8-*Hydroxyquinaldic Acid.*

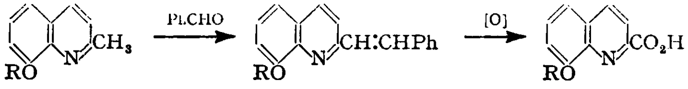
By H. Irving and A. R. Pinnington.

[Reprint Order No. 5480.]

8-Hydroxyquinaldic acid, a potential chelating agent, is obtainable by demethylation of 8-methoxyquinaldic acid prepared from 8-methoxyquinaldine by treatment with selenium dioxide or more conveniently by oxidation of its 2-styryl derivative.

During an investigation of the structure of xanthurenic acid, Musajo and Minchilli (*Ber.*, 1941, **74**, 1839) obtained a few milligrams of 8-hydroxyquinaldic acid (III; R = H) by the catalytic dehalogenation of the 4-chloro-8-hydroxy-acid. The preparation of this substance on a larger scale was undertaken since it combines the functional groups of 8-hydroxyquinoline (" oxine ") and quinaldic acid, two analytical reagents widely used for metals, and as a potentially tridentate chelating agent its reactions with cations of different radii and charges should be of interest.

The oxidation of the methyl group of 8-hydroxyquinaldine (I; R = H) could not be effected without destruction of the benzenoid ring. The phenolic hydroxyl group was therefore protected by methylation, but treatment of 8-methoxyquinaldine (I; R = Me) with selenium dioxide gave only a poor yield of 8-methoxyquinaldic acid (III; R = Me), the main product being an intractable red viscous material from which small amounts of 8-methoxyquinoline-2-aldehyde could be obtained with difficulty.



(I) (II) (III)

By heating 8-methoxyquinaldine (I; R = Me) with anhydrous zinc chloride and excess of benzaldehyde at 150—160° for 10 hr. Tröger and Dunker (*J. pr. Chem.*, 1925, **109**, 88) obtained what they described as 8-methoxy-2-styrylquinoline (II; R = Me), as " a dirty yellow amorphous product "; only the hydrochloride could be purified or analysed. In our hands this method invariably gave an amorphous yellow-green solid, m. p. >360°, which did not decolorise cold permanganate solution or bromine water and was unattacked in acetic acid solution by ozone or by 30% hydrogen peroxide : qualitative tests established the presence of zinc. When, however, 8-methoxyquinaldine in acetic anhydride was condensed with a three-fold excess of benzaldehyde, the zinc chloride being omitted, an excellent yield of authentic 8-methoxy-2-styrylquinoline (II; R = Me) resulted. After purification through the hydrochloride it formed creamy-white crystals, m. p. 100°, with properties agreeing in the main with those of the product which Tröger and Dunker prepared by condensing 8-methoxyquinaldine and benzaldehyde in the absence of zinc chloride and for which they reported analytical results suggesting that it was 2-(2-hydroxy-2-phenylethyl)-8-methoxyquinoline. In pyridine solution the styryl compound (II; R = Me) was oxidised almost quantitatively by cold permanganate solution to 8-methoxyquinaldic acid (III; R = Me). Demethylation proved difficult, in agreement with previous observations with similar derivatives of 8-methoxyquinoline (cf. Phillips, Elbinger, and Merritt, *J. Amer. Chem. Soc.*, 1949, **71**, 3986) but refluxing the 8-methoxy-acid with potassium iodide and 95% phosphoric acid (cf. Furst and Olsen, *J. Org. Chem.*, 1951, **16**, 412) gave 8-hydroxyquinaldic acid (III; R = H) in almost theoretical yield. The m. p. (211°) of the compound after recrystallisation from aqueous dioxan was depressed by recrystallisation from aqueous alcohol, probably in consequence of unusually ready ester formation : we have noted similar behaviour with 4-chloro(or 4-bromo)-8-hydroxyquinaldic acid.

The condensation of aromatic aldehydes with heterocyclic compounds possessing a reactive methyl group may yield side-chain alcohols or styryl compounds according to conditions, the presence of acetic anhydride or zinc chloride favouring the latter (cf. Tröger and Dunker, *loc. cit.*; Royer, *J.*, 1949, 1803), while in the absence of zinc chloride the secondary alcohol is often stated to be the sole product. Phillips, Elbinger, and Merritt (*loc. cit.*) condensed 8-hydroxyquinaldine (I; R = H) with benzaldehyde in the absence of zinc chloride and obtained a product, m. p. 104—105° after vacuum distillation, which they formulated as 8-hydroxy-2-styrylquinoline (II; R = H) although the analytical figure (Found: N, 5·47%) lay between the values for the styryl compound (5·67%) and the alcohol (5·28%) and no chemical evidence of side-chain unsaturation was advanced. However, the hydrolysis with alcoholic sodium hydroxide or with hydrochloric acid of 8-acetoxy-2-styrylquinoline (II; R = Ac), obtained by condensing 8-hydroxyquinaldine with benzaldehyde in acetic anhydride as solvent, gave authentic 8-hydroxy-2-styrylquinoline, m. p. 103—104°, identical with a specimen made by the procedure described by Phillips *et al.* (*loc. cit.*).

The oxidation of 8-hydroxy-2-styrylquinoline by aqueous permanganate proved difficult to control, and the best yield of 8-hydroxyquinaldic acid (20%) could not be reproduced consistently. The most convenient route to this acid is therefore through the styryl derivative of 8-methoxyquinaldine.

8-Hydroxyquinaldic acid gives a deep green colour with traces of ferric ions. Its coloration and precipitation reactions with other inorganic ions will be reported elsewhere.

EXPERIMENTAL

8-*Methoxyquinaldine* (I; R = Me).—The preparation of this base has been examined by numerous workers since Doebner and Miller (*Ber.*, 1884, **17**, 1698) obtained it in low yield. *o*-Nitrophenol, picric acid, and arsenic pentoxide have been recommended as oxidising agents but Phillips, Elbinger, and Merritt (*loc. cit.*) found that there is no effective oxidising agent specially to be preferred when αβ-unsaturated compounds are condensed with *o*-anisidine, and omit one in their preparation of 8-methoxyquinoline. Although Spivey and Curd (*J.*, 1949, 2656) found the use of *m*-nitrobenzenesulphonic acid as a water-soluble oxidising agent trebled the yield of 5- and 7-chloroquinaldines in the Doebner–Miller synthesis, it showed no special value in the present preparation. If, however, the reactants are preheated before addition of oxidising agent, and the duration of heating and the proportion of *o*-nitrophenol are limited to the values given below, the tedious steam-distillation of excess of oxidant can be avoided, while the formation of tar is reduced and the overall yield improved.

Crotonaldehyde (40 g., 1·14 mol.) was added during 15 min. to a solution of *o*-anisidine (61·5 g., 1 mol.) and *o*-nitrophenol (7·0 g., 0·1 mol.) in 10N-hydrochloric acid (100 ml.) previously heated to 100°. After a further 2 hours' heating the mixture was cooled and very slowly neutralised with concentrated aqueous sodium hydroxide. Next morning the semisolid product was collected, washed thoroughly with water, and dried in air. Distillation at 22—28 mm. gave 8-methoxyquinaldine, b. p. 145—160° which was recrystallised from hot benzene (animal charcoal), giving needles (38—42 g.; 44—49%), m. p. 125°.

8-*Methoxy*-2-*styrylquinaldine* (II; R = Me).—8-Methoxyquinaldine (3·0 g.), freshly distilled benzaldehyde (2·76 g.), and acetic anhydride (8·0 g.) were refluxed for 3 hr. at 160°. After being cooled the mixture was poured into water (100 ml.), and cautiously neutralised with sodium hydroxide solution. The viscous solid which then separated was taken up in ether (3 × 100 ml.), and after filtration the solution was saturated with dry hydrogen chloride; 8-*methoxy*-2-*styrylquinoline hydrochloride* then separated and was crystallised from hot 10N-hydrochloric acid, forming bright yellow needles, m. p. 226° (decomp.) (Found: Cl, 11·7. $C_{18}H_{15}ON,HCl$ requires Cl, 11·9%). Neutralisation of a cold aqueous solution of this hydrochloride with dilute sodium hydroxide gave 8-*methoxy*-2-*styrylquinoline* as needles, m. p. 100° (from aqueous alcohol) (Found: C, 82·8; H, 5·9. $C_{18}H_{15}ON$ requires C, 82·8; H, 5·8%). Its properties agreed closely with those of the product described by Tröger and Dunker (*loc. cit.*) as 2-(2-hydroxy-2-phenylethyl)-8-methoxyquinoline. Their preparation of alleged 8-methoxy-2-styrylquinoline by condensation of 8-methoxyquinaldine and benzaldehyde in the presence of zinc chloride, gave, in our hands, even when the experimental conditions were widely varied, only an amorphous substance containing zinc which sintered below 300° but had not melted at 360°. It was completely insoluble in hydrochloric acid, acetic acid, and all common solvents except cold pyridine and boiling nitrobenzene. It was unchanged by boiling dilute acids or alkalis, and by oxidising agents such as ozone, hydrogen peroxide, or potassium permanganate.

8-*Methoxyquinaldic Acid* (III; R = Me).—(a) *By oxidation of* 8-*methoxy*-2-*styrylquinoline.* 8-Methoxy-2-styrylquinoline (6·3 g.) dissolved in pyridine (20 ml.) was cooled in ice-water and shaken continuously while 4% aqueous potassium permanganate was added slowly until the colour just persisted. The precipitate of manganese dioxide was collected and washed well with hot water. The washings and the yellow filtrate were combined, concentrated to 50 ml. on a water-bath, and filtered while hot. On acidification a dense yellow precipitate separated and was collected, pressed dry, and washed with ether (3 × 50 ml.). The residual crude 8-methoxyquinaldic acid (3·9 g.; m. p. 150°) was crystallised from benzene containing a little alcohol; golden-yellow needles of the *monohydrate,* m. p. 158—159°, separated (Found: C, 59·5; H, 5·0; N, 6·2. $C_{11}H_9O_3N,H_2O$ requires C, 59·7; H, 5·0; N, 6·3%).

On recrystallising this monohydrate from hot water, large crystals of the *dihydrate,* m. p. 121—122°, were obtained (Found: C, 55·1; H, 5·2. $C_{11}H_9O_3N,2H_2O$ requires C, 55·2; H, 5·4%). The dihydrate is the form stable in moist air but it may be transformed into the monohydrate at 100° or by recrystallisation from benzene–alcohol. When heated *in vacuo* in a drying pistol the monohydrate slowly loses weight; but this is due rather to sublimation than to loss of water since there is no change in the melting point of the residue.

(b) *From the oxidation of* 8-*methoxyquinaldine with selenium dioxide.* Freshly sublimed, finely powdered selenium dioxide (6·14 g.) was added during 15 min. to a solution of 8-methoxyquinaldine (6·36 g.) in boiling xylene (100 ml.). The theoretical weight of selenium separated almost immediately and was filtered off from the boiling solution. On removing the solvent in a current of air, yellow crystals separated together with a red viscous material. Purification of the yellow crystals gave 8-methoxyquinaldic acid monohydrate (0·6 g.), m. p. 159° (from benzene containing a little alcohol). The red viscous material was extracted with hot benzene, filtered, and the solvent allowed to evaporate slowly in the air. From the pale yellow solid which separated (1·6 g.), accompanied by a considerable amount of red viscous material, fractional crystallisation from aqueous alcohol, followed by vacuum sublimation, and finally a series of recrystallisations from water gave 8-*methoxyquinoline*-2-*aldehyde* as faintly green, long needles, m. p. 102° (Found: C, 70·3; H, 4·4. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·8%). The 2 : 4-*dinitrophenylhydrazone* formed orange plates from 95% alcohol, m. p. 260° (decomp.) (Found: N, 28·0. $C_{17}H_{13}O_5N_5$ requires N, 28·3%).

8-*Hydroxyquinaldic acid* (III; R = H).—A mixture of 8-methoxyquinaldic acid monohydrate (1·3 g.), potassium iodide (3·25 g.), and syrupy phosphoric acid (10·9 g.) was refluxed at 215—225°. A red colour appeared in the condenser, and heating was continued until this vanished (about 2 hr.). When cold the mixture was poured into vigorously stirred water (100 ml.); crude 8-hydroxyquinaldic acid [1·35 g.; m. p. 195° (with sublimation and decomp.)] separated as a yellow solid. This was collected, after being set aside overnight, and freed from accompanying tarry material first by solution in 1% potassium hydroxide and reprecipitation from the filtered solution by hydrochloric acid, then by careful neutralisation of its solution in sodium hydrogen carbonate solution. Finally it was crystallised from aqueous dioxan, forming fine yellow crystals, m. p. 211°, which when powdered readily cohere as a more orange product (Found: C, 63·5; H, 3·8; N, 7·75. $C_{10}H_7O_3N$ requires C, 63·5; H, 3·7; N, 7·4%). To avoid introducing metallic impurities only "AnalaR" reagents and redistilled pure solvents were used in this preparation.

8-Hydroxyquinaldic acid is insoluble in light petroleum, benzene, xylene, or chloroform; it is soluble in hot alcohol, dioxan, amyl alcohol, and glacial acetic acid, and readily soluble in acetone and in dilute solutions of alkalis and mineral acids. A dilute solution of the acid in acetone gave a deep green colour with traces of ferric iron. Attempts to crystallise this acid from aqueous alcohol resulted in lowering of the melting point by 10—20°, the bright yellow colour fading to a pale straw. This behaviour (which has also been observed in these laboratories with 4-bromo-8-hydroxyquinaldic acid) may be due to partial esterification, for the original melting point is recovered by dissolution in aqueous bicarbonate and precipitation with acid.

8-*Acetoxy*-2-*styrylquinoline* (II; R = Ac).—8-Hydroxyquinaldine (5·2 g.), prepared according to Phillips, Emery, and Price (*Analyt. Chem.*, 1952, **24**, 1033), was heated for 3 hr. at 160° with benzaldehyde (5·3 g.) and acetic anhydride (7·0 g.). After cooling, the pale red oil was poured slowly into vigorously stirred water (100 ml.), a yellow solid immediately separating. 5% Sodium hydroxide solution was then added until a slight, permanent alkaline reaction was obtained. The precipitate, which was contaminated with benzaldehyde, was collected and dried. After recrystallisation successively from aqueous alcohol, aqueous dioxan, and light petroleum (b. p. 60—80°), 8-*acetoxy*-2-*styrylquinoline* (4·3 g.) separated as very pale brown needles, m. p. 119—120°, which were insoluble in 2N-sodium hydroxide (Found: C, 78·6; H, 5·1. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2%).

Hydrolysis. 8-Acetoxy-2-styrylquinoline (5·5 g.) was refluxed for 2 hr. with 5% sodium hydroxide solution (50 ml.). The mixture was neutralised with 5N-hydrochloric acid, and the 8-hydroxy-2-styrylquinoline which then separated was dried and recrystallised from light petroleum and then from aqueous alcohol forming yellow crystals (3·2 g.), m. p. 102—103°, which readily decolorised potassium permanganate solution (Found: C, 82·3; H, 5·5. Calc. for $C_{17}H_{13}ON$: C, 82·6; H, 5·3%). It did not depress the melting point of a sample prepared in 36% yield by Phillips, Elbinger, and Merritt's method (*loc. cit.*) (Found: C, 82·3; H, 5·3%). Oxidation with aqueous potassium permanganate in the cold gave 8-hydroxyquinaldic acid, but in variable yield.

THE INORGANIC CHEMISTRY LABORATORIES,
SOUTH PARKS ROAD, OXFORD.

[*Received, June* 19*th*, 1954.]