[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

SUBSTITUTED BROMOQUINOLINES[1]

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Received January 6, 1947

Very few bromoquinolines have been prepared from the corresponding 2- or 4-hydroxyquinoline by the reaction either with phosphorus pentabromide or phosphoryl tribromide. Claus and co-workers (1) have prepared 2-bromoquinoline and 4-bromoquinoline by the action phosphorus pentabromide on carbostyril and 4-hydroxyquinoline, respectively. Meyer and Heimann (2) prepared 2,4-dibromoquinoline in a similar manner from 4-hydroxycarbostyril. 4-Bromo-6-methoxyquinaldine has been prepared by Slater (3) through the action of phosphoryl tribromide on 4-hydroxy-6-methoxyquinaldine.

The present paper deals with the preparation of several bromoquinolines from the corresponding hydroxyquinolines, and the relative reactivity of the bromine and chlorine atom with some secondary amines. The replacement of the hydroxyl group by bromine proceeded smoothly, except in the case of 4-hydroxyquinaldine. In this instance about one-third of the product proved to be a dibromo compound. It would seem more reasonable that the extra bromine atom entered position 3 rather than anywhere in the benzene ring side. This bromination was probably due to the reaction between bromine, which resulted from the dissociation of phosphorus pentabromide, and 4-hydroxyquinaldine before replacement of the hydroxyl group. It would not seem likely that the second bromine atom entered the methyl group since no halogen test was obtained with alcoholic silver nitrate. Hammick (4) has reported that ω-bromoquinaldine does react readily with alcoholic silver nitrate solution. The behavior with sodium methoxide solution would indicate that one bromine atom (position 4) was much more reactive than the other one. Likewise, even though the one analysis leaves much to be desired, the condensation product of the dibromo compound and benzaldehyde certainly indicates that both bromine atoms remained in the molecule. Ozonization of the styryl derivative and decarboxylation of the acid gave a small amount of a compound which melted at 79–82°. The melting point of 3,4-dibromoquinoline has been reported as 82° (1b).

EXPERIMENTAL

Phosphoryl tribromide. The substance was prepared essentially according to the directions of Booth and Seegmiller (5). The method was modified slightly in that the phosphorus pentabromide was prepared in a finely divided form and the phosphoric anhydride-phosphorus pentabromide mixture was heated in an oil-bath at 100–103°. To reduce the formation of phosphorus tribromide by the decomposition of phosphorus pentabromide, excess bromine was added and then was removed in vacuum prior to vacuum distillation of the phosphoryl tribromide.

Phosphorus pentabromide. Finely divided phosphorus pentabromide was obtained by adding slowly the theoretical amount of phosphorus tribromide to a cold, vigorously stirred

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[1] Constructed mainly from a Senior Thesis submitted by Max M. Marsh.

solution of 240 g. of bromine in 600–1000 ml. of low-boiling (30–60°) petroleum ether. The petroleum ether was decanted from the phosphorus pentabromide and the latter substance washed several times with petroleum ether and the last of the hydrocarbon removed in a vacuum desiccator. The yield was 628 g.

4-Hydroxyquinaldine. A solution of 46.5 g. (0.5 mole) of aniline and 63 g. (0.55 mole) of methyl acetoacetate in 150 ml. of methylene chloride and 2 drops of dilute hydrochloric acid was refluxed, using a water trap with the reflux condenser, until no more water was collected. Most of the methylene chloride was removed by distillation, then the last of the solvent removed in vacuum, and enough warm phenyl ether added to the crude methyl β-anilinocrotonate to dissolve it. The phenyl ether solution of the crude anilinocrotonate was added to 350 ml. of boiling phenyl ether at a rate which did not allow the temperature to fall below 245°. The heating was continued until no more methyl alcohol distilled from the reaction mixture. After the solution cooled to room temperature, 75–100 ml. of low-boiling ligroin was added, the 4-hydroxyquinaldine removed and washed with three 100-ml. portions of petroleum ether, and dried at 80°. The yield was 71.4 g. (89.8%); m.p. 226–228.5°.

The substance was pure enough for subsequent work but may be recrystallized from ethyl alcohol; m.p. 229–230° [Lit. (7), 230–231°].

2-Bromolepidine. 4-Methylcarbostyril (118 g.; 0.75 mole) was mixed with 215 g. (0.75 mole) of phosphoryl tribromide and heated in an oil-bath at 120°. The mixture liquefied in about thirty minutes, then solidified completely, but it was heated for another hour. The reaction mixture was treated cautiously with ice, and after about 50 g. of ice had been added, it was poured into 800 ml. of ice and water. The 2-bromolepidine was precipitated by addition of sodium hydroxide solution while the temperature was kept down by the addition of ice. The solid was washed successively with water, one per cent sodium bicarbonate solution, then water, and finally dried in air at 50°. The yield of crude 2-bromolepidine was 151 g. (90.7%); m.p. 73–75°. A 25-g. portion was recrystallized from ethyl alcohol and from ligroin (b.p. 55–65°) giving 17.5 g. which melted at 81–81.5°; b.p. 125–126° (1 mm.).

Anal. Calc'd for $C_{10}H_8BrN$: N, 6.30. Found: N, 6.11.

Similar results were obtained using phosphorus pentabromide.

2-Bromo-6-methoxylepidine. Five and five-tenths grams (0.029 mole) of 2-hydroxy-6-methoxylepidine and 18 g. (0.027 mole) of phosphorus pentabromide were mixed thoroughly then heated at 70–80° for thirty minutes and at 120° for one hour. After hydrolysis of the reaction mixture with ice and water, and neutralization of the solution with sodium hydroxide, the solid was washed, and recrystallized from 20 ml. of a benzene-ligroin mixture (1:1). The yield of 2-bromo-6-methoxylepidine was 2.8 g. (42%); m.p. 137–142°. Recrystallization of one gram of the substance from 20 ml. of ethyl alcohol gave short, white needles of 2-bromo-6-methoxylepidine melting at 144–145°.

Anal. Calc'd for $C_{11}H_{10}BrNO$: Br, 31.70. Found: Br, 31.77.

4-Bromoquinaldine. This substance was prepared like the 2-bromo-6-methoxylepidine, using 20 g. (0.126 mole) of 4-hydroxyquinaldine and 30 g. (0.07 mole) of phosphorus pentabromide. The crude bromo compound was extracted with 50 ml. portions of hot ligroin (b.p. 60–90°), the ligroin extracts concentrated to 35–40 ml., and refrigerated. Five grams of a white crystalline solid, A, which melted at 84.5–85.5° was obtained. (This substance was subsequently shown to be 3,4-dibromoquinaldine.) After removal of the ligroin from the filtrate, it was distilled in vacuum to give 7 g. (25.2%) of 4-bromoquinaldine; b.p. 88–90° (1 mm.).

Anal. Calc'd for $C_{10}H_8BrN$: Br. 35.99. Found: Br, 35.61.

3,4-Dibromoquinaldine (A). The substance gave no precipitate with alcoholic silver nitrate.

Anal. Calc'd for $C_{10}H_7Br_2N$: Br. 53.11. Found: Br, 53.05.

3-Bromo-4-methoxyquinaldine. Four grams (0.013 mole) of substance A was refluxed for five hours with a solution of 1 g. of sodium in 20 ml. of methanol, then the solution diluted with 150 ml. of water and allowed to stand in an ice-bath. The solid was first recrystallized from ethyl alcohol, then from ligroin (b.p. 60–90°). The yield of white crystalline solid was 2.2 g. (68.8%); m.p. 54–56°.

Anal. Calc'd for $C_{11}H_{10}BrNO$: Br, 31.70. Found: Br, 31.76.

3,4-Dibromo-2-styrylquinoline. Three grams (0.01 mole) of substance A was heated with 1.1 g. of freshly distilled benzaldehyde and 2 g. of anhydrous zinc chloride for 2.5 hours. After cooling, it was extracted twice with concentrated hydrochloric acid, then washed with dilute sodium bicarbonate solution, dried, and recrystallized from benzene. A yield of 0.4 g. of a yellow microcrystalline solid was obtained; m.p. 145.5–147°.

Anal. Calc'd for $C_{17}H_{11}Br_2N$: Br, 41.08. Found: Br, 42.56.

Two-tenths gram of the above styryl derivative was suspended in 20 ml. of glacial acetic acid and ozonized to the corresponding carboxylic acid according to the method of Kaslow and Stayner (6). One-tenth gram of an acid which melted with decomposition at 132–133° was obtained; presumably this substance is 3,4-dibromoquinaldic acid. The acid was decarboxylated by heating in an oil-bath at 150°. The fused mass was dissolved in 5 ml. of hot ethyl alcohol, and water was added dropwise until a faint cloudiness was produced. A yield of 15 mg. of a microcrystalline solid was obtained; m.p. 79–82°. This value checks the melting point recorded for 3,4-dibromoquinoline (1b).

Ethyl 4-bromoquinaldate. This substance was prepared in an entirely analogous manner from 8 g. (0.037 mole) of ethyl 4-hydroxyquinaldate and 10 g. (0.023 mole) of phosphorus pentabromide as described for 4-bromo-6-methoxyquinaldine. After purification by recrystallization from a benzene-ligroin solution (10:1), a yield of 6 g. (58.3%) of light tan crystals was obtained; m.p. 91–92°. An additional 2 g. of lower-melting material was obtained from the mother liquor.

Anal. Calc'd for $C_{12}H_{10}BrNO_2$: Br, 28.53. Found: Br, 28.54.

4-Bromoquinaldic acid. Five grams (0.018 mole) of ethyl 4-bromoquinaldate was refluxed for 24 hours with a solution of 1.5 g. (0.038 mole) of sodium hydroxide in 30 ml. of water. The cooled solution was acidified with just enough dilute hydrochloric acid to dissolve the solid, then dilute ammonia water was added until no more precipitation occurred. The solid was recrystallized from 80% ethyl alcohol. A yield of 3.5 g. (77.8%) of fine, light tan needles was obtained; m.p. 159–164° (dec.). Further recrystallization did not change the decomposition temperature.

Anal. Calc'd for $C_{10}H_6BrNO_2$: Br, 31.71. Found: Br, 31.97.

6-Methoxy-2-piperidinolepidine. A solution of 2.42 g. (0.01 mole) of 2-bromo-6-methoxylepidine in 5 ml. of piperidine was refluxed for four hours, the solution diluted with 100 ml. of water, and the solid removed and recrystallized from ethyl alcohol; a yield of 1.9 g (77%) of light colored solid was obtained; m.p. 96.5-98°. [Lit. (8), m.p. 97° yield 61%].

2-Morpholinolepidine monohydrochloride. A solution of 2.5 g. (0.0112 mole) of 2-bromolepidine in 5 ml. of morpholine was heated on the steam-bath for five hours, then cooled, diluted with 100 ml. of water, the oil extracted, dried, and the solvent removed by distillation. The residue was dissolved in 25 ml. of absolute ethyl alcohol and dry hydrogen chloride bubbled into the solution until no more precipitate formed. The yield of monohydrochloride was 3 g. (99%); it melted with decomposition at 250–255°. The substance may be recrystallized from absolute ethyl alcohol.

Anal. Calc'd for $C_{14}H_{17}ClNO_2$: Cl, 13.39. Found: Cl, 13.24.

Under identical conditions of reaction and isolation, 2 g. (0.0112 mole) of 2-chlorolepidine gave 2.35 g. (78%) yield of 2-morpholinolepidine monohydrochloride.

SUMMARY

The preparation of 2-bromolepidine, 2-bromo-6-methoxylepidine, 4-bromoquinaldine, ethyl 4-bromoquinaldate, and 4-bromoquinaldic acid has been described. A by-product formed during the preparation of 4-bromoquinaldine has been tentatively identified as 3,4-dibromoquinaldine. It has been shown

that 2-bromolepidine and 2-bromo-6-methoxylepidine react faster with morpholine and piperidine, respectively, than do the corresponding 2-chloro compounds.

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