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SUBSTITUTED PHENYLQUINOLINES[1]

C. E. KASLOW AND ROBERT M. SUMMERS[2]

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In the study of the nitration and halogenation of phenylquinolines, it is necessary to synthesize by independent methods the appropriately substituted phenylquinolines as reference compounds. This report deals with the preparation of some halogen substituted 7-phenylquinolines. These were synthesized from the properly substituted biphenyl.

4′-Chloro-3-nitrobiphenyl was prepared by the action of sulfuryl chloride, with aluminum chloride catalyst, upon *m*-nitrobiphenyl. Blakely and Scarborough (1) reported its preparation by the action of chlorine and either ferric chloride or iodine upon *m*-nitrobiphenyl; however no yield of the product was reported. In the present work it was found that the sulfuryl chloride method described in the experimental gave yields which were consistently 35–40%. Many methods of chlorination were tried. Chlorination of *m*-nitrobiphenyl in carbon tetrachloride using either iodine or iron as a catalyst yielded a maximum of 16% of 4′-chloro-3-nitrobiphenyl. When *m*-nitrobiphenyl was chlorinated at an elevated temperature, 70–75°, with chlorine gas and anhydrous aluminum chloride either in nitrobenzene solvent or without a solvent, the yield of the desired substance was 20–26% along with about 10% of *m*-chloronitrobenzene. Apparently cleavage of the biphenyl also occurred under these conditions. In control experiments on nitrobenzene, no *m*-chloronitrobenzene could be isolated.

Bromination of *m*-nitrobiphenyl in either carbon tetrachloride or carbon disulfide, with aluminum chloride-iron catalyst, gave 70–78% yields of 4′-bromo-3-nitrobiphenyl. Either catalyst by itself was not as effective as when both were used. It has been reported (1) that a quantitative yield is obtained by the addition of bromine to a mixture of ferric chloride and *m*-nitrobiphenyl.

2-Chloro-3′-nitrobiphenyl was obtained in 10–12% yield by the decomposition of *m*-nitrobenzenediazo hydroxide in chlorobenzene. The structure of the substance was proven by reduction to 2-chloro-3′-aminobiphenyl and subsequent oxidation of this substance. The only product isolated was *o*-chlorobenzoic acid. 4′-Chloro-3-nitrobiphenyl was also shown to be present among the coupling products from the decomposition of the diazohydroxide in chlorobenzene.

Since the 7-phenyl-4-hydroxyquinolines were also desired, the quinoline syntheses were carried out through the well known Conrad-Limpach (2) method as well as by the Skraup reaction. Condensation of the substituted aminobiphenyls with ethyl ethoxalylacetate was accomplished without difficulty. Ring closure of the crude ethyl β-carbethoxy-β-biphenylaminoacrylate in Dowtherm

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[1] Abstracted from a portion of a thesis submitted to the faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

[2] Present address: The B. F. Goodrich Research Center, Brecksville, Ohio.

A at 250° gave a high yield, in all instances, of the aryl-4-hydroxyquinaldic ester. Only one substance was isolated in these cases. Ring closure could give either the 5- or 7-aryl compound. In the case of *m*-aminobiphenyl, the substance was shown to be ethyl 7-phenyl-4-hydroxyquinaldate. The ester from ring closure was saponified, then the phenyl-4-hydroxyquinaldic acid was decarboxylated and by treatment with phosphoryl trichloride, the 4-hydroxy compound was converted to phenyl-4-chloroquinoline. Catalytic hydrogenolysis of the latter substance yielded a phenylquinoline which melted at 57–58°. Since 5-phenylquinoline is reported (3) to melt at 82–83°, this substance had to be the isomeric 7-phenylquinoline. The Skraup reaction on *m*-aminobiphenyl gave only one substance, in 22% yield, which was the same phenylquinoline as was obtained from the Conrad-Limpach method. The formation of the 7-substituted quinoline in this instance is in line with a study reported by Bradford, Elliot and Rowe (4).

The reactions invoved in getting to the 7-aryl-4-chloroquinolines went smoothly but the hydrogenolysis of the 4-chloroquinolines gave some trouble. When the reduction was carried on in glacial acetic acid, there was considerable conversion to the 4-hydroxyquinolines (5). With methyl or ethyl alcohol as the solvent, the 7-arylquinoline obtained was difficult to purify. Except for the substances described in the experimental, the results are summarized in Table I.

EXPERIMENTAL

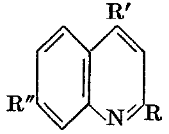
3-Nitro-4'-chlorobiphenyl. To a solution of 20 g. (0.1 mole) of 3-nitrobiphenyl (6) in 200 ml. of carbon tetrachloride contained in a 500-ml. three-necked flask equipped with a stirrer, condenser, thermometer, and a dropping-funnel, was added 0.5 g. of anhydrous aluminum chloride and 0.1 g. of sulfur. The reaction mixture was warmed slowly and 14.2 g. (0.105 mole) of sulfuryl chloride was added during a one-half hour period. During this time, two 0.3-g. portions of anhydrous aluminum chloride were added. The evolution of a gas became noticeable at 55°. The temperature was maintained at 55–60° for six hours; then the mixture was refluxed for 30 minutes. Water (100 ml.) was added and the organic layer was extracted with 100 ml. of 1.5 *N* sulfuric acid, then with two 100-ml. portions of 1.5 *N* sodium hydroxide, followed by drying over magnesium sulfate. After removal of the solvent, the residue was vacuum-distilled. The fraction which distilled at 138–144° (0.2 mm.) was collected. The semi-solid material (19 g.) was recrystallized from 90% methyl alcohol. The yield of light yellow needles was 9 g. (38%), m.p. 90–91.5°. The melting point reported (1) previously for this substance was 89°.

2-Chloro-3'-nitrobiphenyl. *m*-Nitroaniline (142 g., 1.03 moles) was heated on a steam-bath with 500 ml. of 25% hydrochloric acid in a 5-l. flask until most of the solid was dissolved, then it was cooled rapidly and diazotized at 3–7° with a solution of 72 g. (1.04 moles) of sodium nitrite in 125 ml. of water. Chlorobenzene (3.3 l.) was added to the cold diazonium salt solution. The solution was stirred vigorously and maintained at 2–4° while a solution of 465 g. (2.7 moles) of sodium acetate trihydrate in 400 ml. of water was added over a two-hour period. After an additional two hours, the solution was allowed to warm to room temperature and the stirring was continued for two days. The chlorobenzene layer was separated and dried over potassium carbonate. After removal of most of the chlorobenzene by distillation, the residue was vacuum-distilled at 0.2–0.5 mm. The liquid was redistilled at 0.25 mm., yielding 55 g. (27%) of a light yellow oil, b.p. 145–150°. The oil congealed to a solid, m.p. 46–53°, after standing for a day. The substance was recrystallized once from hexane and three times from methyl alcohol to give white needles, m.p. 64.6–65.2° (10% yield).

Anal. Calc'd for $C_{12}H_8ClNO_2$: N, 5.99. Found: N, 5.77.

TABLE I

SUBSTITUTED PHENYL QUINOLINES,



R″	R′	R	Yield, %	M.P., °C.	Solvent	Formula	Analysis			
							Calc'd		Found	
							Hal.	N	Hal.	N
7-C_6H_5	OH	$CO_2C_2H_5$	58	206.5–208	[a]	$C_{18}H_{15}NO_3$		4.78		5.01
7-(4′-ClC_6H_4)-	OH	$CO_2C_2H_5$	75	263–264	[a]	$C_{18}H_{14}ClNO_3$	10.84		11.17	
7-(4′-BrC_6H_4)-	OH	$CO_2C_2H_5$	83	262–264	[a]	$C_{18}H_{14}BrNO_3$	21.50		21.19	
7-C_6H_5-	OH	CO_2H	94	262 (dec.)	[b]	$C_{16}H_{11}NO_3$		5.28		5.28
7-(4′-ClC_6H_4)-	OH	CO_2H	99	275 (dec.)	[b]	$C_{16}H_{10}ClNO_3$	11.85		11.72	
7-(4′-BrC_6H_4)-	OH	CO_2H	100	279 (dec.)	[b]	$C_{16}H_{10}BrNO_3$	23.25		23.64	
7-C_6H_5-	OH	H	66	267–268	[c]	$C_{15}H_{11}NO$		6.34		6.42
7-(4′-ClC_6H_4)-	OH	H	100	293–295	[a]	$C_{15}H_{10}ClNO$	13.89		14.05	
7-(4′-BrC_6H_4)-	OH	H	98	295–298	[a]	$C_{15}H_{10}BrNO$	26.66		26.55	
7-C_6H_5-[g]	Cl	H	94	89.8–90.2	[f]	$C_{15}H_{10}ClN$		5.84		5.89
7-(4′-ClC_6H_4)-	Cl	H	88	130–131	[f]	$C_{15}H_9Cl_2N$	25.91		26.02	
7-(4′-BrC_6H_4)-	Cl	H	82	134–135	[a]	$C_{15}H_9BrClN$	36.26		36.00	
6-C_6H_5-[h]	Cl	H	84	90–90.5	[f]	$C_{15}H_{10}ClN$	14.82	5.84	14.65	6.07
7-C_6H_5-[i]	H	H	31	57–58	[d]	$C_{15}H_{11}N$		6.83		7.01
7-(4′-ClC_6H_4)-	H	H	63	99–100	[e]	$C_{15}H_{10}ClN$	14.82		14.87	
7-(4′-BrC_6H_4)-	H	H	41	106.5–107.5	[e]	$C_{15}H_{10}BrN$	28.20		28.03	

[a] 95% Ethyl alcohol. [b] Purification by solution in dilute NaOH or Na_2CO_3 and precipitation of the carboxylic acid by the addition of hydrochloric acid to the hot solution. [c] Pyridine. [d] Ligroin, b.p. 30–60°. [e] Ligroin, b.p. 65–75°. [f] 50–70% Ethyl alcohol. [g] Picrate, m.p. 199–200°. *Anal.* Calc'd for $C_{21}H_{13}ClN_4O_7$: N, 11.95. Found: N, 11.40. [h] Picrate, m.p. 206–207.3°. *Anal.* Calc'd for $C_{21}H_{13}ClN_4O_7$: N, 11.95. Found: N, 12.40. [i] Picrate, m.p. 212.3–213°. *Anal.* Calc'd for $C_{21}H_{14}N_4O_7$: N, 12.93. Found: N, 12.99.

2-Chloro-3′-aminobiphenyl. A solution of 10 g. (0.043 mole) of a 2-chloro-3′-nitrobiphenyl in 100 ml. of absolute ethyl alcohol and 0.2 g. of Adams platinum catalyst was hydrogenated in a Parr apparatus at an initial hydrogen pressure of 45 p.s.i. After the hydrogenation was complete, the catalyst was removed and the solvent was distilled. The residual oil congealed to a white crystalline mass. The substance was recrystallized from ligroin (b.p. 35–60°) to yield 7.8 g. (90%) of white needles, m.p. 47–48°.

Anal. Calc'd for $C_{12}H_{10}ClN$: N, 6.88. Found: N, 6.77.

Acetylation of the amine in the customary way gave 2-chloro-3′-acetamidobiphenyl, m.p. 123–124°, after recrystallization from 50% ethyl alcohol.

Anal. Calc'd for $C_{14}H_{12}ClNO$: N, 5.71. Found: N, 5.82.

2-Chloro-3′-aminobiphenyl hydrochloride, m.p. 253–256° (sealed tube), was obtained as white plates by recrystallization from dilute hydrochloric acid.

Anal. Calc'd for $[C_{12}H_{11}ClN]^+Cl^-$: Cl^-, 14.79. Found: Cl^-, 14.85.

Structure proof for 2-chloro-3′-aminobiphenyl. The amine (0.72 g.) was refluxed for 45 minutes with 2.7 g. of potassium permanganate in 70 ml. of water. The solution was acidified with sulfuric acid, the manganese dioxide reduced with sodium bisulfite, and the cold solution was extracted with benzene. The benzene solution was extracted next with 20 ml. of 5% sodium hydroxide solution and the solution was acidified with hydrochloric acid. The white solid was removed and recrystallized from 4 ml. of hot water. A yield of 34 mg. of white needles, m.p. 138–138.5°, was obtained. A mixture melting point with an authentic sample of *o*-chlorobenzoic acid gave no depression, m.p. 138–139°.

3-Aminobiphenyl, 4′-chloro-2-aminobiphenyl, and 4′-bromo-3-aminobiphenyl were prepared from the corresponding nitrobiphenyls by catalytic reduction in the same way as described for 2-chloro-3′-aminobiphenyl. The melting points of the amines were the same as reported by Blakely and Scarborough (1).

Ethyl 4-hydroxy-6-(2′-chlorophenyl)quinaldate. A solution of 10 g. (0.049 mole) of 2-chloro-3′-aminobiphenyl, 3 drops of 3 *N* sulfuric acid, and 9.4 g. (0.050 mole) of ethyl ethoxalylacetate in 150 ml. of chloroform in a 500-ml. round-bottom flask surmounted with a water separator, was refluxed until no further quantity of water could be collected. The chloroform was removed by distillation; the last of the solvent was removed in a vacuum, leaving a clear yellow oil. The crude ethyl β-carbethoxy-β-[3-(2′-chlorophenyl)anilino]acrylate was added slowly to 300 ml. of boiling Dowtherm A contained in a 1-l. round-bottom flask to which a condenser was attached for condensation of the ethyl alcohol distilled from the reaction mixture. The heating was continued until there was no further distillation of alcohol. After the solution cooled to room temperature, it was diluted with 50 ml. of ligroin (b.p. 30–60°), and the yellow crystalline mass was removed by filtration, washed with two 100-ml. portions of ligroin, and finally was digested in 100 ml. of refluxing ligroin. The yield of slightly yellow solid was 10.8 g. (66%), m.p. 225–227°. The melting point was raised to 230–231° by recrystallization from 95% ethyl alcohol.

Anal. Calc'd for $C_{18}H_{14}ClNO_3$: Cl, 10.84. Found: Cl, 10.94.

4-Hydroxy-7-(2′-chlorophenyl)quinaldic acid. The ester (9.5 g., 0.029 mole) was refluxed for one hour with 200 ml. of 5% sodium hydroxide, the solution was diluted to one liter, and then was treated with Norit and filtered while hot. Upon acidification of the hot solution, followed by filtration and drying of the white solid, a yield of 8.3 g. (95%) was obtained; m.p. 262–263° (dec.). The melting point could not be changed by further attempts at purification.

Anal. Calc'd for $C_{16}H_{10}ClNO_3$: C, 64.11; H, 3.36.
Found: C, 64.47; H, 3.67.

4-Hydroxy-7-(2′-chlorophenyl)quinoline. Diphenyl ether (125 ml.) was heated to 230° in a 500-ml. round bottom flask and 7.5 g. (0.025 mole) of the above quinaldic acid was added. The solution was heated slowly to 250°, when gradual solution and decarboxylation occurred. After there was no further evolution of carbon dioxide, the solution was allowed to cool, then 30 ml. of ligroin (b.p. 30–60°) was added and the slightly gray-colored solid was collected. The solid was washed with ligroin then digested by refluxing with 35 ml. of ligroin.

The yield was 6.4 g. (100%), m.p. 224–226°. The melting point was raised to 225.5–226.5° by recrystallization from ethyl alcohol.

Anal. Calc'd for $C_{15}H_{10}ClNO$: Cl, 13.89. Found: Cl, 14.07.

4-Chloro-7-(2'-chlorophenyl)quinoline. A mixture of 5.5 g. (0.02 mole) of the corresponding 4-hydroxyquinoline and 60 ml. of phosphoryl trichloride was warmed gently, then refluxed for one hour. About two-thirds of the phosphoryl trichloride was removed by distillation and the residual warm solution was poured onto 400 g. of ice. The solid was pulverized and the solution was neutralized with concentrated ammonia water; ice was added to keep the solution cold. After the solid was removed and washed with three 100-ml. portions of water, it was recrystallized, with decolorizing charcoal treatment from 120 ml. of 75% ethyl alcohol. The yield of slightly pink-colored needles was 4.9 g. (83%). The substance melted at 94.3–95°, resolidified and melted again at 102.5–103°. Recrystallization of the substance from the dilute alcohol elevated the melting point to 94.8–95.5°, then the liquid crystallized and it melted again at 103–103.6°.

Anal. Calc'd for $C_{15}H_9Cl_2N$: C, 65.68; H, 3.31.

Found: C, 66.14; H, 3.32.

The *picrate* of 4-chloro-7-(2'-chlorophenyl)quinoline was prepared in the customary way and it was recrystallized from ethyl alcohol. The yellow silky needles melted at 167–169°.

Anal. Calc'd for $C_{21}H_{12}Cl_2N_4O_7$: N, 11.13. Found: N, 10.64.

7-(2'-Chlorophenyl)quinoline. A solution of 2.2 g. (0.008 mole) of 4-chloro-7-(2'-chlorophenyl)quinoline in 60 ml. of absolute methyl alcohol with 0.82 g. of anhydrous sodium acetate and 0.2 g. of 5% palladium-charcoal was hydrogenated in a Parr apparatus at an initial hydrogen pressure of 45 p.s.i. After there was no further absorption of hydrogen, the catalyst was removed and the solvent was distilled in a vacuum. The residual liquid was distilled at 0.02 mm. pressure. The yield was 1.3 g. (68%).

Anal. Calc'd for $C_{15}H_{10}ClN$: Cl, 14.82. Found: Cl, 14.57.

SUMMARY

The preparation of 7-phenylquinoline and several substituted 7-phenylquinolines have been described. Starting from 3-aminobiphenyl, 4'-chloro-3-aminobiphenyl, 4'-bromo-3-aminobiphenyl, and 2-chloro-3'-aminobiphenyl, respectively, these amines were condensed with ethyl ethoxalylacetate, then the aminoacrylates were subjected to the Conrad-Limpach ring closure to give the 7-aryl-4-hydroxyquinaldic esters. The esters were converted to the quinaldic acids which, in turn, were decarboxylated to the 7-aryl-4-hydroxyquinolines. Treatment of the 4-hydroxyquinolines with phosphoryl trichloride gave the 4-chloro compounds which were converted by hydrogenolysis to the 7-arylquinolines.

An improved method for the preparation of 4'-chloro-3-nitrobiphenyl is described. The formation 2-chloro-3'-nitrobiphenyl by the diazohydroxide method is also reported.

BLOOMINGTON, INDIANA

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