

U. S. Army Coating and Chemical Laboratory

The Synthesis of Substituted 8-Quinolinols

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2-Isopropyl-8-quinolinol was prepared by alkylation of 8-methoxyquinoline followed by demethylation. The 7-isopropyl-8-quinolinol was prepared in three steps from *o*-isopropylphenol. The reaction of 5-chloromethyl-8-quinolinol hydrochloride with alcohols, amines, ethylene glycols and ether-alcohols gave the corresponding 5-substituted derivatives of 8-quinolinol.

In connection with other studies it was necessary to prepare derivatives of 8-quinolinol (1) containing such groups as alkyl, hydroxy, alkoxy, amino and polyethylenoxy. The alkyl derivatives were position isomers, 2-isopropyl- and 7-isopropyl-8-quinolinol. The 2-isomer (IV) was prepared by alkylation of 8-methoxyquinoline (II) (1) with isopropyllithium at low temperature following the procedure applied to quinoline (2) and 8-quinolinol (3), and demethylation of the intermediate (III). The 2-isopropyl-8-quinolinol (IV) is a crystalline solid in contrast to the known *n*-propyl isomer (3), 2-propyl-8-quinolinol which is a liquid.

The 7-isopropyl-8-quinolinol (IX) was prepared by a three-step synthesis from 2-isopropylphenol (V). Nitration of V with a molar excess of nitric acid gave a mixture of two compounds, liquid 2-isopropyl-6-nitrophenol (VI), and solid 2-isopropyl-4,6-dinitrophenol (VII), which were separated. The infrared spectra of VI and VII confirm their structure by showing in both compounds hydroxyl group bands at 3175 and 3125 cm^{-1} respectively, due to the hydrogen bonding to the *ortho* nitro group (4). According to Fileti (5) nitration under different conditions gives a mixture of two nitro isomers, a liquid presumably impure 2-isopropyl-6-nitrophenol, and a solid 2-isopropyl-4-nitrophenol. Reduction of VI produced the 2-isopropyl-6-aminophenol which, because of its susceptibility to oxidation, was not isolated but converted to its hydrochloride salt (VIII). The hydrochloride (VIII) gave by the Skraup reaction the crystalline quinolinol (IX).

The required 5-substituted derivatives of 8-quinolinol were synthesized from 5-chloromethyl-8-quinolinol hydrochloride (X) whose structure was recently established (6, 7). The starting X, prepared by chloromethylation of 8-quinolinol (6, 7, 8), is difficult to purify (7) because of its great reactivity. Usually it contains small amounts of unreacted 8-quinolinol and 5,5'-methylenebis-8-quinolinol (XI). The chloromethyl compound (X) was readily hydrolyzed to 5-hydroxymethyl-8-quinolinol (XII) and therefore the alcohol (XII) was often found as a by-product in the reaction mixture obtained upon treatment of X with hydroscopic reagents. It was found in this study that prolonged chloromethylation of 8-quinolinol at

room temperature followed by slow crystallization afforded crystals of higher purity and in good yield.

The treatment of X with alcohols gave the ethers XIII, XIV, XV, and XVI. Condensation of X with secondary amines afforded the tertiary amines XVII, XVIII, and XIX in high yield. However, from the reaction of X with *n*-propylamine only the tertiary amine (XX) could be isolated in pure form although an excess of the propylamine was used. The ether-alcohols XXI and XXII and the polyethers XXIII, XXIV, and XXV were obtained by allowing X to react with ethylene glycol, diethylene glycol and the appropriate derivatives of the glycols. A 14-20 molar excess of the glycols was used to obtain only the monosubstituted products XXI and XXII.

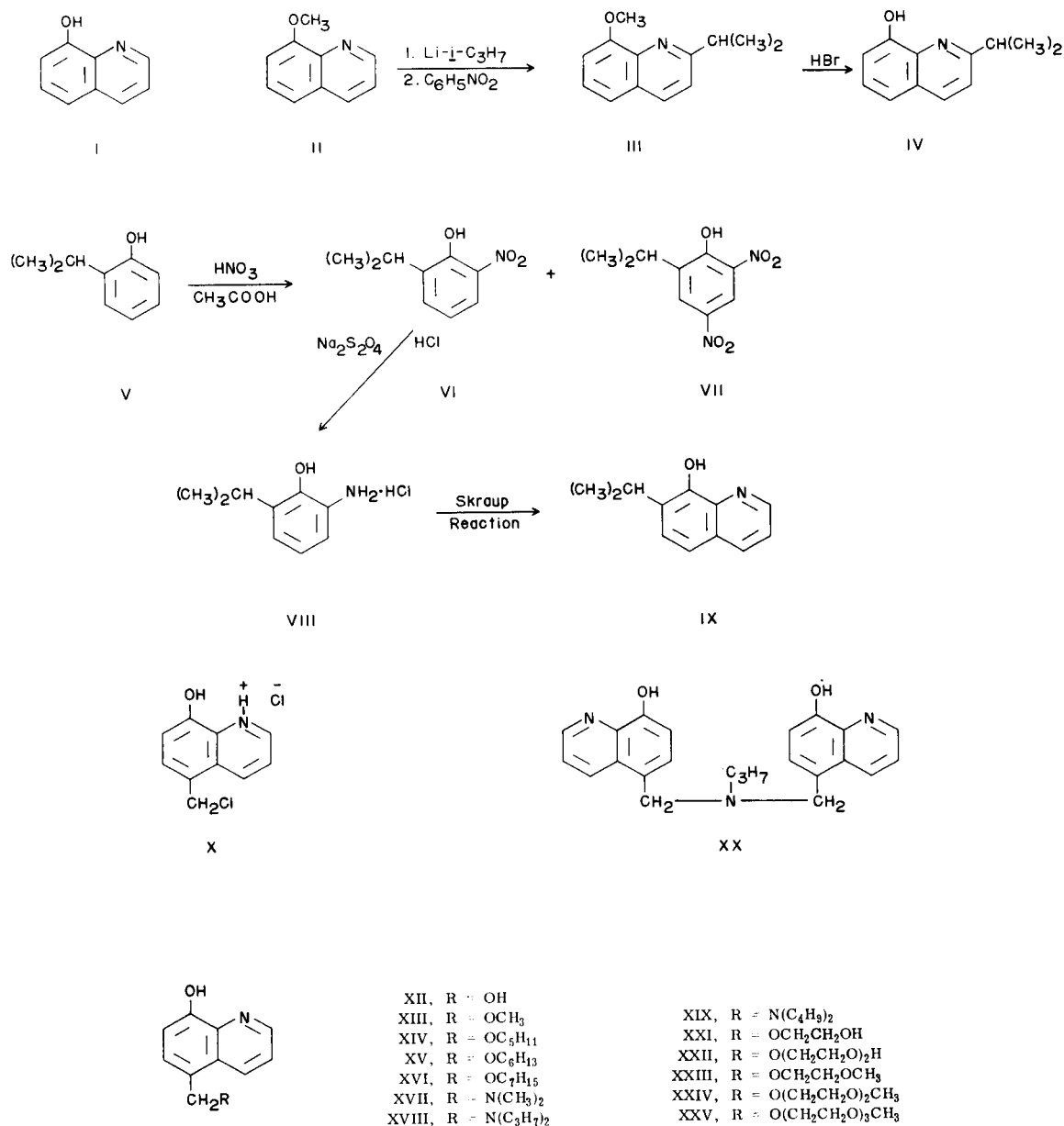
EXPERIMENTAL (9)

2-Isopropyl-8-quinolinol (IV).

Sixty ml. (0.13 mole) of a 2.16 molar solution of isopropyllithium was cooled to -20° under an atmosphere of helium. A solution of 15.9 g. (0.1 mole) of 8-methoxyquinoline in 200 ml. of ether was introduced over a period of 45 minutes while the temperature was maintained at -25 to -35° by cooling in a dry ice-acetone bath. The reaction mixture was allowed to come to 0° and then poured onto ice. Ether extraction gave, after removal of the solvent, a yellow oil 2-isopropyl-8-methoxy-1,2-dihydroquinoline. The oil was oxidized by heating it at reflux temperature with 70 ml. of nitrobenzene for 20 minutes. After cooling the solution was diluted with ether and then washed with 2 *N* hydrochloric acid. The combined aqueous washings were made alkaline with sodium hydroxide and the precipitated oil extracted with ether. The ether was removed by distillation and the oily residue (9.4 g.) 2-isopropyl-8-methoxyquinoline was hydrolyzed by heating at reflux with 40 g. of 49% hydrobromic acid over a period of 12 hours. The excess of hydrobromic acid was removed by vacuum distillation and the residue made alkaline with an aqueous solution of sodium bicarbonate. The precipitated brown solid was separated by filtration and purified by steam distillation. The collected distillate (1.5 l.) gave 3.7 g. (20%) of 2-isopropyl-8-quinolinol, m.p. $84-88^{\circ}$. Recrystallization from pentane raised the melting point to $89-91^{\circ}$.
Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}$: C, 77.00; H, 6.95; N, 7.54. Found: C, 76.93; H, 6.80; N, 7.54.

2-Isopropyl-6-nitrophenol (VI) and 2-Isopropyl-4,6-dinitrophenol (VII).

To a stirred solution of 90 ml. (1.42 mole) of concentrated (70%, d, 1.42) nitric acid in 180 ml. of glacial acetic acid cooled to -15° was introduced dropwise over a period of 2.5 hours a solution of 90 g. (0.66 mole) of freshly distilled *O*-isopropylphenol in 90 ml. of glacial



acetic acid. During the addition the temperature was maintained at -15 to -12°. An additional 90 ml. of glacial acetic acid was added and the mixture stirred for one hour more. The reaction mixture was then poured into 4 l. of water, and steam distilled. The distillate gave two main fractions, the first containing 5 l. and another 50 l. The first fraction, after ether extraction and removal of the solvent, gave a liquid residue. The second fraction containing a yellow solid afforded by filtration 68.4 g. of VII melting at 53-55°. The liquid residue, from the first fraction, contained as impurities acetic and nitric acids. The acids were removed by distillation at 70-80° (bath temperature) and 0.1 mm. The liquid residue was dissolved in ether and the ethereal solution washed with an aqueous solution of sodium bicarbonate. The alkaline washings gave upon acidification an additional 6.2 g. of VII, melting at 53-55°. The ethereal solution was concentrated and the residue purified by distillation to afford 21 g. (18%) of 2-isopropyl-6-nitrophenol, yellow liquid, b.p. 131-135°/20 mm., n_D^{25} 1.5550.

Anal. Calcd. for C₉H₁₁NO₃: C, 59.67; H, 6.08; N, 7.73. Found: C, 59.62; H, 5.94; N, 7.75.

The combined yellow solid (74.6 g., 50%) was recrystallized from hexane to give pure VII, m.p. 54-55°.

Anal. Calcd. for C₉H₁₀N₂O₅: C, 47.79; H, 4.42; N, 12.39. Found: C, 47.80; H, 4.38; N, 12.34.

These compounds were homogenous on gas-liquid chromatography using a column of 20% apiezon L on chromosorb W containing 3%

phosphoric acid.

7-Isopropyl-8-quinolinol (IX).

To a stirred solution of 9.05 g. (0.05 mole) of 2-isopropyl-6-nitrophenol in 240 ml. of 0.25 N sodium hydroxide was introduced sodium hydrosulfite (39 g., 0.225 mole) over a period of 15 minutes. The mixture was stirred for 30 minutes and then heated at reflux for 5 minutes. After cooling, it was extracted with ether and the ether layer dried over anhydrous sodium sulfate. Hydrogen chloride gas was passed through the ethereal solution. The precipitated solid was filtered and washed with ether to give 5.6 g. (60%) of VIII, m.p. 228-230° dec. The product darkens on standing.

A mixture of 10 g. (0.0525 mole) of 2-isopropyl-6-aminophenol hydrochloride, 20 g. (0.22 mole) of glycerol, 22.5 g. (0.1 mole) of sodium *m*-nitrobenzenesulfonate, and 100 ml. of 65% sulfuric acid was stirred and heated at reflux (about 140°) over a period of 4 hours. The mixture was cooled, diluted with water and adjusted to pH 3 with a 15% solution of sodium hydroxide. The precipitated tarry impurity was removed by filtration and the filtrate made alkaline with sodium bicarbonate; a dark colored product precipitated. The crude product (7.7 g.) was purified by sublimation at 80-120° (bath temperature) and 0.1 mm. to give 2.6 g. (25%) of IX, which upon recrystallization from hexane melted at 39-40°.

Anal. Calcd. for C₁₂H₁₈NO: C, 77.00; H, 6.95; N, 7.49. Found: C, 77.14; H, 6.99; N, 7.47.

5-Chloromethyl-8-quinolinol hydrochloride (X).

A mixture of 101.5 g. (0.7 mole) of 8-quinolinol, 250 ml. (3 moles) of concentrated hydrochloric acid, and 250 ml. (3.3 moles) of 37% formaldehyde was stirred while hydrogen chloride gas was passed into the solution over a period of 6 hours. The mixture was kept overnight at room temperature. The yellow crystals which had formed were filtered, washed with ether and dried in the presence of anhydrous calcium chloride and potassium hydroxide at 45-50° *in vacuo* to give 146 g. (91%), m.p. 281-283° dec. [Lit. (8) m.p. 283° dec.].

Anal. Calcd. for $C_8H_8ClNO \cdot HCl$: molecular weight, 229.9. Found by titration with sodium hydroxide: mol. weight, 224.9.

5-Methoxymethyl-8-quinolinol (XIII).

A mixture of 23 g. (0.1 mole) of 5-chloromethyl-8-quinolinol hydrochloride and 250 ml. of anhydrous methanol was heated at reflux temperature for 2 hours. The mixture was poured into 1200 ml. of water and made alkaline with 10% sodium bicarbonate solution. The product which precipitated was filtered, then dissolved in ether and the ethereal solution washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the remaining solid (15 g., 79%) melted at 78-80°. It was recrystallized from hexane, m.p. 79-80°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82; N, 7.41. Found: C, 69.78; H, 5.31; N, 7.43.

5-Pentyloxymethyl-8-quinolinol (XIV).

In a similar manner, 5-chloromethyl-8-quinolinol hydrochloride and 1-pentanol gave the crude product, b.p. 128-129°/0.05 mm., m.p. 45-50° in a yield of 40%. Repeated recrystallization from hexane yielded a pure product, m.p. 52.5-53.5°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 73.47; H, 7.75; N, 5.71. Found: C, 73.29; H, 7.68; N, 5.75.

5-Hexyloxymethyl-8-quinolinol (XV).

In a similar manner, 5-chloromethyl-8-quinolinol hydrochloride and 1-hexanol gave the crude product, b.p. 150-155°/0.3 mm., m.p. 40-42° in a yield of 45%. The pure material melted at 42-43°.

Anal. Calcd. for $C_{14}H_{14}NO_2$: C, 74.13; H, 8.11; N, 5.40. Found: C, 74.09; H, 7.98; N, 5.44.

5-Heptyloxymethyl-8-quinolinol (XVI).

Similarly, 5-chloromethyl-8-quinolinol hydrochloride and 1-heptanol gave the pure product, m.p. 52-52° in a yield of 23%.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 74.73; H, 8.42; N, 5.13. Found: C, 74.80; H, 8.23; N, 5.14.

5-Dimethylaminomethyl-8-quinolinol (XVII).

Liquid dimethylamine (45 g., 1 mole) was added to ice-cooled hexane (250 ml.). To this stirred solution was introduced 5-chloromethyl-8-quinolinol hydrochloride (46 g., 0.2 mole) over a period of 10 minutes. The mixture was allowed to come to room temperature, stirred for 30 minutes and then boiled for an additional 90 minutes. It was then cooled and diluted with ether. The precipitate which was formed, dimethylamine hydrochloride was filtered and washed with ether. The combined filtrate was washed with water and dried. After removal of the solvents it gave 28.8 g. (72%) of XVII, m.p. 100-105°. The product was purified by sublimation at 90°/0.1 mm. followed by recrystallization from ligroin (60-90°) to yield a sample melting at 113-115°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86. Found: C, 71.28; H, 6.92; N, 13.82.

5-Di-*n*-propylaminomethyl-8-quinolinol (XVIII).

The product was prepared in a yield of 98% by reacting in a similar manner 5-chloromethyl-8-quinolinol hydrochloride with a hexane solution of di-*n*-propylamine, m.p. 83-84° (after sublimation at 100°/0.1 mm. and crystallization from hexane).

Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.42; H, 8.53; N, 10.85. Found: C, 74.04; H, 8.46; N, 10.74.

5-Di-*n*-butylaminomethyl-8-quinolinol (XIX).

In a similar manner 5-chloro-8-quinolinol hydrochloride and di-*n*-butylamine in hexane gave XIX in a yield of 77%, m.p. 69-70° (sublimation at 120°/0.1 mm., followed by recrystallization from hexane).

Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 75.52; H, 9.09; N, 9.79. Found: C, 75.04; H, 9.02; N, 9.74.

N,N-Bis-(8-hydroxy-5-quinolylmethyl)propylamine (XX).

A mixture of 23 g. (0.1 mole) of 5-chloromethyl-8-quinolinol hydro-

chloride, 30 g. (0.5 mole) of *n*-propylamine and 200 ml. of hexane was stirred at reflux for 2 hours. After cooling the precipitate *n*-propylamine hydrochloride was filtered and washed with ether and benzene. Concentration of the filtrate gave as first crop 5.4 g. (29%) of crystals melting at 155-159°. Recrystallization from benzene raised the melting point to 158-160°.

Anal. Calcd. for $C_{23}H_{23}N_3O_2$: C, 73.99; H, 6.17; N, 11.26. Mol. weight, 373. Found: C, 74.50; H, 6.04; N, 11.18. Mol. weight by titration with perchloric acid, 396.

Further concentration of the filtrate containing hexane gave several successive crops which melted over a wide range of temperature.

5-(2-Hydroxyethoxymethyl)-8-quinolinol (XXI).

To a stirred ethylene glycol (248 g., 4 moles), dried earlier over molecular sieves was added 5-chloromethyl-8-quinolinol hydrochloride (46 g., 0.2 mole). After stirring for 4 hours at 120°, the mixture was cooled and poured into 2 l. of ether. The lower oily layer, containing hydrochloride salt was separated, washed with ether and then dissolved in water. The aqueous solution, after being made alkaline with sodium bicarbonate, gave 28 g. (64%) of a solid, m.p. 103-106°. Fractional distillation afforded XXI, b.p. 190-200°/0.1 mm., which was recrystallized from benzene, m.p. 108-109°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94; N, 6.39. Found: C, 65.74; H, 5.52; N, 6.34.

5-(7-Hydroxy-2,5-dioxheptyl)-8-quinolinol (XXII).

Similarly, 5-chloromethyl-8-quinolinol hydrochloride and diethylene glycol gave the pure product in a yield of 13.5%, m.p. 61-62° (after sublimation at 150-160°/0.05 mm. followed by crystallization from benzene).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.88; H, 6.46; N, 5.32. Found: C, 63.78; H, 6.38; N, 5.34.

5-(2-Methoxyethoxymethyl)-8-quinolinol (XXIII).

Similarly, 5-chloromethyl-8-quinolinol hydrochloride and ethylene glycol monomethyl ether gave the compound in a yield of 43%, b.p. 137-142°/0.1 mm., m.p. 70-71° (crystallization from heptane).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44; N, 6.01. Found: C, 66.94; H, 6.41; N, 5.97.

5-(2,5,8-Trioxanonyl)-8-quinolinol (XXIV).

Similarly, 5-chloromethyl-8-quinolinol hydrochloride and diethylene glycol monomethyl ether gave the compound in a yield of 54%, b.p. 172-174°/0.05 mm., n_D^{24} 1.5742.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.98; H, 6.86; N, 5.05. Found: C, 64.94; H, 6.82; N, 4.98.

5-(2,5,8,11-Tetroxadodecyl)-8-quinolinol (XXV).

Similarly, 5-chloromethyl-8-quinolinol hydrochloride and triethylene glycol monomethyl ether gave the compound in a yield of 27.5%, b.p. 200-206°/0.2 mm., n_D^{25} 1.5585.

Anal. Calcd. for $C_{17}H_{23}NO_5$: C, 63.55; H, 7.17; N, 4.36. Found: C, 63.42; H, 7.09; N, 4.40.

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