

Beckmann Rearrangement of Oximes of Certain Quinolyl Ketones¹

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Some early work has been done on the Beckmann rearrangement of oximes of quinolyl ketones. Matsumara (7) reported the rearrangement of 5-acetyl-8-hydroxyquinoline oxime to 5-acetamido-8-hydroxyquinoline and likewise 5-benzoyl-8-hydroxyquinoline was rearranged to the corresponding 5-benzamido compound. These rearrangements were carried out at 100° in a sealed tube containing a solution of the oxime in glacial acetic acid and acetic anhydride which had been saturated with hydrogen chloride. In a later publication (8), it was reported that thionyl chloride in ether caused the rearrangement of 5-benzoyl-8-hydroxyquinoline oxime to the anilide of 8-hydroxy-5-quinolinecarboxylic acid. Rearrangement in concentrated sulfuric acid was reported to also give the anilide. However, it was reported that the oxime of 5-acetyl-8-hydroxyquinoline was rearranged with thionyl chloride and sulfuric acid to give the same product as with acetic anhydride.

Howitz and Kopke (2) reported the isolation of two oximes of 8-benzoylquinoline, one melted at 121° and the other at 165°. The lower melting oxime was rearranged in ether by phosphorus pentachloride to give 8-benzamidoquinoline while the higher melting oxime gave 8-quinolinecarboxanilide. Matsumara (7, 8) did not mention the isolation of more than one form of the oxime of 5-benzoyl-8-hydroxyquinoline.

Recently, Huntress and Walter (3) have studied the rearrangement of the oximes of 2-benzoylpyridine. Two oximes were isolated; the lower melting one was rearranged in chloroform using thionyl chloride to give 2-benzamidopyridine while the higher melting form rearranged under the same conditions to 2-pyridinecarboxanilide. The authors found that both oximes gave the same product, α -picolinic acid and sulfanilic acid, when rearranged in concentrated sulfuric acid and the product subjected then to hydrolysis. They reported that the use of phosphorus pentachloride in ether did not give as good results as the thionyl chloride method. Huntress and Walter also reported that rearrangement of the benzenesulfonyl and p-toluenesulfonyl esters of the oximes occurred smoothly by merely refluxing solutions of the ester in solvents such

¹ Abstracted from portions of theses submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Master of Arts, in the Department of Chemistry, Indiana University, by J. D. G. (July, 1948) and J. C. G. (November, 1947).

as chloroform or benzene. In some cases, rearrangement occurred without heating.

The configuration of the oximes may be deduced from the knowledge that the group trans to the hydroxy group of the oxime moves to the nitrogen atom during rearrangement.

In the work reported in this paper, both the syn and anti-phenyl oximes of 6-benzoylquinoline were obtained since both benzoic acid and 6-quinolinecarboxylic acid were obtained by hydrolysis of the rearranged substances. The individual oximes were not isolated. The oxime of 6-acetyl-4-chloroquinoline was of one configuration. Rearrangement of the oxime gave 6-acetamido-4-chloroquinoline, therefore the oxime must have been the syn-methyl. The yield of 6-amino-4-chloroquinoline though was rather low since there was extensive replacement of the chlorine atom by the hydroxy group during hydrolysis of the 6-acetamido compound. The melting point recorded for 6-acetamido-4-chloroquinoline ranges from 206° to 212° (4,5,1) which is in rather close agreement with the melting point of the substance isolated from the Beckmann rearrangement. The melting point of the substance obtained by hydrolysis of the 6-acetamido-4-chloroquinoline agrees with that of 6-amino-4-chloroquinoline reported by Jacini (4) but not with the value, 145°, reported by Kermack (5). Phosphorus pentachloride in ether or in benzene gave better results than did the use of either thionyl chloride or sulfuric acid. The Beckmann rearrangement of the oxime of 6-acetyl-4-hydroxyquinoline gave unworkable tarry materials.

The 6-acetyl-4-hydroxyquinoline was prepared from methyl acetate and *p*-aminoacetophenone by the well-known Conrad-Limpach method but boiling diphenyl ether was used as the medium for ring closure of the crotonate.

Experimental

p-Aminoacetophenone.—To a 2-liter three-necked flask fitted with a mechanical stirrer and a reflux condenser fitted with a trap to absorb hydrogen chloride, was added 270 g. (2 moles) of acetanilide, 530 ml. of carbon disulfide and 420 g. (5.35 moles) of acetyl chloride. The stirrer was started and about 5 g. portions of anhydrous aluminum chloride added through the third neck of the flask, stoppering it after each addition and waiting until the reaction subsided before more aluminum chloride was added; the total amount used was 934 g. (7 moles). The reaction mixture was refluxed for about thirty minutes, then the upper layer removed and the lower brown-colored layer was poured onto chipped ice. The cold mixture was stirred well, then the crude *p*-aminoacetophenone removed by filtration. The crude wet substance was refluxed for thirty minutes with a solution of 550 ml. of concentrated hydrochloric acid in 750 ml. of water, then the acid was just neutralized with sodium hydroxide, the aniline removed by steam distillation. After cooling in an ice bath, the *p*-aminoacetophenone was removed by filtration and purified by recrystallization from about three liters of boiling water after treatment with 5-10 g. of decolorizing charcoal. The yield of yellow

crystalline material was 155.4 g. (58.2%), m.p. 103-105°. The melting point (2) recorded for p-aminoacetophenone is 104-106°.

Methyl β -(p-acetylanilino)-crotonate.—A 500 ml. round bottomed flask was fitted with a reflux condenser and a watertrap for use with a heavier than water liquid. A solution of 200 ml. of methylene dichloride, 65.7 g. (0.5 mole) of pure p-aminoacetophenone, 61.5 g. (0.53 mole) of methyl acetoacetate and three drops of 10% hydrochloric acid were refluxed until no more water was collected in the trap. The methylene dichloride was removed by distillation on a steam bath. After the residue cooled, the solid was triturated with 200 ml. of ligroin, filtered and washed twice with 100 ml. portions of ligroin. The yield of the crotonate, after drying in an air bath was 110 g. (95.3%), m. p. 80-83°. A portion of the crotonate was recrystallized twice from boiling ligroin (90-60° range), giving yellow-colored needles, but the melting point did not change.

Anal. Calc'd. for $C_{12}H_{13}NO_3$: N,6.06%. Found: N,6.49%.

6-Acetyl-4-hydroxyquinaldine.—A 1-liter three-necked flask was fitted with a mechanical stirrer, a separatory funnel and an exit tube 10 mm. in diameter with about a 6 in. vertical section connected to a water cooled condenser set downward for distillation. About 450 ml. of diphenyl ether was added to the flask then heated to boiling and a hot solution of 76 g. (0.34 mole) of crude methyl β -(p-acetylanilino)-crotonate in 125 ml. of diphenyl ether was added to the stirred boiling diphenyl ether at a rate so as not to allow the temperature to fall below 240°. After no more methyl alcohol distilled, the reaction mixture was allowed to cool, the solid was collected on a Buechner funnel, then washed with 150 ml. of a diphenyl ether-ligroin mixture (2:1) and finally with two 125 ml. portions of ligroin. The yield of crude 6-acetyl-4-hydroxyquinaldine was 56 g. (82%), m. p. 315-320 (dec.). The substance was obtained as light tan-colored crystals after recrystallization from 95% ethyl alcohol; m. p. 327-329°. The recovery of recrystallized material was 80%.

Anal. Calc'd. for $C_{12}H_{11}NO_2$: N,6.96%. Found: N,6.85%.

6-Acetyl-4-chloroquinaldine.—Crude, dry 6-acetyl-4-hydroxyquinaldine (35.3 g., 0.175 mole) was added portion-wise to 56.7 g. (0.37 mole) of phosphoryl trichloride and the reaction mixture was warmed a few minutes after all of the solid was in solution. The liquid mass was poured onto about 400 g. of ice, then the solution nearly neutralized with sodium hydroxide, the tarry material removed by filtration and the chlorocompound precipitated by neutralization of the clear filtrate. The solid was collected on a Buechner funnel, washed thoroughly with both water and a very dilute sodium bicarbonate solution, then dried at 70°. The yield of the crude substance was 36.7 g. (95.5%), m. p. 133-136°. The 6-acetyl-4-chloroquinaldine was purified by recrystallization from dilute ethyl alcohol (35%) and also from ligroin (b. p. 70-110°); the yield of light tan-colored crystals was 29.4 g. (77%); m. p. 137-137.5°.

Anal. Calc'd. for $C_{12}H_{10}ClNO$: Cl, 16.18%. Found: Cl, 16.33%.

6-Benzoylquinoline.—A 1-liter three-necked flask was fitted with a mechanical stirrer, thermometer, separatory funnel and a reflux condenser. The flask was supported in an oil bath. Added to the flask were 90 g. (0.45 mole) of p-aminobenzophenone, 130 ml. of glycerol, 42 g. of boric acid and 78 g. of arsenic pentoxide. The mixture was warmed to 115° and stirred until it became homogenous then 54 ml. of concentrated sulfuric acid was added at a rate so as to allow a gradual rise in temperature but not go above 130°. After all of the sulfuric acid had been added, the temperature was allowed to rise slowly to 138-140° where it was maintained for about seven hours. After cooling, the reaction mixture was poured onto ice, then the solution neutralized with concentrated ammonia water and the solid removed. The gummy mass was shaken with excess 10% sodium hydroxide and benzenesulfonyl chloride, the aqueous layer separated and the water-insoluble portion treated with excess dilute hydrochloric acid. The acid solution was filtered, then ice added to the filtrate and the solution made slightly alkaline to litmus by the addition of sodium hydroxide. The brown-colored solid was collected by filtration and after drying in the air, it weighed 62 g.; m. p. 33-39°. The crude 6-benzoylquinoline was purified by three recrystallizations from dilute (30%) ethyl alcohol. The substance was obtained as a white, flocculent type solid melting at 42-43°.

Anal. Calc'd for $C_{16}H_{11}NO$: N, 6.01%. Found: N, 6.07%.

6-Benzoylquinolinium Picrate.—The picrate was prepared by the addition of a saturated alcohol solution of picric acid to 0.5 g. of 6-benzoylquinoline in 10 ml. of 95% ethyl alcohol. The picrate was removed by filtration and recrystallized three times from absolute ethyl alcohol. It was a finely crystalline bright yellow solid melting at 212-214°.

Anal. Calc'd for $C_{22}H_{14}N_4O_8$: N, 12.12%. Found: N, 10.87, 11.00%.

6-Benzoylquinoline Oxime.—Five grams (0.02 mole) of 6-benzoylquinoline and 2.1 g. (0.03 mole) of hydroxylamine hydrochloride was added to a solution of 2 g. (0.05 mole) of sodium hydroxide in 125 ml. of absolute ethyl alcohol and the mixture refluxed for about fifteen minutes. Most of the alcohol was removed by distillation, then the mass poured into about 500 ml. of water containing 0.5-1.0 ml. of concentrated sulfuric acid. After standing for some time, the solid was collected on a Buechner funnel, washed and then dried at 70°. The yield of the crude oxime was 3.2 g. (61%), m. p. 174-190°. Recrystallization of one gram of crude 6-benzoylquinoline oxime from ethyl alcohol gave 0.7 g. of light yellow crystals, m. p. 204-206°.

Anal. Calc'd for $C_{16}H_{12}N_2O$: N, 11.29%. Found: N, 11.25%.

6-Acetyl-4-chloroquinaldine Oxime.—This oxime was prepared in a similar manner from 19.5 g. (0.49 mole) of 6-acetyl-4-chloroquinaldine. The yield of the crude oxime was 35.2 g. and possessed a very wide indefinite melting point range. To purify the oxime, 25.2 g. of the crude substance was refluxed with 800 ml. of absolute alcohol, the solution

filtered and the oxime allowed to crystallize. After two recrystallizations, the yield was 14 g., m. p. 191-193°.

Anal. Calc'd. for $C_{12}H_{11}ClN_2O$: Cl, 15.12%. Found: Cl, 15.28%.

6-Acetyl-4-hydroxyquinaldine Oxime.—The substance was prepared from 12.2 g. (0.066 mole) of 6-acetyl-4-hydroxyquinaldine using the same ratio of reagents and conditions as in the preparation of 6-benzoylquinoline oxime. The yield of oxime was 12.6 g. (96%). The crude substance was dissolved in boiling ethylene glycol, the oxime allowed to separate, the solid washed with ethylene glycol, then boiled with two 50 ml. portions of ethyl alcohol. The recovery of the recrystallized oxime was 92%. The oxime was a light gray color and melted at 304-305°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: N, 12.96%. Found: N, 12.98%.

Beckmann Rearrangement of 6-Benzoylquinoline Oxime.—A 1-liter three-necked flask was equipped with a sealed stirrer and a reflux condenser with a calcium chloride attached. Eight grams (0.034 mole) of powdered 6-benzoylquinoline oxime and 500 ml. of anhydrous ether was added to the flask and the mixture stirred vigorously. Phosphorus pentachloride (14 g., 0.07 mole) was added in 12 portions over a period of about three hours while the temperature was maintained no higher than -10° . The temperature was allowed to rise to that of the room after an additional hour and the stirring was continued while the reaction mixture was refluxed for thirty minutes. Most of the ether was removed by distillation and the residue hydrolysed by the addition of ice. A portion of the acid was neutralized by sodium hydroxide, the solution filtered and the filtrate made slightly alkaline. The brown sticky solid which precipitated became hard and glossy after standing some time. The yield was 4 g. A small portion was recrystallized from absolute ethyl alcohol which yielded a white solid melting at 140-145°.

Anal. Calc'd. for $C_{10}H_{12}NO_2$: N, 11.29%. Found: N, 11.33%.

Three grams of the crude rearranged substance was refluxed for three hours with 30 ml. of 20% hydrochloric acid, then the solution made alkaline and the oil extracted with ether. The aqueous layer was warmed, then filtered and the cold filtrate acidified. The solid which separated was recrystallized from hot water giving a white crystalline acid which melted at 119-120°. A mixed melting point with benzoic acid showed no depression. The acid filtrate was made alkaline with concentrated ammonia water, then neutralized with acetic acid. After standing for a day, the solid was collected on a Buechner funnel and recrystallized from dilute ethyl alcohol. The substance melted at 285-288° (dec.). The melting point (9) recorded for 6-quinoline-carboxylic acid is 290-291°.

Beckmann Rearrangement of 6-Acetyl-4-chloroquinaldine Oxime.—Benzene (500 ml.) was added to a 1-liter three-necked flask containing 12.4 g. (0.052 mole) of powdered crude 6-acetyl-4-chloroquinaldine oxime. The flask was equipped with a mechanical stirrer and condenser, then immersed in a cooling bath and 22 g. (0.106 mole) of phosphorus

pentachloride added in eight portions over a period of three hours while the mixture was stirred vigorously and the temperature was maintained at about 0°. After the reaction mixture warmed to room temperature, it was stirred for one hour then most of the benzene removed on a steam bath. Ice was added to the residue and the solution was boiled gently for a short time to remove the remainder of the benzene. The acidic solution was partially neutralized with sodium hydroxide, treated with 5 g. of norite and filtered through a Buechner funnel. After making the cold filtrate slightly alkaline with sodium hydroxide, a yield of 9.8 g. (79%) of a tan-colored solid was obtained, m. p. 176-180°. A small amount of the amide was purified by several recrystallizations from benzene; m. p. 205-206.5°.

Anal. Calc'd. for $C_{12}H_{11}ClN_2O$; N,11.94%. Found: N,12.34%.

A mixture of 3.5 g. of 6-acetamido-4-chloroquinaldine was refluxed for fifteen minutes with 10 ml. of 20% hydrochloric acid, then the solution filtered and made slightly alkaline. A yield of 2.6 g. of brown solid melting at 129-137° was obtained. The substance was extracted with hot benzene yielding a solid, which after recrystallization from benzene, melted at 169-169.5°.

Anal. Calc'd. for $C_{10}H_9ClN_2$; Cl,18.44%. Found: Cl,18.25%.

Summary

The Beckmann rearrangement on the oxime of 6-acetyl-4-chloroquinaldine resulted in the formation of 6-acetamido-4-chloroquinaldine. The oxime of 6-benzoylquinoline was a mixture of syn and anti forms and on rearrangement and hydrolysis of the mixed amides from the rearrangement, gave both benzoic acid and 6-quinoline-carboxylic acid. Several new quinoline compounds have been reported, namely, 6-acetyl-4-hydroxyquinaldine, 6-acetyl-4-chloroquinaldine, 6-benzoylquinoline and the oximes of these substances.

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