

Bromination of Phenylquinolines¹

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Although there are numerous references to work on bromination of quinolines in which there are present groups such as the hydroxy, methyl and so forth, no study has been made on the bromination of phenylquinolines. Recently, it was reported that the treatment of 3-bromo-4-hydroxy-2-phenylquinoline at an elevated temperature with an excess of phosphorus pentabromide gave a tetrabromo-2-phenylquinoline (4). It was also reported that a small amount of tribromo-2-phenylquinoline was obtained as a byproduct when 4-hydroxy-2-phenylquinoline was heated with excess phosphorus pentabromide. No attempt was made to identify either substance.

This work has been repeated under the same conditions as reported (4) but the high yield of polybrominated substances could not be obtained. When 3-bromo-4-hydroxy-2-phenylquinoline was treated with a large excess of phosphorus pentabromide, most of the product was identified as 3,4-dibromo-2-phenylquinoline with only small amounts of impure higher melting substances. The tribromo-2-phenylquinoline was proven to be incorrect since a mixed melting point determination with 3,4-dibromo-2-phenylquinoline showed no depression. In the present work, it was also shown that a small amount of 3,4-dibromo-2-phenylquinoline was actually produced when 4-hydroxy-2-phenylquinoline was heated with phosphorus pentabromide. Substitution of bromine into position 3 has been reported previously (5) when phosphorus pentabromide was used. The substitution could have occurred before replacement of the hydroxy group had taken place. When 4-bromo-2-phenylquinoline was heated with excess phosphorus pentabromide some 3,4-dibromo-2-phenylquinoline was produced; much starting material was recovered and some impure material of higher melting point was also obtained. Treatment of 3,4-dibromo-2-phenylquinoline in the same manner likewise did not yield polybrominated products which could be purified.

It was decided to investigate the action which anhydrous aluminum chloride might have on the bromination. When 3,4-dibromo-2-phenylquinoline was heated with the above catalyst in nitrobenzene, a mixture of polybrominated substances was obtained from which a pure tetrabromo-2-phenylquinoline was isolated in a rather low yield. A logical procedure as a part of the structure proof of the compound seemed to be oxidation. Thus oxidation of a 4-hydroxy-2-phenylquinoline should yield the corresponding N-benzoylanthranilic acid. A trial oxidation of 4-hydroxy-2-phenylquinoline by potassium permanganate in glacial acetic acid gave N-benzoylanthranilic acid but oxidation in dilute sodium carbonate solution gave only benzoic acid. When the oxidation was stopped before all of the hydroxy-quinoline was gone, it was possible

¹Contribution No. 534 from the Chemistry Laboratory of Indiana University.

to isolate some N-benzoylanthranilic acid. However oxidation of 3-bromo-2-phenyl-4-hydroxyquinoline in glacial acetic acid gave an inseparable mixture which upon saponification yielded benzoic acid and 5-bromoanthranilic acid. The latter substance was identified through a mixed melting point determination with authentic 5-bromoanthranilic acid which was prepared according to the method of Wheeler and Oates (7). It is quite obvious that the bromine which was liberated during the oxidation reacted with the N-benzoylanthranilic acid yielding the 5-bromo derivative. When the bromoquinoline was oxidized in sodium carbonate solution only benzoic acid could be isolated.

A trial hydrolysis of 3,4-dibromo-2-phenylquinoline showed it to be entirely resistant to boiling sodium hydroxide solution but on heating it in glacial acetic acid according to the method of Cutler and Surrey (1), replacement of the bromine atom in position 4 by the hydroxy group occurred readily. When 3,4,x,x-tetrabromo-2-phenylquinoline was heated in glacial acetic acid to give 4-hydroxy-3,x,x-tribromo-2-phenylquinoline then the latter substance oxidized by potassium permanganate in sodium carbonate solution, only m-bromobenzoic acid was isolated. No pure substance could be isolated from the oxidation in glacial acetic acid. Hydrolysis of the tribromo compound, then oxidation in sodium carbonate likewise gave only m-bromobenzoic acid. Thus, meta substitution in the 2-phenyl group is established.

Experimental

4-Hydroxy-2-phenylquinoline, 4-bromo-2-phenylquinoline and 3-bromo-4-hydroxy-2-phenylquinoline were prepared according to the method reported previously (4). Phosphoryl tribromide was prepared according to the method of Gerrard and coworkers (2); in the formation of the intermediate phosphorus pentabromide, it was found to be better to cool the stirred solution of phosphorus tribromide in petroleum ether while the bromine was being added.

3,4-Dibromo-2-phenylquinoline.—Five grams (0.017 mole) of 3-bromo-4-hydroxy-2-phenylquinoline was heated for one hour at 105° with 10 g. of phosphoryl tribromide, then the cold reaction mixture was added to 100 ml. of water and after standing thirty minutes, the solution was heated for a half hour. After cooling, it was made strongly alkaline with sodium hydroxide. The crude solid was removed by filtration, washed, then dried and finally refluxed with 150 ml. of ligroin (b.p. 60-90°). After the solution was filtered, the filtrate was concentrated to 50 ml. The 3,4-dibromo-2-phenylquinoline crystallized as white needles. The yield was 5.6 g. (88%), m.p. 149.5-150°.

Anal. Calc'd for $C_{15}H_9Br_2N$: Br, 44.08%. Found: Br, 44.43%

Action of Glacial Acetic Acid on 3,4-Dibromo-2-phenylquinoline.—One gram of 3,4-dibromo-2-phenylquinoline was dissolved in 12 g. of glacial acetic acid and the solution refluxed for two hours. After cooling, the solution was poured into 25 ml. of water, the solid removed and dried then extracted with 50 ml. of boiling ligroin. The insoluble portion (0.89 g.) was recrystallized from 45 ml. of absolute

ethyl alcohol, giving 0.45 g. of a white solid which melted at 275-278°. A mixed melting point determination with 3-bromo-4-hydroxy-2-phenylquinoline showed no depression.

2-(p-Bromophenyl)-4-hydroxyquinoline.—Ethyl p-bromobenzoylacetate was prepared in a 70% yield from p-bromobenzoyl chloride and ethyl acetoacetate in the manner described by Hale and Tharp (3). The ethyl p-bromobenzoylacetate (31 g.) was added to a solution of 11.2 g. (0.12 mole) of aniline in 150 ml. of carbon tetrachloride, two drops of dilute hydrochloric acid added and the solution refluxed under a condenser attached to a heavier-than-water liquid separator until the theoretical amount of water was collected. After removal of the carbon tetrachloride, the oil was dissolved in 25 ml. of diphenyl ether and the solution added to 100 ml. of boiling diphenyl ether. After cooling, the solid was removed by filtration and washed with a 50-ml. portion of benzene and two 50-ml. portions of ligroin, then the solid refluxed with 200 ml. of benzene. The residue (17.7 g.) was recrystallized from 380 ml. of pyridine yielding 15.5 g. of light yellow colored flakes. Recrystallization from n-butyl cellosolve gave a 40% yield of white solid which melted at 323-324°. The recorded (4) melting point is given as 320-321°.

3-Bromo-2-(p-bromophenyl)-4-hydroxyquinoline.—A stirred solution of 2.9 g. (0.01 mole) of 2-(p-bromophenyl)-4-hydroxyquinoline in 85 ml. of glacial acetic acid at 70° was treated with a solution of 2 g. (0.012 mole) of bromine in 10 ml. of glacial acetic acid, then heated on steam bath for ten minutes. The cold solution was diluted with 75 ml. of water containing 2 g. of sodium hydroxide the solid removed by filtration, washed and recrystallized from 100 ml. of methyl cellosolve. The yield was 3.1 g. (85%) of white solid which melted at 285.5-287°.

Anal. Calc'd for $C_{15}H_8Br_2NO$: Br, 42.22%. Found: Br, 42.72%.

3,4,4'-Tribromo-2-phenylquinoline.—This substance was prepared from 2.5 g. (0.0066 mole) of 3-bromo-2-(p-bromophenyl)-4-hydroxyquinoline in a manner exactly analogous to the method for the preparation of 3,4-dibromo-2-phenylquinoline. The yield of crude substance was 2.6 g. (91%). A portion of the solid was recrystallized from absolute ethyl alcohol, giving light, fluffy needles which melted at 222.8-223.8°.

Anal. Calc'd for $C_{15}H_5Br_3N$: Br, 54.29%. Found: Br, 54.49%.

N-(m-Bromobenzoyl)-5-bromoanthranilic Acid.—The preparation of this substance was based on a general procedure of Steiger (6). A solution of 3.5 g. (0.016 mole) of 5-bromoanthranilic acid (7) in 81 ml. of 2 N sodium hydroxide was placed in a 3-necked flask and the solution cooled to 0-1°. While the solution was stirred and kept cold, 3.6 g. (0.016 mole) of m-bromobenzoyl chloride and 8.1 ml. of 2 N sodium hydroxide were added simultaneously. The solution was stirred for thirty minutes while it warmed to room temperature. The sodium N-(bromobenzoyl)-5-bromoanthranilate was removed by filtration. The salt was added to 200 ml. of water, enough 5 N hydrochloric acid added to be in excess and the mixture stirred vigorously for thirty minutes. The yield of crude acid was 4.7 g. (76%); m. p., 236.5-239°. Recrystallization from absolute ethyl alcohol raised the melting point to 245-247°.

Anal. Calc'd for $C_{14}H_6Br_2NO_2$: Br, 40.10%. Found: Br, 40.05%.

Bromination of 3,4-Dibromo-2-phenylquinoline.—A. A mixture of 20 g. (0.055 mole) of 3,4-dibromo-2-phenylquinoline, 29 g. (0.22 mole) of anhydrous aluminum chloride and 55 g. (0.45 mole) of nitrobenzene was heated on a steam bath in a two-necked flash fitted with a condenser and dropping funnel. The contents were protected against moisture. Bromine (35.6 g., 0.22 mole) was added dropwise over a period of fourteen hours and the heating was continued for another ten hours. The red-colored reaction mixture was poured into 100 ml. of water, decolorized with sodium bisulfite and the nitrobenzene removed by steam distillation. The nondistillable solid was dried and extracted by refluxing twice with 300-ml. portions of ligroin. A yield of 10.3 g. of light pink solid was obtained from the ligroin. After recrystallization from absolute ethyl alcohol, the yield of solid was 7.7 g., m.p. 170-178°. Alternate recrystallization of 1.5 g. of the substance from absolute ethyl alcohol and from ethyl carbitol finally gave 0.2 g. of white flaky solid which melted at 179-181°.

Anal. Calc'd for $C_{15}H_7Br_2N$: Br, 61.42%. Found: Br, 61.50%.

B. A mixture of 10 g. (0.028 mole) of 2-phenyl-3,4-dibromoquinoline, 14.7 g. (0.11 mole) of anhydrous aluminum chloride, 27.7 g. (0.23 mole) of nitrobenzene and 9 g. (0.055 g.) of bromine were sealed in a pyrex carius tube and heated at 100° for 24 hours. After removal of the nitrobenzene by steam distillation, the dried residue was extracted with 350 ml. of boiling ligroin, yielding 6.1 g. of solid which melted at 164-174°. Recrystallization did not raise the melting point nor shorten the range appreciably.

Action of Glacial Acetic Acid on Bromination Product, B.—Four and nine-tenths grams of the product from B which melted at 166-175° was dehalogenated by treatment with glacial acetic acid as described previously. The yield of solid was 4.7 g.; recrystallization of the substance from 220 ml. of absolute ethyl alcohol gave 1.7 g. of solid which melted at 270-270.5°. A mixed melting point determination with 3-bromo-4-hydroxy-2-phenylquinoline (m.p. 278.5-280°) was 249-275°.

Anal. Calc'd for $C_{15}H_8Br_2NO$: Br, 42.22%. Found: Br, 41.12%.

Oxidation of 3,x-Dibromo-4-hydroxy-2-phenylquinoline.—Five-tenths gram of the above substance, obtained when the bromination product B was refluxed with glacial acetic acid, was heated with 25 ml. of 10% sodium carbonate solution while 2.5 g. of potassium permanganate was added portionwise. After two hours, the solution was clarified with sodium bisulfite and the hot solution acidified with hydrochloric acid. The white precipitate was removed and recrystallized from boiling water. The yield of solid was 0.05 g., m.p. 149-153°. A mixed melting point determination with m-bromobenzoic acid showed no depression.

When 1 g. of the crude tetrabromo compound, 2-phenyl-3,4,x,x-tetrabromoquinoline, of somewhat shorter melting range was heated with glacial acetic acid, then the resulting crude tribromo-4-hydroxy-2-phenylquinoline oxidized with potassium permanganate in sodium carbonate solution, only m-bromobenzoic acid was isolated.

Oxidation of 3-Bromo-4-hydroxy-2-phenylquinoline.—A solution 7 g. of 3-bromo-4-hydroxy-2-phenylquinoline in 100 ml. of glacial acetic acid

was refluxed while 13 g. of potassium permanganate was added portion-wise over a period of 2.5-3 hours. The solution was poured into 300 ml. of water, decolorized with sodium bisulfite and the tan colored precipitate removed. The solid was refluxed for two hours with 50 ml. of 5% sodium hydroxide solution, then solution treated with 2 g. of Norite and filtered. The alkaline filtrate was neutralized with concentrated hydrochloride acid, then the addition continued until no more solid seemed to redissolve. After filtering, the solution was carefully neutralized with sodium hydroxide and the solid removed. After three recrystallizations from benzene and toluene and finally from water there was obtained a light colored solid which melted at 207.5-209°. A mixed melting point determination with 5-bromoanthranilic acid (m.p. 209-209°) showed no depression.

Summary

Bromination of 3,4-dibromo-2-phenylquinoline in nitrobenzene using anhydrous aluminum chloride introduced a bromine atom in meta position in the phenyl group. It was shown that oxidation of a 3-bromo-4-hydroxyquinoline in acetic acid solution gave a bromoanthranilic acid. The preparation of 3,4-dibromo-2-phenylquinoline, 3,4,4'-tribromo-2-phenylquinoline, 3-bromo-2-(p-bromophenyl)-4-hydroxyquinoline and N-(m-benzoyl)-5-bromoanthranilic acid is described.

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