

Substituted Quinolineacetic Acids^{1, 3}

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It was of interest to prepare several substituted quinolineacetic derivatives since at the time this work was begun very few had been recorded in literature.

The ethyl esters of both 2- and 4-quinolineacetic acids have been prepared by Borsche and co-workers (1). These were synthesized from the quinolinepyruvic ester obtained by condensation of quinaldine and lepidine, respectively, with ethyl oxalate. 3-Carbostyrylacetic acid (7) has been obtained by ring closure of *o*-aldehydosuccinanic acid. More recently, 2- and 4-quinolineacetic acid esters have been reported by Weiss and Hauser (8) who obtained them through the carbethoxylation of quinaldine and lepidine, respectively, using ethyl carbonate and potassium amide. Jones and co-workers (4) prepared the ethyl esters 3-, 6- and 8-quinolineacetic acid during a study of penicillin precursors. Ethyl 4-hydroxy-2-methyl-6-quinolineacetate (5) has been obtained from methyl acetoacetate and ethyl *p*-aminophenylacetate. The highly substituted 4-carboxy-2-(2-thienyl)-3-quinolineacetic acid (3) was obtained through the Pfitzinger reaction between isatin and β -(2-thenoyl)-propionic acid. 8-Quinolineacetic acid preparation from 8-acetylquinoline by the Willgerodt reaction has been reported in a patent (2).

This report deals with the preparation of substituted 6- and 8-quinolineacetic acids obtained through the condensation of ethyl ethoxalylacetate with ethyl esters of 4- and 2-aminophenylacetates and subsequent ring-closure in boiling phenyl ether. The use of *p*-aminophenylacetonitrile instead of ethyl *p*-aminophenylacetate gave the corresponding 2-carbethoxy-4-hydroxy-6-quinolineacetonitrile. Attempts at decarboxylation of IV did not yield 4-hydroxy-6-quinolineacetonitrile; only high wide-range melting substances were obtained which could not be purified to workable materials. Likewise, no identifiable materials could be isolated from the decarboxylation of III. Carbon dioxide was liberated freely in both instances.

Experimental

Ethyl 2-Carbethoxy-4-hydroxy-6-quinolineacetate (I).—A solution of 13.7 g. (0.076 mole) of ethyl *p*-aminophenylacetate and 15g. (0.08 mole) of ethyl ethoxalylacetate in 75 ml. of methylene chloride with a drop of dilute hydrochloric acid was refluxed under a condenser with

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trap for a heavier than water liquid until no more water was collected. After removal of the solvent, the oily residue was dissolved in warm diphenyl ether and added dropwise over a period of twenty minutes to 100 ml. of boiling diphenyl ether. After no further quantity of ethyl alcohol distilled, the reaction mixture was allowed to cool, the solid removed by filtration, washed with diphenyl ether and petroleum ether then recrystallized from 70-80% ethyl alcohol. The yield of light tan colored solid was 12.1 g. (53%), m.p. 187-188.5°.

Anal. Calc'd. for $C_{16}H_{17}NO_5$: N, 4.61%. Found: N, 4.87%.

2-Carboethoxy-4-hydroxy-6-quinolineacetonitrile (II).—This substance was prepared from p-aminophenylacetonitrile according to the method described above. Recrystallized from methyl cellosolve, the substance melted at 220-227°; the yield was 53%.

Anal. Calc'd for $C_{14}H_{12}N_2O_3$: N, 10.93%. Found: N, 11.25%

2-Carboxy-4-hydroxy-8-quinolineacetic acid (III).—Ethyl o-aminophenylacetate hydrochloride (21.6 g., 0.1 mole) was condensed with 23.3 g. of ethyl sodium ethoxalylacetate in absolute ethyl alcohol according to the method described by Lisk and Stacy (6). Ring closure of the crude azomethine was accomplished in 800 ml. of boiling diphenyl ether. After the reaction mixture cooled, no solid could be induced to separate so the diphenyl ether was heated with 300 ml. of 5% sodium hydroxide solution under a reflux condenser while the mixture was stirred mechanically. After separating the aqueous layer and neutralization with concentrated hydrochloric acid, the yield of the dicarboxylic acid was 17.6 g. (71%), m.p. 236-238°. Attempts at further purification did not raise the melting point.

Anal. Calc'd for $C_{12}H_8NO_5$: N, 5.67%. Found: N, 5.57%.

2-Carboxy-4-hydroxy-6-quinolineacetonitrile (IV).—Five grams (0.02 mole) of II was refluxed for 20 minutes with 25 ml. of 5% aqueous sodium hydroxide, the hot solution filtered and added dropwise to cold hydrochloric acid. The yield of light tan colored solid was 4.1 g. (92%), m.p. 256-258°. After recrystallization from glacial acetic acid, the substance melted at 257.5-258°.

Anal. Calc'd. for $C_{12}H_8N_2O_3$: N, 12.28%. Found: N, 11.90%.

Upon attempted recrystallization of II by boiling 40 g. of the substance in 300 ml. of glacial until solution occurred (30-40 minutes) then the solution cooled, a solid crystallized in almost theoretical yield which proved to be identical with IV. Apparently transesterification had occurred during the heating process.

2-Carboethoxy-4-chloro-6-quinolineacetonitrile (V).—A solution of 7.7 g. (0.05 mole) of phosphoryl trichloride in 50 ml. of dry benzene was added to 6.4 g. (0.025 mole) of II contained in a 200 ml. flask. The mixture was warmed and shaken at 60° for twenty minutes, then the reaction mixture was hydrolysed in ice-water and the semisolid mass isolated, neutralized and recrystallized from dioxane. The yield of long

fine needles of slightly tan solid was 1.0 g. (18%) which melted at 205.5-206°.

Anal. Calc'd for $C_{14}H_{11}ClN_2O_2$: N, 10.20%. Found: N, 10.60%.

Ethyl 2-Carbethoxy-4-hydroxy-6-quinoline- α -cyanoacetate (VI).—A mixture of 0.2 mole of sodium ethoxide and 25.6 g. (0.1 mole) of 2-carbethoxy-4-hydroxy-6-quinolineacetone in 200 ml. of purified ethyl carbonate was heated at 55-60° in a 500-ml. three-necked flask equipped with a stirrer and a 24-inch column packed with glass helices. The pressure was maintained at about 100 mm. while the reaction mixture was heated during a twelve hour period. A portion of the ethyl carbonate was removed by distillation, the solid collected by filtration then triturated with dilute acetic acid. The yield of the crude substance was 30 g., m.p. 155-165°. After recrystallization from ethyl acetate, the substance melted at 168-170°, yield 13 g. (45%).

Anal. Calc'd for $C_{17}H_{15}N_2O_5$: N, 8.53%. Found, N, 8.38%.

2-Carboxy-4-hydroxy-6-quinolineacetic acid (VII).—A solution of 49.2 g. (0.19 mole) of II in 300 ml. of 7-8% sodium hydroxide was refluxed until tests (8 hours) indicated that no more ammonia was being evolved. After treatment of the hot solution with Norite and filtration, it was acidified with concentrated hydrochloric acid. The yield of VII was 98%, the substance melted at 286-288° with decomposition. VII may be recrystallized from methyl cellosolve.

Anal. Calc'd. for $C_{12}H_9NO_5$: N, 5.6%. Found: N, 5.42%.

Saponification of I and IV gave substances which were identical with VII.

2-Carboxy-4-chloro-6-quinolineacetic acid (VIII).—A suspension of 12.4 g. (0.05 mole) of VII was mixed with 100 ml. of benzene containing 30.6 g. (0.2 mole) of phosphoryl trichloride. was kept at 60° for four hours, then the solid triturated with water and dissolved 125 ml. of hot ethylene glycol. After filtration, 25 ml. of n-butyl alcohol was added and the substance allowed to crystallize. The yield was 7 g. (53%) of tan-colored crystals, m.p. 230-232°. Recrystallization did not change the melting point.

Anal. Calc'd for $C_{12}H_8ClNO_4$: N, 5.27%. Found: N, 4.94%.

2-Carboxy-6-quinolineacetic acid (IX).—Seven grams (0.026 mole) of VIII was hydrogenated in ethyl alcohol at 40 p.s.i. using palladium—charcoal catalyst. After six hours, the solid was removed by filtration, then triturated with 5% sodium hydroxide solution to dissolve the crude IX. After filtration of the solution, it was acidified with dilute hydrochloric acid. The yield of crude IX was 4.2 g. (67%). After recrystallization from acetic acid, the substance melted at 270-272°.

Anal. Calc'd for $C_{12}H_9O_4N$: N, 6.06%. Found: N, 5.88%.

2-Carboxy-4-Methoxy-6-quinolineacetic acid (X).—Two grams of VIII was refluxed for one hour with 25 ml. of absolute methyl alcohol

in which one gram of sodium had been dissolved. After cooling, 20 ml. of water was added and the solution added slowly to cold dilute nitric acid. The crude X (m.p. 272-275°) was recrystallized from methyl cellosolve as white needles. The yield was 1.2 g. (61%) and the purified X melted at 272.5-274°.

Anal. Calc'd. for $C_{13}H_{11}NO_5$: N, 5.36%. Found: N, 5.44%.

2-Carboxy-4-Chloro-8-quinolineacetic acid (XI).—This substance was prepared from 4 g. of III by the same procedure as was used in the case of VIII, except that the benzene and phosphoryl trichloride were removed in vacuum. The yield was 4 g. (93%). The substance melted with decomposition at 252-253°.

Anal. Calc'd. for $C_{12}H_8ClNO_4$: N, 5.27%. Found: N, 5.22%.

2-Carboxy-4-hydroxy-5 (and 7)-quinolineacetic acid (XII).—This substance was prepared from 36 g. (0.168 mole) ethyl m-aminophenylacetate hydrochloride and 44 g. (0.19 mole) of ethyl sodium ethoxalylacetate exactly as in the case of III. After treatment of the crude XII with Norite in dilute sodium hydroxide it was obtained on acidification with hydrochloric acid as a light cream colored solid which melted with decomposition at 220-250°. The yield was 13 g. (31%).

Anal. Calc'd for $C_{12}H_9NO_5$: N, 5.67%. Found: N, 5.78%.

Summary

The Conrad-Limpach type of reaction was used to prepare ethyl 2-carbethoxy-4-hydroxy-6-quinolineacetate and ethyl 2-carbethoxy-4-hydroxy-6-quinolineacetonitrile from ethyl ethoxalylacetate and ethyl p-aminophenylacetate and p-aminophenylacetonitrile, respectively. 2-carbethoxy-4-hydroxy-6-quinolineacetonitrile was saponified partially to give 2-carboxy-4-hydroxy-6-quinolineacetonitrile or could be saponified completely to the dicarboxylic acid depending upon the conditions. Carbethoxylation of 2-carbethoxy-4-hydroxy-6-quinoleacetonitrile in ethyl carbonate solution by sodium ethoxide gave ethyl 2-carbethoxy-4-hydroxy-6-quinoline- α -cyanoacetate. 2-Carboxy-4-hydroxy-8-quinolineacetic acid was obtained by the saponification of the ester obtained by the condensation of ethyl ethoxalylacetate with ethyl o-aminophenylacetate.

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