3, R = aryl
Va. R_1 = C_2H_5, R = aryl



VI

VIII

It has been previously reported[6] that methyl β-amino-α-(*N*-arylimidoyl) crotonate (V; prepared[7] by the action of an imidoyl chloride (I) on methyl β-aminocrotonate) eliminates methanol and acetonitrile when heated at 250° furnishing a 2-aryl-4-hydroxyquinoline (IV). Treatment at 170° with polyphosphoric acid is now found to convert the ester (V) into a 2-aryl-3-acetyl-4-hydroxyquinoline in 60–80% yield. An intermediate 3-acetimidoyl derivative (VII) is probably formed first which becomes hydrolyzed to the 3-acetylquinoline (II) during the subsequent treatment of the reaction mixture with water.

The bases thus obtained had correct analyses for 2-aryl-3-acetyl-4-hydroxyquinolines (II) and in support of this formulation was the following: (i) β-Arylaminocinnamates (VIII) when similarly treated[8] with polyphosphoric acid at 170° underwent cyclization to a 2-phenyl-4-hydroxyquinoline (IV.R = C_6H_5) demonstrating the feasibility of the synthesis of II from V. (ii) The same quinoline (II) resulted from the use of either the methyl (V) or ethyl (Va) crotonate in the reaction. (iii) In the case of methyl β-amino-α-(*N*-methylbenzimidoyl)-crotonate (VI. X = CH_3), which on account of the nature of the *N*-substituent is incapable of cyclizing to a 4-hydroxyquinoline derivative, the product of the reaction was notably benzoylacetone; a base similar to those formed from the other crotonates (V) was not obtained. The *N*-ethyl ester (VI. X = C_2H_5) behaved likewise.

The infrared spectra of the polyphosphoric acid-reaction products in the solid state (potassium bromide disc) were compared with those of some reference 2-aryl-4-hydroxyquinolines (IV) and found to accord with their representation as 2-aryl-3-acetyl-4-hydroxyquinolines (II). In both sets of substances hydroxyl absorption was absent and a strong band at 6.15–6.25 μ (which in several instances overlapped and merged with the neighboring aromatic C=C vibration near 6.25 μ) was due to the amide form of the 4-hydroxyquinoline absorbing in the carbonyl stretching region (*cf.* Mason[9]). In this respect the spectra of several reference 2-aryl-4-chloroquinolines were instructive as they revealed the C=N absorption at 6.20–6.25 μ to be weak.

In the NH-stretching region the spectra of compounds II and IV were similar in appearance with peaks at 3.1 μ and near 3.25 μ; the latter band was usually merged with that due to CH stretching near 3.3 μ.

The quinolines (II) in addition, all showed a strong acetyl-carbonyl absorption at 5.90–5.96 μ and in this respect 2-phenyl-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5; X = H) was unique in displaying two obvious peaks (at 5.90 μ and 5.96 μ). Absorption at 14.1 μ in the quinolines (II) as well as in the 4-hydroxyquinolines (IV) and 4-chloroquinolines was weak or absent (*cf.* Bellamy[10]) and in all these compounds the bands of benzene were relatively invarient near 6.25, 6.40, 6.75, and 7.0 μ with additional bands near 6.15–6.25 (amide-CO or C=N), 6.50, 6.65, and 6.90 μ (*cf.* Katritzky[11]).

Treatment of the bases (II) with excess phenylhydrazine in acetic acid solution yielded colorless crystalline derivatives which on account of the nitrogen analysis and their insolubility in alkali were formulated as pyrazoles (IX) rather than hydrazones (X). The infrared spectra of these derivatives revealed the absence of NH, acetyl-CO, and amide-CO stretching vibrations (in this respect being similar to the 2-aryl-4-chloroquinolines) lending support to the above formulation.

(1) Desai and Shah, *J. Ind. Chem. Soc*, **26**, 121 (1949)
(2) Kulkarni and Shah, *J. Ind. Chem. Soc.*, **27**, 111 (1950).
(3) Kulkarni, Thakor, and Shah, *J. Ind. Chem. Soc.*, **28**, 688 (1951).
(4) Singh and Nair, *J. Am. Chem. Soc.*, **78**, 6105 (1956).
(5) Bangdiwala and Desai, *J. Ind. Chem. Soc.*, **31**, 553 (1954).
(6) Staskun, *J. S. Afr. Chem. Inst.*, **9**, 89 (1956).
(7) Staskun and Stephen, *J. Chem. Soc.*, 4696 (1956).
(8) B. Staskun and Israelstam, in press.
(9) Mason, *J. Chem. Soc.*, 4874 (1957).
(10) Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen, 1954, p. 235.
(11) Katritzky, *Quart. Revs.*, **13**, 4 (1959).

TABLE I

INFRARED SPECTRA

3-Acetyl-4-hydroxyquinoline derivative	Band Wave Length (μ)		
	NH	CO	
		Acetyl	Amide
2-Phenyl	3.1(w)sh; 3.25(m)	5.90(s); 5.96(s)	6.15(s)
2-Phenyl-6-CH_3	3.1(w) ; 3.28(m)	5.91(s)	6.20(s)
2-Phenyl-6-OCH_3	3.1(m)sh; 3.25(s)	5.94(s)	6.25(s)
2-Phenyl-8-CH_3	3.1(w)sh; 3.25(m)b	5.93(s)	6.23(s)
2-Phenyl-6,8-diCH_3	3.1(w)sh; 3.3(m)b	5.92(s)	6.25(s)
2-*o*-Tolyl	3.1(m)sh; 3.25(m)	5.91(s)	6.20(s)
2-*p*-Tolyl	3.1(m)sh; 3.25(m)	5.91(s)	6.20(s)
2-Phenyl, oxime	3.1(s) ; 3.25(m)b	a	6.18(s)
2-Phenyl, pyrazole	a ;[3.3(w)]+	a	[6.25(w)]*
2-Phenyl-6,8-diCH_3, pyrazole	a ;[3.25(w)]+	a	[6.15(w)]*
2-*p*-Tolyl, pyrazole	a ;[3.25(w)]+	a	[6.20(w)]*
4-Hydroxyquinoline derivative			
2-Phenyl	3.1(m); 3.25(s)	a	6.12(s)
2-Phenyl-8-CH_3	3.1(m); 3.25(m)	a	6.17(s)
2-*p*-Tolyl	3.1(w); 3.3(m)	a	6.17(s)
4-Chloroquinoline derivative			
2-Phenyl	a; (3.3(w))+	a	[6.20(w)]*
2-Phenyl-8-CH_3	a; (3.3(w))+	a	[6.20(w)]*
2-*p*-Tolyl	a; (3.3(w))+	a	[6.25(w)]*
4-phenyl-2-hydroxyquinoline	3.0(w); 3.2(m)b	a	6.05(s)

a = Absent; sh = Shoulder; b = Broad; + = C H stretching; * = C=N stretching; s = Strong; w = Weak; m = Medium.

The alkali-soluble oxime of 2-phenyl-3-acetyl-4-hydroxyquinoline absorbed in the NH and amide–CO stretching regions and displayed no acetyl–CO peak and was accordingly formulated as XI.

Unlike the 2-aryl-4-hydroxyquinolines (IV) which readily furnish 4-chloro derivatives on reaction with phosphorus oxychloride,[6] the quinolines (II) when similarly treated were recovered unchanged and attempts to prepare the 2-phenyl-3-acetyl-4-chloroquinoline described by Singh and Nair (*loc. cit.*) were unsuccessful.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Infracord Model 137 Spectrophotometer; 0.8–1.0 mg. substance per 300 mg. of potassium bromide.

Preparation of 2-aryl-3-acetyl-4-hydroxyquinolines (II). *General procedure.* The crotonate (V)[6,7] (0.5–1 g.) was mixed with about ten times its weight of polyphosphoric acid and heated with stirring in an oil bath at 165–175° for 15 min. The clear orange solution (which no longer effervesced) was cooled somewhat (to *ca.* 60–70°) and treated with water when a portion of the quinoline (II) separated. Generally, the diluted mixture was made alkaline with sodium hydroxide, filtered from negligible impurity, and treated with charcoal. Acidification with acetic acid deposited the base (II) in practically pure form in 60–80% yield. A recrystallization from dilute ethanol sufficed to furnish the pure substance.

The colorless products were soluble in 10% sodium hydroxide to give colorless solutions (Shah, *et al.*[1,2] report their quinolines as giving yellow alkaline solutions) from which they could be recovered unchanged on addition of acetic acid. They were insoluble in ether and in dilute ammonia, sparingly soluble in cold, readily in hot dilute hydrochloric acid, and dissolved in glacial acetic acid. Treatment with 2,4-dinitrophenylhydrazine readily formed an orange-red crystalline derivative.

2-Phenyl-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = H). This was obtained as colorless feathery needles, m.p. 250–251° (lit; yellow needles,[1,3] m.p. 282–284°; 289°; colorless plates,[4] m.p. 246–248°) which gave a slight claret coloration with alcoholic ferric chloride. The same quinoline resulted when ethyl β-amino-α-(*N*-phenylbenzimidoyl)crotonate (Va.R = C_6H_5, X = H) replaced the methyl ester (V.R = C_6H_5, X = H) in the reaction.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.56; H, 4.94; N, 5.32. Found: C, 77.51; H, 4.85; N, 5.49%.

The oxime (XI) was obtained by dissolving the base and a slight excess of hydroxylamine sulfate in 50% ethanol, making the solution just alkaline with sodium hydroxide and refluxing for 30 min. On cooling tiny crystals, m.p. 270–274°, separated. Recrystallization from dilute ethanol furnished the colorless product, m.p. 282–284°, dec. (lit.[4] m.p. 285° dec.) soluble in dilute alkali and less soluble than the parent quinoline in ethanol.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: N, 10.07. Found: N, 9.71%.

Action of phenylhydrazine. The quinoline (II. R = C_6H_5, X = H; 0.1 g.) was dissolved in warm 50% acetic acid (5 c.c.) an excess of phenylhydrazine (0.2 c.c.) added and the solution refluxed for 30 min. The mixture was diluted with water and the derivative (IX. R = C_6H_5, X = H) (formed in good yield) filtered off. Colorless feathery crystals from dilute ethanol, m.p. 165–166°; they were insoluble in hot 10% sodium hydroxide.

Anal. Calcd. for $C_{23}H_{17}N_3$: N, 12.54. Found: N, 12.48%.

2-Phenyl-4-hydroxyquinoline when similarly treated was recovered unchanged.

The 2,4-dinitrophenylhydrazone (orange crystals) prepared in the usual manner had m.p. 296–298° dec. (lit,[4] m.p. 294° dec.).

Action of phosphorus oxychloride alone and together with phosphorus pentachloride. (i) The base (II. R = C_6H_5, X = H; 0.1 g.) and phosphorus oxychloride (1 c.c.) after heating on the water bath for 2 hr. was cooled and poured onto ice to

yield the unchanged compound (m.p. 240–250°) soluble in dilute alkali.

(ii) A mixture of the quinoline (0.2 g.), phosphorus oxychloride (4 c.c.), and phosphorus pentachloride (0.3 g.) was kept at 120° for 1.5 hr., cooled, and poured onto ice. After making ammoniacal, the tan-colored product was removed and triturated with dilute alkali when it all dissolved. Acidification of the alkaline solution with acetic acid gave unchanged material m.p. 215–248°; colorless needles from dilute ethanol, m.p. and m.m.p. 250–251°.

2-Phenyl-6-methyl-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = 6-CH_3) formed as colorless feathery crystals, m.p. 263–264° (lit.,[1,2] m.p. 255°; 263°).

Anal. Calcd. for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 5.17%.

2-Phenyl-8-methyl-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = 8-CH_3) formed colorless needles, m.p. 211–212° (lit.[1] m.p. 215°) which gave a claret coloration with alcoholic ferric chloride. The same base resulted on employment of ethyl β-amino-α-(*N*-*o*-tolylbenzimidoyl)crotonate (Va. R = C_6H_5, X = 2-CH_3) in the reaction.

Anal. Calcd. for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 5.15%.

The quinoline was recovered unchanged after warming with phosphorus oxychloride on the water bath for 1 hr.

The *pyrazole* was obtained as colorless silky needles, m.p. 140–141°, insoluble in hot 10% sodium hydroxide.

Anal. Calcd. for $C_{24}H_{19}N_3$: N, 12.03. Found: N, 12.13%.

2-Phenyl-6,8-dimethyl-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = 6,8-diCH_3). The methyl and ethyl crotonates (V and Va; R = C_6H_5, X = 2,4-diCH_3) both yielded the same quinoline as colorless crystals, m.p. 216–217°, which gave a claret coloration with ferric chloride. The base was recovered unchanged after heating with phosphorus oxychloride on the water-bath for 1 hr.

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84. Found: C, 78.12; H, 5.63%.

The *pyrazole* was obtained as colorless feathery crystals, m.p. 160–161°.

Anal. Calcd. for $C_{25}H_{21}N_3$: N, 11.57. Found: N, 11.70%.

2-Phenyl-6-methoxy-3-acetyl-4-hydroxyquinoline (II. R = C_6H_5, X = 6-OCH_3). The crude product from methyl β-amino-α-(*N*-*p*-anisylbenzimidoyl)crotonate (V. R = C_6H_5, X = 4-OCH_3) was recrystallized twice from dilute ethanol (charcoal) and obtained as colorless plates m.p. 290–292° (lit,[1] m.p. 270°).

Anal. Calcd. for $C_{18}H_{15}NO_3$: N, 4.78. Found: N, 4.99%. The *pyrazole* crystallized from dilute ethanol as colorless needles, m.p. 192–194°.

2-o-Tolyl-3-acetyl-4-hydroxyquinoline (II. R = *o*-$C_6H_4CH_3$, X = H). Methyl β-amino-α-(*N*-phenyl-*o*-toluimidoyl)crotonate (V. R = *o*-$C_6H_4CH_3$, X = H) yielded the quinoline as colorless crystals m.p. 256–257° (lit,[2] m.p. 251–252°) which showed no coloration with ferric chloride.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.05. Found: C, 77.50; H, 5.44; N, 5.20%.

2-p-Tolyl-3-acetyl-4-hydroxyquinoline (II. R = *p*-$C_6H_4CH_3$, X = H). The base was obtained as colorless shining plates m.p. 239–240° (lit,[2] not melted at 297°) and showed no coloration with ferric chloride.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.05. Found: C, 77.37; H, 5.54; N, 5.10%.

The *dinitrophenylhydrazone* had m.p. 284–286° dec. (lit,[2] not melted at 300°). The *pyrazole*, colorless feathery needles, m.p. 185°, was insoluble in alkali.

Anal. Calcd. for $C_{24}H_{19}N_3$: N, 12.03. Found: N, 12.11%.

Action of polyphosphoric acid on methyl β-amino-α-(N-methylbenzimidoyl)crotonate (VI. X = Me). The ester (1 g.) and polyphosphoric acid (6 g.) were stirred and heated at 170° for 15 min. during which period effervescence occurred. After cooling somewhat, water was added to the orange solution when benzoylacetone (0.2 g.; m.p. 52–56°) separated; colorless crystals from dilute ethanol, m.p. and m.m.p. with authentic benzoylacetone 56–57°. The acid filtrate on making alkaline deposited a small amount of a yellow base (m.p. 135–158°, soluble in dilute acid to give a yellow solution, and not further investigated) and contained acetophenone. Methyl β-amino-α-(*N*-ethylbenzimidoyl)-crotonate (VI. X = C_2H_5) similarly yielded benzoylacetone, some yellow base and acetophenone.

Acknowledgment. The author thanks Mr. K. Pegel for obtaining the infrared spectra of the compounds listed in the table and the Iscor Laboratories for the C & H analyses reported.

JOHANNESBURG, SOUTH AFRICA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinolizinium Salts. I. Synthesis of 2-Hydroxy-3-bromo-1,2,3,4-tetrahydroquinolizinium Bromide

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A two-step method for preparing tetrahydroquinolizinium salts has been devised. This method involves the condensation of certain α,β-unsaturated aldehydes with 2-picolyllithium and subsequent cyclization by the addition of bromine to the unsaturated alcohol. The alcohol formed in the initial step does not undergo the typical allylic rearrangement seen in many α,β-unsaturated alcohols in acidic solution. This method overcomes many of the difficulties involved in former syntheses and makes possible the preparation of a number of potentially useful therapeutic agents.

The hydroxyoctahydroquinolizines and hydroxytetrahydroquinolizinium compounds are of potential therapeutic value because of their similarity in structure to other therapeutic agents and because the octahydroquinolizine ring is present in a number of physiologically active alkaloids such as the Lupine, Sparteine, Reserpine, Yohimbine, Veratrine, and Berberine alkaloids. To date only a few references to these compounds having physiological activity have been reported. Soine[3] has prepared

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