[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Certain 4-Hydroxyquinolines from Aniline and β-Ketonitriles. Cyclizations of Nitriles through Amides by Means of Polyphosphoric Acid

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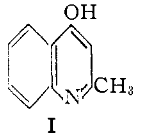
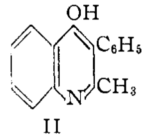
Certain 4-hydroxyquinolines were prepared from aniline and appropriate β-ketonitriles by a new method in which intermediate anils (or crotonates) were cyclized by means of polyphosphoric acid. At least in one case, this method has been superior to the Conrad–Limpach method.

Although 2-methyl-4-quinolinol (I) is prepared in good yield from aniline and acetoacetic ester by the Conrad–Limpach type of cyclization of the intermediate anil (or crotonate),[2] 2-methyl-3-phenyl-4-quinolinol (II) has been obtained from aniline and ethyl α-phenylacetoacetate by this method in only 4% yield.[3]

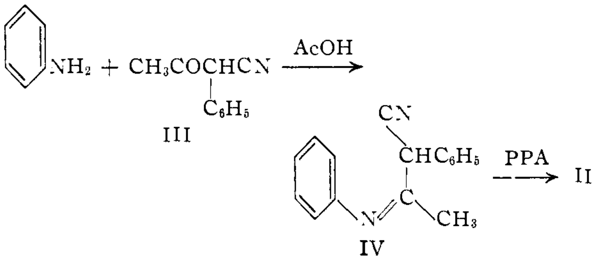


I

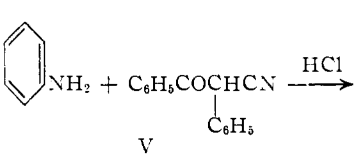


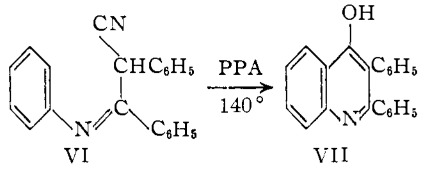
II

In the present investigation, II was obtained from aniline and α-acetyl-α-tolunitrile (III) in 56% yield[4] employing acetic acid to catalyze the formation of anil IV, and polyphosphoric acid (PPA) to effect its cyclization. The yields in the two steps were 71 and 79%, respectively. Also, the first step as well as the second was effected by polyphosphoric acid in a single process to form II in 39% yield.

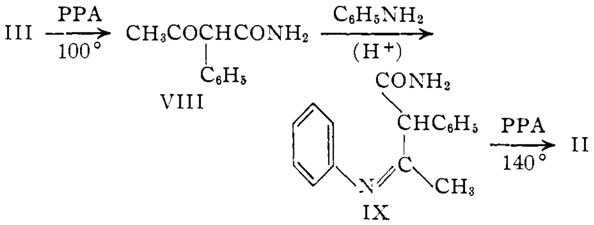


Similarly 2,3-diphenyl-4-quinolinol (VII) was obtained in 34% yield from aniline and α-benzoyl-α-tolunitrile (V). This yield could probably be improved since the formation of the intermediate anil (VI) was realized in only 39% yield. Product VII was obtained from the anil in 87% yield.

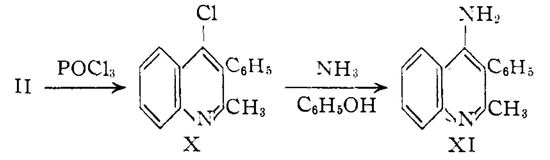




The present method appears to involve the conversion of the anil-nitrile (IV or VI) to the corresponding anil-amide which undergoes cyclization eliminating ammonia. Thus, not only are nitriles known to be converted to amides by polyphosphoric acid,[5] but anil-amide IX, prepared from β-ketoamide VIII and aniline, was shown to undergo cyclization to form II under the conditions employed with anil IV (at 140°). It is possible that some of the anil-amide was converted to the corresponding carboxylic acid which underwent cyclization, eliminating water. β-Ketoamide VIII was prepared from β-ketonitrile III with polyphosphoric acid at a somewhat lower temperature (at 100°).[6]



It should be pointed out that the cyclization of anil-amide IX must not involve dehydration to form the corresponding amine (XI) followed by hydrolysis, since this amine was shown to be stable under similar conditions. Amine XI was prepared from II by means of phosphorus oxychloride and ammonia. One attempt to prepare it from anil-amide IX by means of phosphorus pentoxide was unsuccessful. A similar cyclization, involving dehydration, has been reported with certain substituted amides.[7]



Finally it should be mentioned that anil-amide IX was found to undergo cyclization to form II

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(1) Eli Lilly Fellow, 1952–1954.

(2) G. A. Reynolds and C. R. Hauser, *Org. Syntheses*, **29**, 42 (1949); **29**, 70 (1949).

(3) W. J. Adams and D. H. Hey, *J. Chem. Soc.*, 1521 (1951).

(4) Even if this yield could be equaled by the Conrad–Limpach method with aniline and ethyl α-phenylacetoacetate, the present method would presumably be preferable since this ester has generally been prepared from nitrile III; see ref. 3, and R. H. Kimball, *et al.*, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 284.

(5) H. R. Snyder and C. T. Elston, THIS JOURNAL, **76**, 3039 (1954).

(6) When nitrile III was treated with polyphosphoric acid at 140°, the formation of amide VIII was accompanied by the production of an unidentified product which is being studied further.

(7) C. C. Price and V. Boekelheide, THIS JOURNAL, **68**, 1246 (1946).

(in 16% yield) on refluxing in Dowtherm in which reaction the evolution of ammonia was detected readily.

Experimental[8]

2-Methyl-3-phenyl-4-quinolinol (II). (A) From Aniline and α-Acetyl-α-tolunitrile (III).—A mixture of 39.8 g. (0.25 mole) of α-acetyl-α-tolunitrile (III), 23.3 g. (0.25 mole) of aniline, 0.5 ml. of acetic acid and 50 ml. of benzene was heated on a metal-bath for 4 hours at 140°, the water formed being removed by means of a separator[2] attached to the condenser. After cooling, ligroin (b.p. 60–90°) was added, and the mixture allowed to stand at room temperature. The precipitated anil (IV) was collected on a funnel and recrystallized from a mixture of benzene and ligroin; yield of slightly yellow plates, 41.9 g. (71%), m.p. 94–96°. After several recrystallizations, a sample melted at 98–100°.

Anal. Calcd. for $C_{16}H_{14}N_2$: N, 11.96. Found: N, 11.82.

The anil of α-acetyl-α-tolunitrile (IV) (3 g., m.p. 94–96°) was stirred and heated at 140° for 30 minutes with 15 g. of polyphosphoric acid. After cooling somewhat, 30 ml. of 1 *N* hydrochloric acid was added and stirring continued until the polyphosphoric acid[9] had decomposed. After neutralization of the solution with sodium hydroxide (to *p*H 5), and cooling, the product was collected on a funnel and recrystallized from acetic acid yielding 2.37 g. (79%) of 2-methyl-3-phenyl-4-quinolinol (II), m.p. 304–308°; lit. m.p. 302–304° dec.[3] A sample, melting at 307–308°, was analyzed.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.86; H, 5.57; N, 5.95. Found: C, 81.80; H, 5.77; N, 5.76.

Larger amounts (up to 60 g.) of anil-nitrile IV were cyclized similarly. Because of some foaming, a 2-l. flask was used in these cases. The reaction mixture, while still warm, was decomposed by pouring it into dilute hydrochloric acid.

Also the 4-quinolinol (II) was prepared directly by stirring and heating a mixture of 3.18 g. (0.02 mole) of α-acetyl-α-tolunitrile and 2 g. of aniline with 20 g. of polyphosphoric acid for 30 minutes at 100° and then for 30 minutes at 140°. The product (1.85 g., 39%) melted at 306–309°. The melting point was not depressed in admixture with a sample of II prepared as described above.

In a blank experiment with amine XI (prepared as described below) and polyphosphoric acid (heated at 140° for 70 minutes), 80% of the amine was recovered.

(B) From Aniline and α-Phenylacetoacetamide (VIII).—α-Phenylacetoacetamide (VIII) was prepared by stirring and heating 12.7 g. (0.08 mole) of α-acetyl-α-tolunitrile (III) with 80 g. of polyphosphoric acid at 100° for 20 minutes. After cooling to room temperature, the reaction mixture was decomposed with ice-water and filtered. The solid keto-amide VIII was washed with water, dried, and recrystallized from a mixture of benzene and ligroin to give 8.0 g. (56%) of colorless crystals, m.p. 125–128° (reported m.p. 131°[10]). This compound gives a strong purple color with ferric chloride solution.

α-Phenylacetoacetamide (VIII) (7.0 g.) was refluxed with 4.2 g. of aniline and 5 drops of acetic acid in 20 ml. of benzene at 135–145° for 7 hours, the water formed being removed as usual.[2] The excess benzene was distilled, and the residue recrystallized from benzene–ligroin to give 6.5 g. of colorless anil-amide IX, m.p. 134–146°. Several recrystallizations raised the melting point to 150–153°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.46; H, 6.38; N, 11.00.

Anil-amide IX (2 g., m.p. 146–151°) was stirred and heated with 10 g. of polyphosphoric acid at 140° for 30 minutes. The solution was worked up as described in A to give 1.60 g. (86%) of colorless 2-methyl-3-phenyl-4-quinolinol (II), m.p. 305–309°. The melting point was not depressed by admixture with a sample of II prepared as described above.

Also anil-amide IX (2 g.) was cyclized by refluxing 3 hours in 60 ml. of Dowtherm. After cooling, 150 ml. of petroleum ether was added. The solid was removed by filtration and recrystallized from acetic acid yielding 0.30 g. (16%) of 2-methyl-3-phenyl-4-quinolinol (II), m.p. 306–309°. The melting point was not depressed by admixture with a sample of II prepared as described above.

2-Methyl-3-phenyl-4-chloroquinoline (X).—2-Methyl-3-phenyl-4-quinolinol (II) (20 g., 0.085 mole) was refluxed with 60 ml. of phosphorus oxychloride for 10 hours. The hot solution was poured onto 400 g. of ice, and the cool (10°) mixture filtered. The solid was suspended in a little water, and after neutralizing with sodium bicarbonate, the mixture was extracted with ether. The solvent was removed from the ether solution, and the residue recrystallized from methanol–water (charcoal) to give 17.2 g. (80%) of colorless crystals of X, melting at 63–65°, and after another recrystallization at 64.5–65.5°.

Anal. Calcd. for $C_{16}H_{12}NCl$: Cl, 13.98. Found: Cl, 14.02.

2-Methyl-3-phenyl-4-aminoquinoline (XI).—Anhydrous ammonia was passed into a refluxing mixture of 15 g. (0.059 mole) for 2-methyl-3-phenyl-4-chloroquinoline (X) and 40 g. of phenol for 21 hours. The resulting solution was added to ice and made strongly alkaline with 6 *N* sodium hydroxide. The solid amine XI was removed by filtration and washed thoroughly with water and with ether; yield 12.7 g., m.p. 225–229°. More (0.95 g.) of the amine, m.p. 224–228°, was isolated from the ether washing; total yield 95%. A sample of this compound was recrystallized from ethanol, and then from ether; it was finally sublimed at 140° (0.5 mm.) to give product melting at 228–231°.

Anal. Calcd. for $C_{16}H_{14}N_2$: N, 11.96. Found: N, 12.00.

2,3-Diphenyl-4-quinolinol (VII).—A mixture of 44.2 g. (0.20 mole) of α-benzoyl-α-tolunitrile (V), 18.6 g. (0.20 mole) of aniline, 0.5 ml. of acetic acid, 1 g. of aniline hydrochloride and 50 ml. of benzene was refluxed (140°) for 7 hours, the water formed being removed as usual.[2] After cooling, ligroin (b.p. 60–90°) was added, and the precipitated anil (VI) was collected on a funnel. It was recrystallized from 95% ethanol to give 23.1 g. (39%) of yellow needles melting at 205–206°, and after another recrystallization at 206–207°.

Anal. Calcd. for $C_{21}H_{16}N_2$: N, 9.45. Found: N, 9.51.

Anil-nitrile VI (7.0 g.) was stirred and heated with 45 g. of polyphosphoric acid at 140–160° for 30 minutes. After decomposing with 80 ml. of cold water, the reaction mixture was filtered, and the solid recrystallized from acetic acid to give 6.12 g. (87%) of 2,3-diphenyl-4-quinolinol (VII), m.p. 344–346° (lit. m.p. 331°[11]).

A sample of VII was converted by phosphorus oxychloride to the corresponding chloro derivative which, after recrystallization from ethanol–water, was obtained as needles, m.p. 119–120° (lit. m.p. 121°[11]). The chloro derivative was refluxed with aniline in phenol to form the corresponding anilino derivative which, after crystallization from 95% ethanol, melted at 197° (lit. m.p. 196–197°[11]). The picrate of the anilino derivative melted at 261–263° (lit. m.p. 259–260°[11]).

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[8] Analysis by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Melting points are uncorrected.

[9] We are indebted to the Victor Chemical Works, Chicago, Ill., for a generous sample of polyphosphoric acid.

[10] J. Schrieber, *Compt. rend.*, **220**, 200 (1945).

[11] K. Dziewonski, *et al.*, *Roczniki Chem.*, **14**, 1123 (1934); *cf.* *C. A.*, **29**, 6235[6] (1935).