[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

The Condensation of Formaldehyde with 6-Quinolinol Derivatives

BY C. E. KASLOW AND SAMUEL RAYMOND[1]

It has been reported by Monti and Verona[2] that 6-quinolinol condenses with formaldehyde in sulfuric acid solution to give a dioxinoquinoline while in alkali the condensation product is a methylene-bis-quinolinol. It was desired to investigate this method as one of the possible routes for the synthesis of some 5,5′-methylene-bis-6-methoxyquinoline derivatives.

The dioxino(5,4-f)quinoline (IV) reported by Monti and Verona,[2] which is a cyclic acetal, proved to be extremely resistant to hydrolysis in dilute acid solution. Fuming hydrochloric acid, however, opened the ring but the product, a quinoline analog of saligenin, immediately lost formaldehyde to give the diquinolylmethane, II. The intermediate was captured by carrying out the ring opening in an acetic anhydride–sulfuric acid mixture. This furnished 6-hydroxy-5-hydroxymethylquinoline diacetate (V), which was deacetylated by sodium ethoxide in absolute alcohol at room temperature to 6-hydroxy-5-hydroxymethylquinoline (VI). The compound lost formaldehyde easily to give 5,5-methylene-bis-6-quinolinol (II). Similar condensations resulting in the elimination of formaldehyde have been reported by Euler.[3]

A corresponding series of reactions was carried out with 8-nitro-6-quinolinol, but the methyl ether of this compound did not react. 8-Nitro-6-quinolinol condensed with formaldehyde in sulfuric acid to give a dioxin formulated as 6-nitrodioxino-(5,4-f)quinoline (VII). 5,5′-Methylene-bis-8-nitro-6-quinolinol (XI) was obtained from this compound by way of the diacetate formed in acetic anhydride. Unlike the corresponding compound without nitro groups, this substance could not be obtained by the direct condensation of 8-nitro-6-quinolinol with formaldehyde in alkali; only tars were obtained.

The oxidation of VII resulted in the formation of the cyclic ester-ether, XII.[4] However, the unavailability of nitrohydroxyquinolinecarboxylic acids as reference compounds prevented the use of this reaction for structure proofs. Unfortunately in the unnitrated series no simple oxidation products could be obtained.

These compounds, I and VI, on nitration show a reaction similar to the nitration of many diphenylmethanes and *o*-substituted phenols. The nuclear substituent is displaced by the nitro group. Thus, on nitration VI lost the methylol substituent and gave the mononitroquinolinol described by Skraup.[5]

Experimental

5,5′-Methylene-bis-6-methoxyquinoline (I).—A solution of 16 g. (0.1 mole) of 6-methoxyquinoline and 3.5 g. (0.05 mole) of 40% formalin in 90 cc. of concentrated sulfuric acid was allowed to stand at room temperature for three days. The mixture was then poured into ice-water and the resulting precipitate of the sulfate filtered. After drying at 60° it weighed 21 g. (98%). It was recrystallized from boiling water as plates, which melted at 265°.

The free base was precipitated from the salt in aqueous solution by the addition of alkali and was recrystallized from benzene, m. p. 230°.

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: N, 8.48. Found: N, 8.47.

5,5′-Methylene-bis-6-quinolinol Diacetate[2] (III).—A solution of 13.0 g. (0.03 mole) of the sulfate of I in 75 ml. of 48% hydrobromic acid was refluxed twenty-four hours. The mixture was then cooled and filtered through a sintered glass funnel. There was obtained 13.0 g. (93%) of the hydrobromide of the dihydroxydiquinolylmethane as light yellow crystals, completely soluble in dilute sodium hydroxide, but insoluble in water or acid.

A solution of 0.23 g. of the hydrobromide in 5 ml. of acetic anhydride was refluxed with 0.2 g. of anhydrous sodium acetate for one hour. The mixture was then poured into water, precipitating 0.12 g. (62%) of the diacetate III, m. p. 198–199°. A mixed melting point with the diacetate prepared according to the method of Monti[2] showed no depression. Monti and Verona reported the melting as 204°.

Nitration of I.—The sulfate of I (0.2 g., 0.5 millimole) was dissolved in 1 ml. of sulfuric acid and 1 ml. of nitric acid added with good cooling. The mixture was kept ten minutes and then poured into 50 ml. of ice-water. Upon neutralization a precipitate was formed which on recrystallization from water weighed 0.1 g. (50%), m. p. 104–105°. Occasionally the product melted at 92–94° but resolidified and melted at 105–106°. This is the melting point reported for 5-nitro-6-methoxyquinoline by Decker.[6]

6-Quinolinol.—A solution of 51.4 g. (0.2 mole) of 6-methoxyquinoline bisulfate in 100 ml. of concd. hydrobromic acid was refluxed twelve hours, poured into ice-water, and exactly neutralized with ammonia, keeping the mixture cold. A total of two liters of water was used to precipitate and wash the compound. The product weighed 27 g. (93%) and had a melting point of 189–190°.

Dioxino(5,4-f)quinoline[2] (IV).—The sulfate of 6-quinolinol was prepared by mixing 29 g. (0.2 mole) of 6-quinolinol with 40 ml. of water and adding 20 ml. of sulfuric acid with cooling. The resulting mixture was dissolved in an additional 120 ml. of sulfuric acid and mixed with 37.5 ml. (0.5 mole) of formalin. The solution was allowed to stand twenty hours at room temperature and then poured into one liter of ice-water. The precipitate of II-sulfate (8 g., 10%) was filtered off and the filtrate was made alkaline with ammonia. The precipitated IV weighed 28 g. (75%) and melted at 117–118°. Recrystallization from water raised the melting point to 118–118.7°.

Hydrolysis of IV.—A solution of 0.94 g. (5.0 millimole) of the dioxin, IV, in 2 ml. of concentrated hydrochloric acid was evaporated to dryness on a water-bath. The residue was completely soluble in dilute sodium hydroxide and gave, on neutralization with carbon dioxide, 0.50 g. (66%) of the dihydroxy-diquinolylmethane. It was identified by formation of the insoluble sulfate and the hydro-

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(2) Monti and Verona, *Gazz. chim. ital.*, **62**, 878 (1932).

(3) Euler, Adler and Friedmann, *Chem. Abst.*, **34**, 1095 (1940).

(4) Cf. Chattaway and Goepp, *J. Chem. Soc.*, 699 (1933).

(5) Skraup, *Monatsh.*, **3**, 551 (1882); **4**, 698 (1883).

(6) Decker, *Ber.*, **42**, 1740 (1909).

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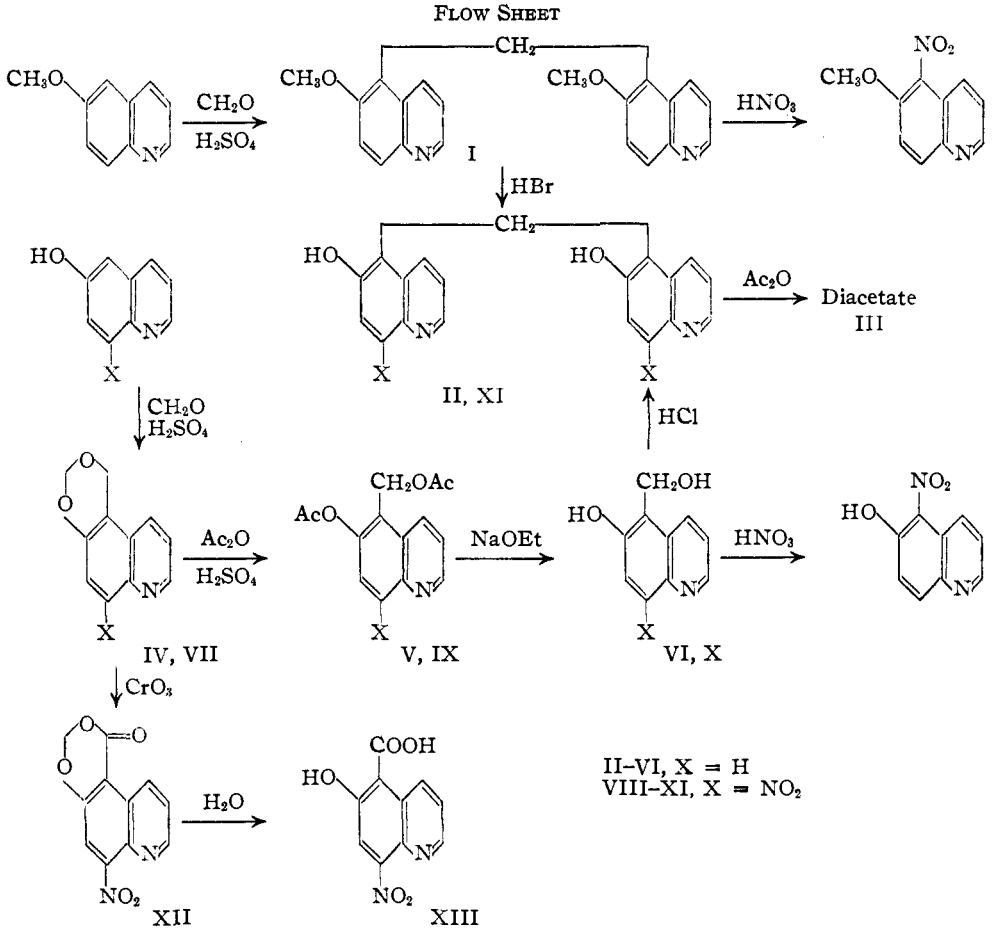

bromide and by conversion to the diacetate, m. p. 196–197°.

No formaldehyde was released, and the starting material was recovered quantitatively, when IV was refluxed in 0.4 *N* acid.

5-Hydroxymethyl-6-quinolinol Diacetate (V).—To a solution of 19 g. (0.1 mole) of IV in 100 ml. of glacial acetic acid was added 50 ml. of acetic anhydride and 15 ml. of concentrated sulfuric acid. The mixture was kept at 20° for eight days. It was then poured into 1 liter of ice and neutralized with 50% sodium hydroxide, adding ice as necessary to keep the temperature below 10°. The precipitate was removed by filtration, washed with two 50-ml. portions of water and dried in vacuum, yield 24 g. (93%), m. p. 103.5°. Recrystallization from 75 ml. of 30% alcohol gave 18.7 g. (72%) of light tan needles which melted at 103.5–103.8°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: N, 5.40. Found: N, 5.42.

5-Hydroxymethyl-6-quinolinol Dihydrate (VI).—The diacetate, V, (11.7 g., 0.045 mole) was deacetylated by treatment with a solution containing two equivalents of sodium (2.07 g.) dissolved in 190 ml. of absolute alcohol. After thirty-six hours, 5 ml. of 4 *N* hydrochloric acid was added and most of the alcohol removed at a reduced pressure. The residue was suspended in water, exactly neutralized and filtered; the yield was 8.0 g. (100%), m. p. 135–137°. The compound decomposed very easily on heating in solution but by working rapidly, 4 g. (50%) which melted at 139°, was obtained on crystallization from dilute alcohol.

Anal. Calcd. for $C_{10}H_9NO_2$: N, 8.00. Calcd. for $C_{10}H_9NO_2 \cdot 2H_2O$: N, 6.64. Found: N, 6.73, 6.67, 6.74.

There was no loss in weight when 0.234 g. of VI was heated in vacuum over phosphoric anhydride at 109° for six hours.

Nitration of VI.—A solution of 0.26 g. (0.1 millimole) of VI in 3 ml. of water and 2 ml. of nitric acid was heated to boiling for three minutes. It was immediately poured into ml. of ice-water and neutralized with potassium carbonate. The yellow precipitate weighed 0.08 g. (40%) and it melted at 135.8–136.2°. Mixed with a sample (m. p. 135.5–136.5°) of 5-nitro-6-quinolinol prepared by the method of Skraup[5] it showed no change in melting point.

8-Nitro-6-quinolinol.—Ninety grams (0.44 mole) of 8-nitro-6-methoxyquinoline in 250 ml. of 48% hydrobromic acid was refluxed five hours. To the resulting mixture of hydrobromic acid and insoluble quinoline salt was added 47 ml. (0.9 mole) of concentrated sulfuric acid in 1 liter of water and the mixture distilled at 25 mm. pressure to dryness on a water-bath. A liter of distilled water was added to the residue and again distilled. The residue was now completely soluble in 1 liter of water. On neutralization with ammonia, 85 g. (100%) of the desired product was obtained.

6-Nitrodioxino(5,4-f)quinoline (VII).—A solution of 19 g. (0.1 mole) of 8-nitro-6-quinolinol and 6.0 g. (0.2 mole) of trioxane in 100 ml. of concentrated sulfuric acid was allowed to stand fourteen days at room temperature. It was then poured into 1 liter of ice-water and neutralized with 195 ml. of 50% sodium hydroxide solution. The precipitate weighed 21 g. (84%) and the substance melted at 187–188°. Two recrystallizations from methyl ethyl ketone and treatment with Norite raised the melting point to 203.5–204°. The yield of the purified VII was 12 g.; an additional 5 g. was obtained from the mother liquors.

Anal. Calcd. for $C_{11}H_8N_2O_4$: N, 12.07. Found: N, 12.14.

Attempts at hydrolysis of VII in dilute hydrochloric acid were unsuccessful; only the unchanged dioxino compound was recovered. Treating with fuming hydrochloric acid caused the formation of a tar from which nothing could be extracted.

8-Nitro-5-hydroxymethyl-6-quinolinol Diacetate (IX).—A solution of 1.16 g. (0.005 mole) of VII in 10 ml. of acetic anhydride, 15 ml. of acetic acid, and 5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for seven days. It was then poured into 200 ml. of water and stirred to hydrolyze the excess anhydride. The precipitate of light yellow needles was filtered and washed, giving 1.15 g. (76%) of pure IX, m. p. 173–173.5. Recrystallization from benzene did not raise the melting point.

Anal. Calcd. for $C_{14}H_{12}N_2O_6$: N, 9.21. Found: N, 9.33.

8-Nitro-5-hydroxymethyl-6-quinolinol (X).—The diacetate, IX, (3.04 g., 0.01 mole) was dissolved in 50 ml. of absolute alcohol containing 0.46 g. (0.02 mole) of sodium. After one and one-half hours the solution was poured into 120 ml. of water and allowed to stand for several hours after neutralization to allow complete precipitation of X. After drying the solid, it was dissolved in benzene, filtered and the benzene solution was concentrated in vacuum at a low temperature to a small volume and diluted with an equal volume of ligroin (b. p. 75–85°). A yield of 1.4 g. (62%) of yellow crystals melting at 97–99° was obtained.

Anal. Calcd. for $C_{10}H_8N_2O_4$: N, 12.83. Found: N, 12.72.

The substance is quite unstable; after standing for several days, the odor of formaldehyde was very noticeable and the material became a dark red color. The main product of decomposition is presumably 5,5′-methylene-bis-8-nitro-6-quinolinol, XI, which can be separated due to its insolubility in benzene. The same substance was obtained when either IX or X was boiled with a dilute aqueous solution of potassium carbonate. A strong odor of formaldehyde was evident. When the solution was neutralized with acetic acid, a quantitative yield of a light brown solid was obtained; the substance showed no indication of melting at 320°.

Oxidation of VII.—To a solution of 1.16 g. (0.005 mole) of VII in 10 ml. of acetic acid was added, at a temperature of 25–30°, a solution of 1.3 g. of chromic anhydride in 10 ml. of acetic acid. The solution became dark green immediately and after five minutes was poured into 200 ml. of water. The resulting precipitate was filtered off and washed with water. A yield of 0.80 g. (65%) of the substance was obtained as short white needles which melted at 219–220°.

Anal. Calcd. for $C_{11}H_6N_2O_5$: N, 11.38. Found: N, 11.33.

The oxidation product was insoluble in cold sodium carbonate solution but dissolved readily on heating. Neutralization precipitated an acidic compound, m. p. 194–195°. The structure of this acid has not been proven as yet but is probably that represented by XIII.

5,5′-Methylene-bis-8-acetamido-6-methoxyquinoline.—A solution of 10.8 g. (0.05 mole) of 8-acetamido-6-methoxyquinoline in 20 ml. of cold concentrated sulfuric acid was treated with 2 ml. (0.025 mole) of formalin and allowed to stand for nine days. The reaction mixture was poured into ice-water, neutralized and the light colored solid removed by filtration. The dried solid weighed 11.5 g. (100%). The substance was recrystallized from boiling xylene as white needles. The recovery was nearly quantitative; m. p. 298–299°.

Anal. Calcd. for $C_{25}H_{24}N_4O_4$: N, 12.79. Found: N, 12.50.

Summary

The condensation of 6-methoxyquinoline with formaldehyde in sulfuric acid solution gave 5,5′-methylene-bis-6-methoxyquinoline, while condensation of 6-quinolinol and 8-nitro-6-quinolinol with formaldehyde in sulfuric acid gave dioxino(5,4-f)-quinoline and 6-nitrodioxino(5,4-f)quinoline, respectively. Treatment of the dioxino compounds in acetic anhydride–sulfuric acid mixture gave the diacetates of 5-hydroxymethyl-6-quinolinol and 8-nitro-5-hydroxymethyl-6-quinolinol. These latter substances converted readily to the corresponding diquinolylmethanes.

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

Analogs of Vitamin A[1]

BY HARRY SOBOTKA AND J. D. CHANLEY

The preparation of vitamin A from β-ionone has recently been described by Arens and Van Dorp[2] and by Isler, Huber, Ronco and Kofler.[3] These accomplished syntheses as well as all other reported efforts[4–8] in the direction of vitamin A alcohol and its methyl ether have been based on β-ionone as starting material, because this substance, derived from the naturally occurring citral, contains 13 of the 20 carbon atoms of axerophthol in properly assembled form.

The following considerations suggested to us the idea to attack the synthesis of vitamin A from simpler starting materials:[9] the supply of lemon grass oil, the primary source of β-ionone, from tropical regions had become precarious during the war. In a series of studies[10] the tendency of isomerization of the β-cyclogeranyl ring was demonstrated under certain conditions, likely to

(1) The work described in this report was initiated under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Mount Sinai Hospital. Part of the material described is contained in classified progress reports to OSRD, dated December 24, 1943, February 25 and April 17, 1944.

(2) Arens and Van Dorp, *Nature*, **160**, 189 (1947); *cf. Rec. trav. chim.*, **65**, 338 (1946).

(3) Isler, Huber, Ronco and Kofler, *Helv. Chim. Acta*, **30**, 1911, (1947); *cf.* Festschrift f. E. Barell, p. 31 (Bale, 1946).

(4) Kuhn and Morris, *Ber.*, **70**, 853 (1937).

(5) Kipping and Wild, *Chem. and Ind.*, **58**, 802 (1939).

(6) Milas, U. S. Patents 2,369,156–168; 2,382,085–086 (1945).

(7) Oroshnik, THIS JOURNAL, **67**, 1627 (1945).

(8) Heilbron and co-workers whose numerous important contributions to this subject are summarized in *J. Chem. Soc.*, 386 (1948); *cf. ibid.*, 727 (1942).

(9) Sobotka, Progress Reports 1942–1944, Final Report 1944 to OSRD, distributed by Office of Production Board, Nos. 77, 214–215 (1947).

(10) Sobotka, Bloch and Glick, THIS JOURNAL, **65**, 1961; Sobotka, Cahnmann, Feldbau and Rosen, *ibid.*, **65**, 2061 (1943); Sobotka, Darby, Glick and Bloch, *ibid.*, **67**, 403 (1945); Sobotka and Bloch, *Chem. Revs.*, **34**, 435 (1944).