ACTA CHEMICA SCANDINAVICA 22 (1968) 2422–2428

Preparation of Quinolyl-3-acetic Acids

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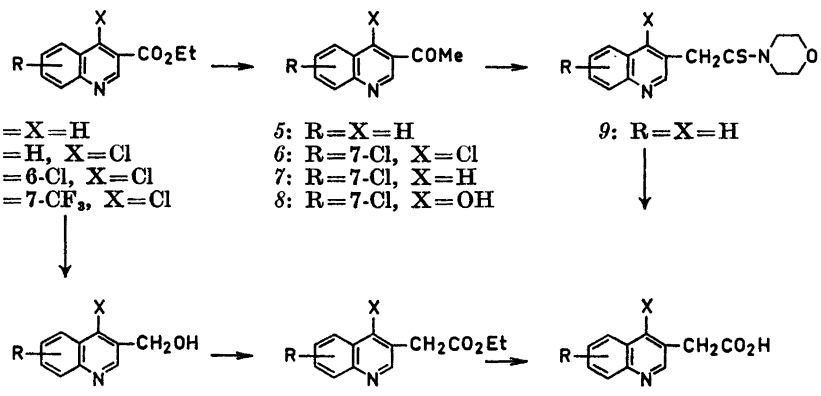
The syntheses of quinolyl-3-acetic acids carrying substituents as chlorine, hydroxyl, or trifluoromethyl in the quinoline nucleus are described. An alternative to the known synthesis of quinolyl-3-acetic acid is given.

Only few quinolylacetic acids have up to now been reported in the literature. The syntheses of quinolyl-2- and 4-acetic acid have been described.[1] Both acids, however, are unstable and decarboxylate forming quinaldine and lepidine, respectively. Quinolyl-6-acetic acid has been synthesized in a Skraup synthesis [2] as well as 8-bromoquinolyl-6-acetic acid.[3] Quinolyl-3-acetic acid (*22*) in the form of its ethyl ester has been prepared from quinolyl-3-carbethoxylate (*1*) *via* the 3-acetyl derivative *5* and following Willgerodt reaction [2] (Scheme 1).

Scheme 1



1: R=X=H
2: R=H, X=Cl
3: R=6-Cl, X=Cl
4: R=7-CF_3, X=Cl

5: R=X=H
6: R=7-Cl, X=Cl
7: R=7-Cl, X=H
8: R=7-Cl, X=OH

9: R=X=H

10: R=X=H
11: R=H, X=Cl
12: R=6-Cl, X=Cl
13: R=7-CF_3, X=Cl

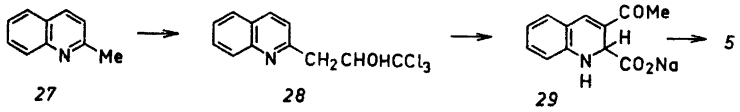
14: R=X=H
15: R=H, X=Cl
16: R=6-Cl, X=Cl
17: R=7-CF_3, X=Cl
18: R=6-Cl, X=OH
19: R=7-CF_3, X=OH
20: R=6-Cl, X=H
21: R=7-CF_3, X=H

22: R=X=H
23: R=H, X=Cl
24: R=6-Cl, X=H
25: R=6-Cl, X=OH
26: R=7-CF_3, X=H

In connection with our work on semisynthetic penicillins [4] we required unsubstituted and substituted quinolylacetic acids. As to our knowledge quinolyl-3-acetic acids carrying substituents in the nucleus are hitherto unknown, and as they even turned out to be rather difficult to prepare, we shall give some viewpoints regarding their synthesis. Furthermore, we report an alternative to the known synthesis of the unsubstituted quinolyl-3-acetic acid (*22*).

In order to obtain this compound a pathway *via* the 3-hydroxymethylquinoline (*10*) obtained by reduction of quinolyl-3-carbethoxylate (*1*) with lithiumaluminium hydride (LAH) seemed possible [5] (Scheme 1). As, however, the reduction of unsubstituted quinolyl-3-carbethoxylate to the hydroxymethyl compound proceeds with rather modest yield [5] we chose a variant of the above mentioned route over 3-acetyl-quinoline (*5*). *5* has been obtained earlier *via* a Claisen condensation, hydrolysis and decarboxylation of the formed *β*-keto ester.[2,6] The required quinolyl-3-carbethoxylate (*1*) may be prepared from quinoline over the 3-cyanoderivative in three steps.[7] We decided, however, to use a way which provided *5* in three steps [8*] starting from commercially available quinaldine (Scheme 2).

Scheme 2



27 28 29

Quinaldine (*27*) was reacted with chloral yielding chloralquinaldine (*28*) which, when warmed with 2 N sodium hydroxide, rearranged in a known way [9] to the red coloured sodium salt *29*; the following treatment with potassium permanganate gave *5*.[1] ** By warming a mixture of *5*, sulfur, and morpholine, quinolyl-3-acetothiomorpholide (*9*) was obtained which gave quinolyl-3-acetic acid (*22*) in good yield upon refluxing with hydrochloric acid.

For the preparation of quinolyl-3-acetic acids carrying substituents in the quinoline nucleus another pathway had to be chosen as the required substituted quinaldines are not so easily available as the unsubstituted quinaldine.[10]

One possible route to this kind of compounds would include the known synthesis of the corresponding 4-hydroxy-3-acetylquinolines [11] that after chlorination in the 4-position with phosphorus oxychloride and consecutive removal of the 4-chloro-substituent might be transferred to the acetic acids *via* a Willgerodt reaction. As the 4-chloro atom in the quinoline ring system usually can be removed by hydrogenolysis we tried this way. We found, however, that for instance 4,7-dichloro-3-acetylquinoline (*6*) was difficult to obtain in a pure state, and that the yields were rather low. Furthermore, attempts to remove the 4-chloro-substituent hydrogenolytically in a number

* This author regarded the oxidation product of *29* erroneously as quinolyl-2-acetaldehyde, *cf.* Ref. 9.

** See page 45 of that reference. Even these authors believed in accordance to Einhorn [8] that they were oxidising sodium quinolyl-2-lactate to quinolyl-2-acetaldehyde, *cf.* Ref. 9.

of different solvents gave only minute amounts of 7-chloro-3-acetylquinoline (*7*), 7-chloro-4-hydroxy-3-acetylquinoline (8) occurring as a by-product.

As 4-chloroquinolyl-3-carbethoxylate (*2*) in contrast to the unsubstituted analogue may be reduced in acceptable yields with LAH to the corresponding hydroxymethyl compound *11* [5] and as, furthermore, 4-chloroquinolyl-3-carbethoxylates with and without substituents in the benzene part of the heteroaromatic nucleus may be prepared in good yields from the usually easily obtainable 4-hydroxyquinolyl-3-carbethoxylates [12] we chose the route *via* the 3-hydroxymethyl compounds (*11—13*, Scheme 1).

4-Chloroquinolyl-3-carbethoxylates (*2—4*) were prepared according to known procedures starting with aniline, 4-chloroaniline and 3-trifluoromethylaniline, respectively.[12]

LAH reduction of *2—4* in tetrahydrofuran (THF) yielded the hydroxymethylquinolines *11—13* which were easily transferred with thionyl chloride to the chloromethyl compounds. Reaction with potassium cyanide in methanol/water and following treatment with ethanolic hydrogen chloride gave the ethyl esters *15—19*.* The 4-chloro substituent could be removed by catalytic hydrogenolysis at normal pressure or in a Parr apparatus. Following hydrolysis yielded the quinolyl-3-acetic acids *24* and *26* which were crystalline compounds soluble in strong acids or in bases. They could be precipitated from their aqueous solutions at pH 1—2.5.

Overall yields were low as the reactions from the chloromethyl- to the cyanomethylquinolines proceeded with bad results, probably because the cyanide ion also reacted at the 4-position of the nucleus. The cyanomethyl compounds were transferred to the ethyl esters rather than hydrolysed directly to the acetic acids in order to avoid substitution of the 4-chloro atom by hydroxyl which might occur under the rather vigorous hydrolysis conditions necessary to transform the nitriles to the carboxylic acids (see, however, footnote *). The corresponding esters could be saponified under very mild conditions without affecting the 4-chloro atom.

Selective hydrogenolysis of the 4-chloro atom was achieved in acidic media using the esters *16* and *17* as starting materials. Under these experimental conditions only the 4-chloro atom was removed, the heteroaromatic nucleus itself and substituents at the benzene part of the nucleus remaining unaffected.

EXPERIMENTAL

Sodium 3-acetyl-1,2-dihydroquinoline-2-carboxylate (29) was obtained following a description of Einhorn [8] starting from chloralquinaldine (*28*).

3-Acetylquinoline (*5*) was prepared from *29* according to a procedure of Borsche and Manteuffel.[1]

Quinolyl-3-thioacetomorpholide (*9*). A mixture of *5* (25 g, 0.146 mole) sulfur (4.7 g, 0.146 mole), and morpholine (26 g, 0.3 mole) was kept at 130° for 15 h, and thereupon

* When 7-trifluoromethyl-4-chloro-3-cyanomethylquinoline was treated with ethanolic hydrogen chloride and worked up in aqueous bicarbonate the product was ethyl 7-trifluoromethyl-4-hydroxyquinolyl-3-acetate (*19*) which could be transferred to the corresponding 4-chloro compound (*17*) by treatment with phosphorus oxychloride. The exchange of chlorine against hydroxyl was to a minor extent even observed if 4,6-dichloro-3-cyanomethylquinoline was treated in the described manner (*cf.* experimental part).

at 145° for 1 h. After treating the reaction mixture with ethanol and filtering from little insoluble material the product 25.6 g (63 %) crystallized after concentration of the filtrate. For analysis part of the product was recrystallized from acetone, m.p. 134–135°. (Found: C 65.93; H 6.02; N 10.18; O 5.98; S 11.93. Calc. for $C_{15}H_{16}N_2OS$: C 66.14; H 5.92; N 10.29; O 5.87; S 11.77).

Quinolyl-3-acetic acid (*22*). *9* (45 g, 0.165 mole) was boiled under reflux in 90 ml of concentrated hydrochloric acid for 10 h. Then most of the acid was evaporated *in vacuo*, about 50 ml of water was added and the mixture was evaporated to about one third of its volume. After neutralization with sodium bicarbonate the solution was washed twice with ether, treated with charcoal, filtered, adjusted to pH 1–2 with 2 N hydrochloric acid and after chilling the crystalline product 27.2 g (87 %) was collected, m.p. 201–203°. (Found: C 70.72; H 5.00; N 7.64; O 17.31. Calc. for $C_{11}H_9NO_2$: C 70.58; H 4.85; N 7.48; O 17.09).

4,6-Dichloroquinolyl-3-carbethoxylate (*3*). To 50 ml of stirred ice-cooled phosphorus oxychloride 6-chloro-4-hydroxyquinolyl-3-carbethoxylate [12] (50.3 g, 0.2 mole) was added in portions. The bath temperature was raised to 90° and kept there for 2½h. Then the bath was removed, dioxane (50 ml) was added and stirring was continued for 5 min. The mixture was poured with vigorous agitation into 2 l of ice water and neutralized with conc. ammonia. After collecting and washing the yellowish crystalline product with ice water it was dried in a desiccator over phosphorus pentoxide as quickly as possible. The dried product may be crystallized from hexane or ligroin, yield 48.0 g (89 %), m.p. 86–87°. (Found: C 53.51; H 3.26; Cl 26.29; N 5.11; O 12.03. Calc. for $C_{12}H_9Cl_2NO_2$: C 53.36; H 3.36; Cl 26.25; N 5.19; O 11.85).

The following compounds were obtained in a similar way: *7-Trifluoromethyl-4-chloroquinolyl-3-carbethoxylate* (*4*) from 7-trifluoro-4-hydroxyquinolyl-3-carbethoxylate,[12] yield 80 %, m.p. 68–71°. (Found: C 51.32; H 3.20; Cl 11.52; F 18.59; N 4.78. Calc. for $C_{13}H_9ClF_3NO_2$: C 51.42; H 2.99; Cl 11.68; F 18.77; N 4.61). *4-Chloroquinolyl-3carbethoxylate* (*2*) from 4-hydroxyquinolyl-3-carbethoxylate,[12] yield 80 %, m.p. 42–44° (lit. 46–47°).[5]

4,6-Dichloro-3-hydroxymethylquinoline (*12*). To a stirred solution of LAH (8.8 g, 0.232 mole) in dry tetrahydrofuran (THF) (400 ml) chilled to −50 to −60° *3* (52 g, 0.193 mole) in dry THF (620 ml) was added at such a rate that the temperature of the mixture did not exceed −50° (about 30 min). Stirring and chilling was continued for another 15 min, then ether (260 ml) saturated with water was added dropwise followed by 60 ml of 5 N sodium hydroxide solution, while the temperature was allowed to rise to 0°. Water (350 ml) was added, the mixture was passed through a filter and the organic layer was separated, washed with brine, dried and evaporated. The residue was crystallized from ethanol yielding 27.6 g (63 %) of product, m.p. 179–181°. (Found: C 52.61; H 3.48; Cl 30.71; N 6.00; O 7.11. Calc. for $C_{10}H_7Cl_2NO$: C 52.66; H 3.10; Cl 31.09; N 6.14; O 7.01).

In a similar way the following compounds were prepared: *7-Trifluoromethyl-4-chloro-3-hydroxymethylquinoline* (*13*) starting with *4*, m.p. 145–147°, yield 49 %. (Found: C 50.64; H 2.81; Cl 13.51; F 21.63; N 5.54. Calc. for $C_{11}H_7ClF_3NO$: C 50.50; H 2.70; Cl 13.55; F 21.78; N 5.35). *4-Chloro-3-hydroxymethylquinoline* (*11*) starting from *2*, m.p. 144–146°, (lit. 147.3–147.5),[5] yield 67 %. The compounds had an IR-absorption band at 3150–3250 cm^{-1} (ν_{O-H}); no absorption in the 1700 cm^{-1} region ($\nu_{C=O}$) was detected.

4,6-Dichloro-3-chloromethylquinoline hydrochloride. To a warm, freshly prepared and filtered solution of *12* (43.4 g, 0.19 mole) in ethanol (2000 ml) dry 4 M hydrogen chloride in ether (70 ml) was added with stirring. The mixture was cooled and after collecting the formed precipitate this was cautiously dissolved in thionyl chloride (100 ml) and boiled under reflux for 3 h. The thionyl chloride was evaporated, benzene (200 ml) was added and the evaporation procedure repeated. After adding benzene (150 ml) to the residue 4 M dry hydrogen chloride in ether (30 ml) was added, the mixture was cooled and the product collected by filtration, m.p. 187–191°, yield 48.6 g (90%).

The following products were obtained in a similar manner starting from the corresponding hydroxymethyl compounds: *7-Trifluoromethyl-4-chloro-3-chloromethylquinoline hydrochloride*, yield 95 %. *4-Chloro-3-chloromethylquinoline hydrochloride*, yield 95 %. The products did not show any IR-absorption band in the region above 3150 cm^{-1} (ν_{O-H}).

4,6-Dichloro-3-cyanomethylquinoline. To a stirred solution of 4,6-dichloro-3-chloromethylquinoline hydrochloride (44.9 g, 0.159 mole) in methanol (235 ml) potassium cyanide (31.4 g, 0.49 mole) in 90 ml of water was added dropwise. The mixture was kept at 80–90° for 5 h. and for another 15 h at room temperature. Water (200 ml) was added, the dark coloured solution was saturated with potassium carbonate and extracted with ethyl acetate. The residue obtained after drying and evaporating the organic phase was extracted several times with boiling heptane, yielding 7.3 g of a yellowish crystalline product, m.p. 138–140°; a second crop (7.4 g, m.p. 133–137°) was obtained after Soxhlet extraction of the residue. Total yield 42%. (Found: C 55.94; H 2.60; Cl 29.74; N 11.82. Calc. for $C_{11}H_6Cl_2N_2$: C 55.72; H 2.55; Cl 29.91; N 11.82).

In a similar way the following products were obtained starting from the corresponding 3-chloromethylquinolines: *7-Trifluoromethyl-4-chloro-3-cyano-methylquinoline*, m.p. 126–131°, yield 29 %. (Found: C 53.45; H 2.42; N 10.23. Calc. for $C_{12}H_6ClF_3N_2$: C 53.26; H 2.23; N 10.35). *4-Chloro-3-cyanomethylquinoline*, m.p. 145°, yield 29 %. (Found: C 65.02; H 3.60; Cl 17.31; N 13.61. Calc. for $C_{11}H_7ClN_2$: C 65.20; H 3.48; Cl 17.50; N 13.82). The compounds had an IR-absorption band in the region 2230-60 cm^{-1} ($\nu_{C\equiv N}$).

Ethyl 4,6-dichloroquinolyl-3-acetate (16). Dry hydrogen chloride was passed into a gently boiling stirred solution of 4,6-dichloro-3-cyanomethylquinoline (10 g) in 200 ml of dry ethanol during 6 h. After evaporation of about two thirds of the solvent *in vacuo* the mixture was neutralized with 2 N sodium bicarbonate and the precipitated *16* was collected by filtration, washed with water and dried (5.2 g, 43 %). The product was crystallized from hexane, m.p. 54.5–56°, IR-absorption at 1710 cm^{-1} ($\nu_{C=O}$). (Found: C 55.16; H 4.00; Cl 24.86; N 4.94; O 11.20. Calc. for $C_{13}H_{11}Cl_2NO_2$: C 54.95; H 3.90; Cl 24.95; N 4.93; O 11.26).

From the aqueous filtrate *ethyl 6-chloro-4-hydroxyquinolyl-3-acetate (18)* crystallized after standing over night at room temperature, m.p. 213–216° (acetone), broad IR-absorption band at 3000 cm^{-1} (ν_{O-H}). (Found: C 58.83; H 4.35; Cl 13.13; N 5.22; O 18.20. Calc. for $C_{13}H_{12}ClNO_3$: C 58.77; H 4.55; Cl 13.34; N 5.27; O 18.06). This product could be transferred into *16* by treatment with phosphorus oxychloride as described for *3*.

In a similar way as described for *16 ethyl 4-chloroquinolyl-3-acetate (15)* was prepared, m.p. 49–53° (petroleum ether), yield 86 %, IR-absorption at 1710 cm^{-1} ($\nu_{C=O}$). (Found: C 62.71; H 5.00; Cl 14.01; N 5.52; O 12.66. Calc. for $C_{13}H_{12}ClNO_2$: C 62.53; H 4.84; Cl 14.20; N 5.61; O 12.81).

On treating trifluoromethyl-4-chloro-3-cyanomethylquinoline with ethanolic hydrogen chloride in the manner described above and evaporating two thirds of the solvent, a precipitate formed on pouring into ice cold sodium bicarbonate solution. This consisted of *ethyl 7-trifluoromethyl-4-hydroxyquinolyl-3-acetate (19)*, yield 94 %, m.p. 242–244°, IR-absorption at 1715 cm^{-1} ($\nu_{C=O}$) and at 3100 cm^{-1} (ν_{O-H}).

Ethyl 7-trifluoromethyl-4-chloroquinolyl-3-acetate (17). *19* (4.8 g, 0.016 mole) in phosphorus oxychloride (5 ml) was warmed to about 80° for 30 min. Dry dioxane (5 ml) was added and the solution was poured into ice water. After adjusting the pH to 8 with 2 N ammonia, collecting the precipitate by filtration and crystallizing from heptane the yield was 1.8 g (35 %), m.p. 78–81°, IR-absorption at 1730 cm^{-1} ($\nu_{C=O}$). (Found: C 52.80; H 3.33; F 18.10; N 4.50. Calc. for $C_{14}H_{11}ClF_3NO_2$: C 52.93; H 3.49; F 17.94; N 4.41).

Ethyl 6-chloroquinolyl-3-acetate (20). *16* (2 g) in glacial acetic acid (160 ml) was hydrogenated over 5 % palladium on charcoal (1.2 g) at normal pressure. The reaction was stopped when slightly more than the theoretical amount of hydrogen had been consumed (16 min). The catalyst was removed and most of the solvent was evaporated *in vacuo*. 1 N hydrochloric acid (20 ml) was added to the residue. After removal of little undissolved material by filtration the filtrate was made alkaline and extracted with ethyl acetate. The product (1.7 g, 85 %) was precipitated as the hydrochloride from the dried ethyl acetate extract by addition of a solution of hydrogen chloride in ether. (Found: Cl 25.57; N 4.44. Calc. for $C_{13}H_{13}Cl_2NO_2$: Cl 24.78; N 4.89).

Ethyl 7-trifluoromethylquinolyl-3-acetate (21). *17* (0.5 g) in 1 N hydrochloric acid (10 ml) was hydrogenated over 5 % palladium on charcoal (0.3 g) on a Parr apparatus for 15 min (the hydrogen pressure changed from 38 to 36.5 psi during that time). After removal of the catalyst and neutralization of the filtrate the crystalline product (0.3 g, 67 %) was collected by filtration, m.p. 63–65°, IR-absorption at 1720 cm^{-1} ($\nu_{C=O}$).

(Found: C 59.29; H 4.11; F 19.99; N 5.15. Calc. for $C_{14}H_{12}F_3NO_2$: C 59.37; H 4.27; F 20.12; N 4.95).

4-Chloroquinolyl-3-acetic acid (*23*). *15* (1.2 g, 0.0048 mole) in 1.2 N methanolic sodium hydroxide (4 ml) was kept at room temperature for 1 h during which time a precipitate was formed. The mixture was chilled and filtered. After dissolving the residue in 10 ml of ice water the product was precipitated by adjusting the pH to 2.0. Yield 0.8 g (75 %), m.p. 150—152° (decomp.), IR-absorption at 1690 cm^{-1} ($\nu_{C=O}$). (Found: C 59.44; H 3.60; Cl 15.96; N 6.24; O 14.31. Calc. for $C_{11}H_8ClNO_2$: C 59.61; H 3.64; Cl 15.99; N 6.32; O 14.44).

7-Trifluoromethylquinolyl-3-acetic acid (*26*). *21* (0.5 g, 0.00178 mole) in 1.2 N methanolic sodium hydroxide (1.5 ml) was left at 25° for 30 min. The formed precipitate was collected by filtration washed with little cold methanol and dissolved in a small amount of water. The pH was adjusted to 2.5 with 2 N hydrochloric acid and the product collected. A second crop was obtained from the methanolic mother liquor by dilution with little water and adjustion of the pH to 2.5, m.p. 201—205° (decomp.), yield 0.335 g (75 %), IR-absorption at 1710 cm^{-1}. (Found: C 56.28; H 3.15; F 22.28; N 5.66. Calc. for $C_{12}H_8F_3NO_2$: C 56.48; H 3.16; F 22.33; N 5.49).

6-Chloroquinolyl-3-acetic acid (*24*) was obtained in a similar manner from *20*, yield 57 %, m.p. 173—176° (decomp.).

6-Chloro-4-hydroxyquinolyl-3-acetic acid (*25*). *18* (3 g, 0.0113 mole) in a mixture of 2 N sodium hydroxide (11.3 ml) and acetone (5 ml) was heated to reflux for 30 min. Water (10 ml) was added and the solution was purified with charcoal. After acidification to pH 1 the product precipitated, yield 1.1 g (41 %), m.p. > 300°. (Found: C 55.75; H 3.52; Cl 14.85; N 5.77; O 20.40. Calc. for $C_{11}H_8ClNO_3$: C 55.60; H 3.39; Cl 14.92; N 5.89; O 20.20).

4,7-Dichloro-3-acetylquinoline (*6*). 7-Chloro-4-hydroxy-3-acetylquinoline (*8*) [11] (10 g) in phosphorus oxychloride (20 ml) was warmed to gently reflux for 30 min. Dioxane (50 ml) was added and the dark brown solution was poured into *ca.* 200 ml of ice water. The pH was adjusted to 8 with conc. ammonia. The product was collected by filtration and dried in a desiccator over phosphorus pentoxide as quickly as possible. Crystallizing from ethanol with addition of charcoal yielded 6 g (55 %), m.p. 99—100°, no IR-absorption in the region above 3100 cm^{-1} (ν_{O-H}). (Found: C 54.95; H 3.02; Cl 29.45; N 5.76; O 6.64. Calc. for $C_{11}H_7Cl_2NO$: C 55.03; H 2.94; Cl 29.53; N 5.84; O 6.66).

5-Chloro-3-acetylquinoline (*7*). *6* (2.4 g, 0.01 mole) in glacial acetic acid (25 ml) was hydrogenolysed over 5 % palladium on charcoal at normal pressure until the theoretical amount of hydrogen (225 ml) had been taken up. After removal of the catalyst the solvent evaporated *in vacuo;* 2 N hydrochloric acid was added to the residue which dissolved partly. After filtering the pH of the filtrate was adjusted to 4—5 yielding 50 mg of product, m.p. 130—133°. (Found: C 64.46; H 4.13; Cl 17.12; N 6.64; O 7.62. Calc. for $C_{11}H_8ClNO$: C 64.25; H 3.92; Cl 17.24; N 6.81; O 7.78). The residue unsoluble in 2 N hydrochloric acid was identified as *7-chloro-4-hydroxy-3-acetylquinoline* (*8*) by comparison with an authentic sample. The hydrogenolysis of 6 was even performed in methanol, ethanol and 2 N hydrochloric acid without improval of the result.

Acknowledgement. The authors are greatly indebted to Drs. Bertil Ekström and Berndt Sjöberg for valuable discussions and to Dr. Brian Pring for reading the manuscript.

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Received March 23, 1968.