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Preparation of 5-Acetyl-8-quinolinol Derivatives

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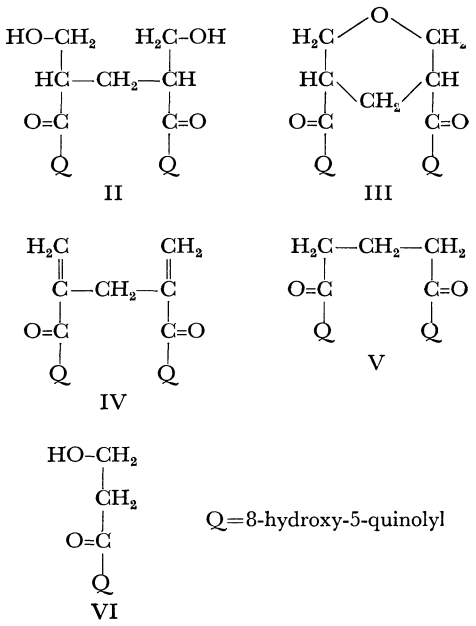
It has been reported[1,2] that 5-acetyl-8-quinolinol (I) was obtained by the Friedel-Crafts reaction of 8-quinolinol and when heated with formalin in the absence of base, I gave 1,5-bis-(8-hydroxy-5-quinolyl)-1,5-dioxopentane (V) instead of the expected methylol compound VI.

In the present experiments, it was found that 8-acetoxyquinolinium chloride on treating with aluminum chloride in nitrobenzene gave 5-acetyl-8-quinolinol (I) with a comparable yield as in the case of the Friedel-Crafts reaction.

The reaction of 5-acetyl-8-quinolinol (I) with formaldehyde as well as bromination of I were investigated.

It was found that reaction of I with formaldehyde in the presence of aqueous sodium hydroxide at room temperature led to the formation of 2,4-bis(8-hydroxy-5-quinolylcarbonyl)-1,5-pentanediol (II). In accordance with the structure II, strong intramolecular hydrogen bond was observed in the region on 3000 cm^{-1} in the IR spectrum of II.

On heating it in crystals at 180°C or in the concentrated sulfuric acid solution at water bath temperature, II was converted into 3,5-bis(8-hydroxy-5-quinolylcarbonyl)tetrahydropyrane (III). On the other hand, on heating of the solution in 30% sulfuric acid on a water bath, II afforded 2,4-bis(8-hydroxy-5-quinolylcarbonyl)-1,4-pentadiene (IV) in a good yield. On heating of ethanol or 6N hydrochloric acid solution of II at water bath temperature, a part of II was converted into



1) K. W. Rosenmund and G. Karst, *Arch. Pharm.* (Weinheim), **279**, 154 (1941); W. Borsche and H. Groth, *Ann. Chem.*, **549**, 238 (1941); K. Matsumura, *J. Amer. Chem. Soc.*, **52**, 4433 (1930).

2) K. Matsumura and C. Sone, *J. Amer. Chem. Soc.*, **53**, 1490 (1931).

III, whereas II could be safely recrystallized from hot benzene without any conversion into III showing that II is unstable to hot protic solvent. It was thought that II might have been formed through V[2] which was obtained through the reaction between 5-acetyl-8-quinolinol (I) and formalin in the absence of base. When V was treated with a mixture of formalin and sodium hydroxide solution, because of its insolubility to the mixture, V was recovered unaltered. From this the formation of II through V is not probable and II may be formed through the condensation of two moles of the methylol compound (VI) with one mole of formaldehyde. To these condensation products, the structures II, III and IV were assigned respectively in consideration of the analytical figures of the free bases, their hydrochlorides and acetyl derivatives.

When brominated with two equivalent atoms of nascent bromine, I gave 5-acetyl-7-bromo-8-quinolinol (VII) which on further bromination produced 5,7-dibromo-8-quinolinol[3] (VIII) in quantitative yield and the expected 7-bromo-5(α-bromoacetyl)-8-quinolinol could not be obtained. VII and VIII exhibited a deep red color with diazotized sulfanilic acid and alkali, showing that these bromines are easily displaced by arylazo group. 5-Acetyl-7-iodo-8-quinolinol,[4] on treating with iodine-potassium iodide or sodium hypoiodite solution at 10°C, no further iodination took place and the initial material was recovered.

Experimental

2,4-Bis(8-hydroxy-5-quinolylcarbonyl)-1,5-pentanediol (II). 5-Acetyl-8-quinolinol (1.87 g, 0.01 mol) was dissolved in a mixture of formalin (37%, 8.1 g, 0.05 mol) and 2.5N sodium hydroxide solution (5 g) with stirring at room temperature. After standing overnight, the solution was acidified (B.T.B. pH 3.6) with dilute acetic acid. A resinous material which soon turned to crystals separated from the solution. It formed orange yellow leaflets containing water of crystallization which was removed on standing *in vacuo* over potassium hydroxide at room temperature or on recrystallization from benzene. Yield, 1.8 g (67%).

Found: H_2O (water of crystallization), 5.21%. Calcd for $C_{25}H_{22}O_6N_2 \cdot 1.5H_2O$: H_2O, 5.71%.

On recrystallization from benzene, it formed light yellow prisms, melting at about 145°C, turning to a solid up to 180°C and unaltered at 300°C. IR (cm^{-1}, KBr) 3500, 3075, 2850 (OH), 1650 (>CO), 1280 (C_6H_5–CO–).

Found: C, 67.42; H, 4.99; N, 6.32%. Calcd for $C_{25}H_{22}O_6N_2$: C, 67.26; H, 4.93; N, 6.28%.

The Hydrochloride of II crystallized as colorless prisms from 3N hydrochloric acid, mp 255°C.

Found: C, 57.15; H, 4.71; N, 5.63%. Calcd for $C_{25}H_{22}O_6N_2 \cdot 2HCl$: C, 57.80; H, 4.62; N, 5.39%.

The Sulfate of II crystallized as columns from 30% sulfuric acid, mp 115—123°C.

Found: C, 43.82; H, 4.72; N, 4.55%. Calcd for $C_{25}H_{22}O_6N_2 \cdot 2H_2SO_4 \cdot H_2O$: C, 44.25; H, 4.43; N, 4.30%.

Tetraacetyl Derivative of II. A mixture of II (100 mg), fused sodium acetate (100 mg) and acetic anhydride (200 mg) was allowed to stand for 7 days at room temperature and then poured into ice water. The product crystallized as glistening colorless plates from ether, mp 115°C.

Found: C, 64.30; H, 5.16; N, 4.59%. Calcd for $C_{33}H_{30}O_{10}N_2$: C, 64.50; H, 4.89; N, 4.56%. The product obtained by heating a mixture of II and acetic anhydride for 3 hr at 130°C formed thick plates when crystallized from ether, mp 108—112°C (Found: N, 4.60%). From the estimated nitrogen content, it is evident that on heating at 130°C with acetic anhydride, dehydration which might be expected to take place between the two primary alcohols did not occur.

Treatment of II with Hot Ethanol. A solution of II (400 mg) in ethanol (20 m*l*) was heated at 80°C for one half hr and the crystals (9 mg), mp 298°C, which separated on cooling, were identified as III by comparison of the IR spectrum with the sample described below.

Treatment of II with 6N Hydrochloric Acid. A solution of II (200 mg) in 6N hydrochloric acid (2 m*l*) was heated at 98°C for 4 hr. The solid, which appeared on addition of sodium acetate to the cooled solution, was collected by filtration and repeatedly washed with hot ethanol. The crystals (10 mg), mp 300°C, which remained undissolved in ethanol were identified as III by comparison of the IR spectrum with that of the sample described below.

3,5-Bis(8-hydroxy-5-quinolylcarbonyl)tetrahydropyran (III). Method A. II (300 mg) was heated at 180° for one hr and the product crystallized as colorless plates from nitrobenzene. Mp: unaltered at 300°C. Yield, 200 mg. IR (cm^{-1}, KBr) 3075 (OH), 1660 (>CO), 1280 (C_6H_5–CO–), 1110, 480 (C–H_2–O–CH_2–).

Found: C, 70.27; H, 4.51; N, 7.11%; mol wt (Mass), 428. Calcd for $C_{25}H_{20}O_5N_2$: C, 70.01; H, 4.67; N, 6.54%; mol wt 428.

Method B. A solution of II (220 mg) in concentrated sulfuric acid (2.2 g) was heated at 100°C for one hr, poured into ice water. The resultant solution was made alkaline with sodium carbonate and then acidified with acetic acid. The separated solid (170 mg) was recrystallized as colorless leaflets from nitrobenzene, mp 300°C. The IR spectrum was identical with that of the product obtained by method A.

The Hydrochloride of III formed long needles on crystallization from 3N hydrochloric acid. The crystals were unaltered at 300°C and completely hydrolysed in water.

Found: C, 54.53; H, 4.85; N, 5.26%. Calcd for $C_{25}H_{20}O_2N_2 \cdot 2HCl \cdot 2.5H_2O$: C, 54.93; H, 4.95; N, 5.13%.

Diacetyl Derivative of III was prepared by heating a mixture III (80 mg), fused sodium acetate (80 mg) and acetic anhydride (400 mg) at 110°C for 3 hr. The product crystallized as colorless needles from acetone, mp 231—234°C.

3) A. Claus and H. Howitz, *J. Prakt. Chem.* [2], **44**, 444 (1891); K. Matsumura and M. Ito, *J. Amer. Chem. Soc.*, **77**, 6672 (1955).

4) K. Matsumura and M. Ito, *J. Org. Chem.*, **25**, 853 (1960).

Found: C, 68.18; H, 4.58; N, 5.55%. Calcd for $C_{29}H_{24}O_7N_2$: C, 67.97; H, 4.69; N, 5.47%.

2,4-Bis(8-hydroxy-5-quinolylcarbonyl)-1,4-pentadiene (IV). A solution of II (1.8 g) in 30% sulfuric acid (18 g) was heated at 95°C for 2 hr and, after cooling, poured into ice water and the solid (1.63 g) which appeared on addition of excess sodium acetate was collected by filtration and dissolved in hot 3N hydrochloric acid. After cooling, the separated fine needles (A) was collected and washed with water. On addition of sodium acetate to the combined filtrate and washings (charcoal), a yellow solid 1.38 g (84%), mp 155°C separated. On recrystallization from benzene (charcoal), it formed colorless prisms, mp 162—165°C (decomp.). IR (cm^{-1}, KBr) 3300 (OH), 1660 (—CO), 1280, 1240 C_6H_5–CO-, 1630 (CH_2=CH–).

Found: C, 73.21; H, 4.75; N, 7.57%. Calcd for $C_{25}H_{18}O_4N_2$: C, 73.17; H, 4.39; N, 6.83%.

(A) was treated with aqueous sodium acetate and the resultant needles, mp 300°C, was identified as III (Found: C, 73.21; H, 4.75; N, 7.57%) by comparison of IR spectrum with that of the sample prepared by another method.

The Hydrochloride of IV. It was prepared by dissolving IV in 3N hydrochloric acid, evaporating the solvent at room temperature to dryness and recrystallizing the residue from ethanol. It formed plates, mp 250°C (decomp.). Found: C, 56.52; H, 4.65; N, 5.79%. Calcd for $C_{25}H_{18}O_4N_2 \cdot 2HCl \cdot 2.5H_2O$:*1 C, 56.82; H, 4.73; N, 5.30%.

Found: C, 61.85; H, 4.27; N, 6.55%. Calcd for $C_{25}H_{18}O_4N_2 \cdot 2HCl$:*2 C, 62.11; H, 4.14; N, 5.80%.

The Diacetyl Derivative of IV. A mixture of IV (150 mg), acetic anhydride (200 mg) and fused sodium acetate (200 mg) was heated at 92°C for 2.5 hr. The product on recrystallization from ether, formed colorless prisms, mp 160—162°C (decomp. with foaming).

Found: C, 69.85; H, 4.99; N, 5.98%. Calcd for $C_{29}H_{22}O_6N_2$: C, 70.45; H, 4.45; N, 5.67%.

Fries Reaction with 8-Acetoxyquinoline.

8-Acetoxyquinolinium Chloride. A mixture of 8-hydroxyquinolinium chloride (1.83 g, 0.01 mol) and acetic anhydride (1.2 g, 0.01 mol) was heated on a water bath for 1.5 hr until complete dissolution resulted. After standing overnight the separated crystals were collected by filtration and dried at room temperature over potassium hydroxide *in vacuo*. Yield 1.9 g (85%). Mp 166—168°C.

Found: C, 58.51; H, 4.58; N, 6.47%. Calcd for $C_{11}H_9O_2N \cdot HCl$: C, 59.06; H, 4.47; N, 6.26%.

5-Acetyl-8-quinolinol. A mixture of 8-acetoxyquinolinium chloride (11.2 g, 0.05 mol), nitrobenzene (50 m*l*) and aluminum chloride (18 g) was gently shaken until complete dissolution resulted. The solution was heated at 75°C for 6 hr, then 85°C for 4 hr and finally 95°C for 5 hr (Calcium chloride tube). After cooling, ice (50 g) and 6N hydrochloirc acid (50 m*l*) were added to the solution. After the nitrobenzene was driven off with steam, the solution (charcoal) was concentrated if necessary and the separated hydrochloride was collected by filtration and washed with 3N hydrochloric acid. The hydrochloride was treated with an excess of aqueous sodium acetate to give the free base (I), yield 5.8—6.2 g (62—66%), mp 108—110°C. It formed colorless needles from benzene, mp 113°C. The identity with that obtained by Friedel-Crafts reaction[1] was established by comparison of IR spectra.

Fries reaction with 8-benzoyloxyquinolinium chloride failed to afford benzoyl-8-quinolinol.

5-Acetyl-7-bromo-8-quinolinol. To the solution of 5-acetyl-8-quinolinol (0.19 g, 0.001 mol) in 0.1N hydrochloric acid (36 m*l*), 0.1N bromate-bromide solution (20 m*l*) was added dropwise with stirring at 5°C. After standing for one hr sodium sulfite was added (iodide-starch paper) to the reaction mixture and the resultant solid was recrystallized from benzene as needles, mp 176°C. It exhibited a deep red color with diazotized sulfanilic acid and dilute sodium carbonate solution. On reaction of one mole of bromine in the form of either bromate-bromide solution or molecular bromine, it gave 5,7-dibromo-8-quinolinol[3] in quantitative yield and its identity was established by comparison of IR spectrum with that of authentic sample.

Found: C, 49.50; H, 3.28; N, 5.22%. Calcd for $C_{11}H_8O_2NBr$: C, 49.64; H, 3.01; ,N 5.26%.

*1 Dried at room temperature *in vacuo* over potassium hydroxide overnight.

*2 Dried at 110°C *in vacuo* over phosphorus pentoxide until constant weight.