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SUBSTITUTED QUINOLINES[1]

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The 6-arylmethyl substituted quinolines and the corresponding 4-hydroxy derivatives were desired for a study of substitution reactions of the side chain aryl groups in quinoline. Neither 6-benzyl- nor 6-triphenylmethyl-quinoline have been reported. However, the use of the Skraup reaction for the preparation of 6-benzhydrylquinoline has been reported (1). Also in a study of the Skraup reaction on *p*-aminoacetophenone, it was stated (2) that *p*-aminobenzophenone was converted successfully to 6-benzoylquinoline, but no data was given for either the reaction or the substance. Recently, the preparation of 6-benzoylquinoline has been reported (3).

Since the corresponding 4-hydroxy quinolines were also desired, these were prepared through a Conrad-Limpach ring closure method. The identity of these substances were proven by conversion to the quinoline prepared by a Skraup reaction.

The condensation of ethyl ethoxalylacetate with the appropriately *para*-substituted aniline offered no particular difficulties. In the case of *p*-triphenylmethylaniline, it was necessary to use only chloroform as a solvent instead of methylene chloride in order to attain a higher reaction temperature. The intermediate ethyl β-arylamino-β-carbethoxyacrylates were solids in the cases of the *p*-benzoyl and the *p*-triphenylmethyl compounds. Ring closure was carried out most satisfactorily in boiling diphenyl ether but it could be accomplished also in Arochlor at 270–280°. Dibutyl phthalate, which has been used satisfactorily in some instances (4), was of no value in these cases. Saponification of the 6-substituted 4-hydroxyquinaldates proceeded smoothly except in the case of 6-triphenylmethyl-4-hydroxyquinaldic acid ester. The sodium salt of the carboxylic acid was not very soluble in hot 5–10% alkali. It was necessary to use 2% sodium hydroxide solution in the saponification. Coprecipitation of the sodium salt also occurred when the alkaline solution was poured into dilute hydrochloric acid, so that it was necessary to digest the hot solution for a long time. Decarboxylation of the substituted quinaldic acids occurred readily either in boiling diphenyl ether or in Arochlor at about 270–280°.

The conversion of the 4-hydroxyquinolines to the 4-chloro compounds offered no difficulties except in the case of 6-triphenylmethyl-4-hydroxyquinoline. In the latter instance, the chloro compound hydrolysed quite readily to give the starting 4-hydroxyquinoline. Removal of the chlorine atom by catalytic hydrogenation gave some trouble in the case of the 6-benzoyl- and the 6-tri-

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phenylmethyl-4-chloroquinoline since considerable acetolysis (5) to the 4-hydroxy compound occurred. This could be recovered from the spent palladium catalyst by extraction with boiling acetic acid.

Purification of the substituted quinolines offered no difficulties except in the case of 6-benzoylquinoline. The substance prepared either by the Skraup reaction or by the Conrad-Limpach method gave a product which, after a crystallization, melted about 40–43° as reported (3) previously. However, when the material was recrystallized persistently and also distilled in a vacuum, the melting point could be raised finally to 59–60° but this entailed quite a loss of material. Other methods for the preparation of 6-benzoylquinoline were more successful. A Friedel-Crafts reaction between benzene and 6-quinolinecarbonyl chloride gave a 26% yield of the purified material. Also, an oxidation of 6-benzylquinoline was carried out using potassium dichromate in dilute sulfuric acid to give a 76% yield of pure 6-benzoylquinoline. The over-all yield from *p*-aminodiphenylmethane is 36% since a Skraup reaction on the latter substance gave a 48% yield of 6-benzylquinoline. The picrate (m.p. 217–218°) and the oxime (m.p. 213–214°) of 6-benzoylquinoline melted somewhat higher than the values previously reported (3).

The reduction of 6-benzoylquinoline with lithium aluminum hydride gave a 74% yield of phenyl-6-quinolylmethanol. The same substance was obtained in a 70% yield by the reaction between phenylmagnesium bromide and 6-quinolinealdehyde.

The aromatic amines, *p*-benzhydrylaniline (6) and *p*-triphenylmethylaniline (7), were prepared according to published methods.

Since the procedure and reaction conditions for the preparation of the other 6-substituted quinolines are analogous to the series for 6-benzylquinoline, they are summarized in Table I.

EXPERIMENTAL[3]

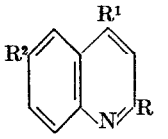
p-Aminodiphenylmethane was prepared by the catalytic hydrogenation of *p*-nitrodiphenylmethane which was obtained by a Friedel-Crafts reaction (8) from *p*-nitrobenzyl chloride. Ethyl ethoxalylacetate was obtained from commercial ethyl sodioethoxalylacetate essentially according to the procedure of Surrey and Hammer (9).

Ethyl 6-benzyl-4-hydroxyquinaldate. A solution of 18.4 g. (0.1 mole) of *p*-aminodiphenylmethane and 21.5 g. (0.11 mole) of ethyl ethoxalylacetate and a drop of dilute hydrochloric acid in 250 ml. of either chloroform or methylene chloride was refluxed under a condenser surmounted on a water-trap for use with heavier-than-water liquids. After no further quantity of water was collected, most of the solvent was removed by distillation and the residual portion was removed in a vacuum. The oily crude ethyl β-carbethoxy-β-(*p*-benzylanilino)acrylate was dissolved in 35 ml. of diphenyl ether and this was allowed to drip into 150 ml. of boiling diphenyl ether. After the ring closure reaction was complete as shown by the amount of ethyl alcohol distillate collected, the solution was allowed to cool, then 50 ml. of ligroin was added and the solid was removed by filtration. After washing and digestion with boiling petroleum ether, a yield of 23.5 g. (81%) of a grey shiny crystalline solid was obtained which melted at 206–209°. After recrystallization from ethyl alcohol, the melting point was raised to 212–213°.

[3] Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois and by Miss Joanna Dickey of the Chemistry Department, Indiana University.

TABLE I

SUBSTITUTED QUINOLINES



R²	R¹	R	M.P., °C.	YIELD, %	EMPIRICAL FORMULA	ANALYSES					
						Calc'd			Found		
						C	H	N	C	H	N
C_6H_5CO	OH	$CO_2C_2H_5$	225–226	82[a]	$C_{19}H_{15}NO_4$	71.03	4.70	4.60	70.17	4.62	4.76
C_6H_5CO	OH	CO_2H	245–246	96[b, c]	$C_{17}H_{11}NO_4$	69.63	3.79		69.61	3.91	
C_6H_5CO	OH	H	244–245	95[a]	$C_{16}H_{11}NO_2$	77.09	4.46		77.23	4.68	
C_6H_5CO	Cl	H	116–117	86[d]	$C_{16}H_{10}ClNO$			5.23			5.37
$(C_6H_5)_2CH$	OH	$CO_2C_2H_5$	198–199	41[a]	$C_{25}H_{23}NO_3$			3.65			3.94
$(C_6H_5)_2CH$	OH	CO_2H	258–259	96[a, c]	$C_{23}H_{19}NO_3$			3.95			4.09
$(C_6H_5)_2CH$	OH	H	216–217	92[e]	$C_{22}H_{19}NO$	84.89	5.50		84.70	5.60	
$(C_6H_5)_2CH$	Cl	H	129–130	71[e]	$C_{22}H_{18}ClN$	80.12	4.88		80.37	5.11	
$(C_6H_5)_2CH$	H	H	102–103[f]	70[g]	$C_{22}H_{19}N$	89.49	5.79		89.48	6.11	
$(C_6H_5)_3C$	OH	$CO_2C_2H_5$	263–264	80[a, b]	$C_{31}H_{25}NO_3$	81.05	5.49		81.59	5.63	
$(C_6H_5)_3C$	OH	CO_2H	258–259	97[c]	$C_{29}H_{21}NO_3$	80.79	4.92		80.43	5.07	
$(C_6H_5)_3C$	OH	H	306–308	95[b]	$C_{28}H_{21}NO$	86.82	5.48		86.75	5.60	
$(C_6H_5)_3C$	Cl	H	187–188	81[a]	$C_{28}H_{20}ClN$	82.86	4.96		83.18	5.32	
$(C_6H_5)_3C$	H	H	182–183	45[a]	$C_{28}H_{21}N$			3.77			3.66

[a] Recrystallized from ethyl alcohol. [b] Recrystallized from Cellosolve (2-ethoxyethanol). [c] Purified by solution in dilute sodium hydroxide and reprecipitation in dilute hydrochloric acid. [d] Recrystallized from dilute ethyl alcohol. [e] Recrystallized from methyl alcohol. [f] Fischer and Frankel (1) reported a melting point of 103–104°. [g] Recrystallized from ligroin.

Anal. Calc'd for $C_{19}H_{17}NO_3$: N, 4.56. Found: N, 4.73.

6-Benzyl-4-hydroxyquinoline. A mixture of 23 g. (0.083 mole) of ethyl 6-benzyl-4-hydroxyquinaldate was refluxed with 125 ml. of 5% sodium hydroxide solution until the solid was dissolved, then treated with Nuchar, filtered, and the filtrate poured into an excess of 6 *N* hydrochloric acid. After the mixture was digested on a hot plate, the solid was removed by filtration, washed, and dried. The yield of 6-benzyl-4-hydroxyquinaldic acid was 21.2 g., m.p. 239–241°. After recrystallization from ethyl alcohol and Cellosolve,[4] the substance melted at 243–244°.

Anal. Calc'd for $C_{17}H_{13}NO_3$: N, 5.02. Found: N, 4.91.

Ten g. (0.036 mole) of the carboxylic acid was added over a four-minute period to 50 ml. of Arochlor preheated to 290°. After maintaining this temperature for five minutes, the solution was cooled and 100 ml. of petroleum ether was added. The solid was removed, washed, and recrystallized from 60 ml. of ethyl alcohol. The yield of 6-benzyl-4-hydroxyquinoline was 8.4 g., m.p. 221–224°. Further recrystallization from ethyl alcohol raised the melting point to 225–226°.

Anal. Calc'd for $C_{16}H_{13}NO$: N, 5.92. Found: N, 5.95.

6-Benzyl-4-chloroquinoline. Phosphoryl trichloride (12 ml.) was added cautiously to 9.4 g. (0.04 mole) of 6-benzyl-4-hydroxyquinoline and the mixture was heated until the solid dissolved. The warm solution was poured onto 300 g. of cracked ice, stirred, and concentrated ammonium hydroxide was added carefully. Ice was added to keep the solution cold. After the solution remained alkaline, the solid was extracted with ether, dried, and the ether was removed by distillation. The residue was distilled at 1 mm. pressure, yielding 9.5 g. of 6-benzyl-4-chloroquinoline which came over at 160–162°. The liquid crystallized to a white solid, m.p. 43–44°.

Anal. Calc'd for $C_{16}H_{12}ClN$: N, 5.52. Found: N, 5.58.

6-Benzylquinoline. A. Reduction of 6-benzyl-4-chloroquinoline. A solution of 16.3 g. (0.065 mole) of 6-benzyl-4-chloroquinoline in 150 ml. of glacial acetic acid containing 5.3 g. of sodium acetate and 2 g. of 5% palladium-Nuchar catalyst (10) was shaken with hydrogen at 45 pounds pressure until there was no further pressure drop. After the catalyst was removed, the acetic acid was removed in a vacuum, and the residue was made slightly alkaline, then extracted with ether and dried. After removal of the ether, the residue was distilled in a vacuum. The yield was 11.7 g. (83%), b.p. 139–142° (1 mm.). The liquid congealed to a white solid, m.p. 79–80°.

Anal. Calc'd for $C_{16}H_{13}N$: N, 6.39. Found: N, 6.36.

B. Skraup Reaction. A mixture of 4 g. of ferrous sulfate, 11.5 g. of boric acid, 23.5 g. (0.13 mole) of *p*-aminodiphenylmethane, 20 g. of *o*-nitrophenol, and 46 g. of glycerol was stirred and heated to 105–107°, then 30 ml. of concentrated sulfuric acid was added over a period of 8–10 minutes. The temperature was maintained at 145–155°. As refluxing continued, the temperature dropped to 138–142°. After one hour at this temperature, the *o*-nitrophenol was removed by steam-distillation and the volume was brought to about 250 ml. The solution was cooled to a −5–0°, and treated with sodium nitrite until a starch-iodide test was positive. After heating the solution on a steam-bath for 45 minutes, it was made alkaline with a 20% sodium hydroxide solution and extracted carefully with three 500-ml. portions of benzene. The benzene was removed by distillation and the residue was extracted with four 200-ml. portions of boiling ligroin. After concentration of the ligroin solution and recrystallization of the 6-benzylquinoline, a yield of 13.8 g. (48%) of tan-colored solid, m.p. 77–79°, was obtained.

6-Benzylquinolinium picrate. A saturated alcoholic solution of picric acid was added to a solution 0.35 g. of 6-benzylquinoline in alcohol. The yellow precipitate was removed and recrystallized alternately from ethyl alcohol and from benzene; m.p. 207–208°.

Anal. Calc'd for $C_{22}H_{16}N_4O_7$: N, 12.50. Found: N, 12.21.

6-Benzoylquinoline. A. Catalytic reduction of 6-benzoyl-4-chloroquinoline. This was

[4] 2-Ethoxyethanol.

carried out exactly like the reduction of 6-benzyl-4-chloroquinoline. An 84% yield of crude 6-benzoylquinoline, m.p. 38–41°, was obtained. The melting point was raised gradually to 57–59° by recrystallization from dilute ethyl alcohol and from ligroin.

B. Skraup reaction. A 63% yield of crude 6-benzoylquinoline, m.p. 36–40°, was obtained by using the procedure reported previously (3). Only through repeated recrystallizations and vacuum-distillation was the melting point raised to 56–58°. Oxidative treatment of crude 6-benzoylquinoline in refluxing 50% acetic acid solution containing chromic acid gave a 50% recovery of the ketone which after one recrystallization from ligroin, melted at 59–60°.

C. Friedel-Crafts reaction. Thionyl chloride (35 ml.) was added to a suspension of 20 g. (0.11 mole) of 6-quinolinecarboxylic acid (11) in 50 ml. of nitrobenzene and this was warmed for 15–20 minutes. After removal of the thionyl chloride in a vacuum, 50 ml. of benzene was added, then this was removed in a vacuum, and the process was repeated with another 50-ml. portion of benzene. An additional 50 ml. of benzene and 25 ml. of nitrobenzene were added, the solution was cooled to 0–5°, and 50 g. of anhydrous aluminum chloride was added. After stirring at 0–5° for three hours, it was allowed to stand at room temperature with intermittent stirring for 10 hours, then heated with stirring at 60° for about 20 hours. The mixture was treated cautiously with about 50 ml. of water, then 50 ml. of concentrated hydrochloric acid was added. The mixture was steam-distilled to remove the benzene and nitrobenzene. The liquid remaining was made strongly alkaline with 40% sodium hydroxide and was extracted with benzene. After the benzene was removed by distillation, a semisolid residue weighing 11 g. remained. Recrystallization of this material from dilute ethyl alcohol and from ligroin gave a 7 g. (26%) yield, m.p. 59–60°. There was no depression of melting point with the previously prepared 6-benzoylquinoline.

D. Oxidation of 6-benzylquinoline. 6-Benzylquinoline (2 g.) was heated on a steam-bath for 2.5 hours with a solution of 7 g. of potassium dichromate in 70 ml. of 30% sulfuric acid. The solution was made strongly alkaline with 20% sodium hydroxide, extracted with ether, dried, and the ether was removed. The residue was recrystallized from dilute alcohol, yielding 1.6 g. of solid, m.p. 59–60°. There was no depression of melting point with 6-benzyolquinoline prepared by other methods.

Phenyl-6-quinolylcarbinol. A. Grignard method. To the Grignard reagent prepared from 1 g. (0.041 mole) of magnesium and 6.3 g. (0.041 mole) of bromobenzene in 50 ml. of absolute ether was added over a period of six minutes, a solution of 3.25 g. (0.021 mole) of 6-quinolinealdehyde (12) in 50 ml. of benzene. The mixture was refluxed for one hour then poured onto 70–100 g. of ice and 4.5 g. of ammonium chloride. The ether layer was removed, washed, and extracted with dilute hydrochloric acid. After neutralizing the cold aqueous layer, the solid was removed, dried and recrystallized twice from 50-ml. portions of benzene. The yield of white fluffy needle clusters was 3.4 g. (70%), m.p. 122–123°. The substance could be recrystallized also from aqueous ethyl alcohol and from ligroin.

Anal. Calc'd for $C_{16}H_{13}NO$: N, 5.95. Found: N, 5.86.

Phenyl-6-quinolylcarbinol picrate. This was prepared in the customary manner in ethyl alcohol; m.p. 183–183.5°.

Anal. Calc'd for $C_{22}H_{16}N_4O_8$: N, 12.10. Found: N, 12.09.

B. Lithium aluminum hydride reduction of 6-benzoylquinoline. One gram (0.026 mole) of lithium aluminum hydride was refluxed with 50 ml. of anhydrous ether until most of the solid was dissolved. The solution was cooled and a solution of 2.7 g. (0.012 mole) of 6-benzoylquinoline in 50 ml. of absolute ether added dropwise while the solution was stirred. After standing for 20–30 minutes, the solution was treated carefully with 1 ml. of water, then 1.5 ml. of 20% sodium hydroxide, and finally with 10 ml. of water. After separation of the ether layer, it was washed with water, dried, and the ether was removed. The solid was recrystallized from benzene, yielding 2 g. of white needle clusters which melted at 122–123°. There was no depression of melting point when mixed with the phenyl-6-quinolylcarbinol prepared from 6-quinolinealdehyde.

Ethyl β-(p-benzoylanilino)-β-carbethoxyacrylate. This substance was prepared by the condensation of *p*-aminobenzophenone and ethyl ethoxalylacetate in a manner similar to that for the corresponding *p*-benzylanilino compound. The yield of crude material recrystallized once from ligroin was 94%. Further recrystallization gave bright yellow needles, m.p. 82–83°.

Anal. Calc'd for $C_{21}H_{21}NO_5$:C, 68.66; H, 5.77.
Found: C, 68.71; H, 5.82.

Ethyl β-(p-triphenylmethylanilino)-β-carbethoxyacrylate. This substance was prepared from *p*-triphenylmethylaniline and ethyl ethoxalylacetate by the method described above. The crude substance was recrystallized from ligroin to give an 86% yield of white needles, m.p. 140–141.5°. Further recrystallization raised the melting point to 142–143°.

Anal. Calc'd for $C_{33}H_{31}NO_4$: C, 78.41; H, 6.17.
Found: C, 78.41; H, 6.20.

SUMMARY

The preparation of 6-benzylquinoline by the Skraup reaction has been described as well as the synthesis through the series of reactions starting with a Conrad-Limpach ring closure of ethyl β-(*p*-benzylanilino)-β-carbethoxyacrylate to ethyl 6-benzyl-4-hydroxyquinaldate and conversion of this through saponification and decarboxylation to 6-benzyl-4-hydroxyquinoline. This was, in turn, converted to 6-benzyl-4-chloroquinoline and the chlorine was removed by hydrogenolysis.

6-Benzoyl-4-chloroquinoline, 6-(benzydryl)-4-chloroquinoline, and 6-(triphenylmethyl)-4-chloroquinoline were also prepared by the same method starting from a Conrad-Limpach ring closure of the corresponding β-anilino-β-carbethoxyacrylate.

6-Benzoylquinoline was prepared also by a Friedel-Crafts reaction between 6-quinolinecarbonyl chloride and benzene as well as by oxidation of 6-benzylquinoline. Lithium aluminum hydride reduction of 6-benzoylquinoline gave phenyl-6-quinolylmethanol. This substance was also formed by a Grignard reaction using 6-quinolinealdehyde.

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REFERENCES

(1) FISCHER AND FRANKEL, *Ber.*, **19**, 749 (1886).
(2) BEREND AND THOMAS, *Ber.*, **25**, 2548 (1892).
(3) KASLOW, GENZER, AND GOODSPEED, *Proc. Indiana Acad. Sci.*, **59**, 134 (1950).
(4) WILLIAMS, M. A. Thesis, Indiana University, 1947.
(5) CUTLER AND SURREY, *J. Am. Chem. Soc.*, **72**, 3394 (1950).
(6) FISCHER AND ROSER, *Ber.*, **24**, 728 (1891).
(7) WITTEN AND REID, *Org. Syntheses*, **30**, 5 (1950).
(8) GABRIEL AND STELZNER, *Ber.*, **29**, 1303 (1896).
(9) SURREY AND HAMMER, *J. Am. Chem. Soc.*, **68**, 113 (1946).
(10) MOZINGO, *Org. Syntheses*, **26**, 77 (1946).
(11) WALEY, *J. Chem. Soc.*, 2008 (1948).
(12) RODIONOV AND BERKENHEIM, *Chem. Abstr.*, **39**, 4077 (1945).