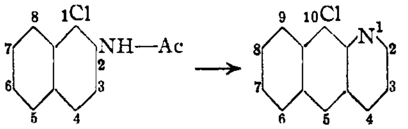
[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Derivatives of 10-Chlorobenzo(g)quinoline

BY FRANCIS H. GERHARDT[1] AND CLIFF S. HAMILTON

Several series of benzoquinolines have been prepared in this Laboratory and studied as intermediates for possible antimalarials.[2] In this particular investigation some nitro and amino derivatives of 10-chlorobenzo(g)quinoline were synthesized.

1-Chloro-2-acetamidonaphthalene (I) was subjected to the Skraup reaction to give 10-chlorobenzo(g)quinoline (V).[3] By the same Skraup procedure, the 5-nitro- (II), 6-nitro- (III), and 8-nitro- (IV) derivatives of (I) yielded, respectively, the 6-nitro- (VI), 7-nitro- (VII) and 9-nitro- (VIII) derivatives of (V). The action of fuming nitric acid on (V) gave chiefly (VI), together with a smaller amount of (VIII).



I V

(II), (III) and (IV) were prepared by chlorination of the corresponding nitroacetamidonaphthalenes by the same procedure[4] used to prepare (I). They were also formed by the nitration of (I); thus the position of the chlorine atom was established.

Morpholine and piperidine condensed with (V) in sealed tubes in poor yields; no reaction occurred with diethylamine. The lability of the chlorine atom of (V) was not markedly increased by the introduction of a nitro group into the benzo ring. Morpholine condensed with (VI) and with (VII) under reflux in poor yields; no reaction occurred with diethylamine in sealed tubes. (VI) was reduced to 6-amino-10-chlorobenzo(g)quinoline with iron and dilute acetic acid.

Treatment of (V) in chloroform with chlorine gave the dichlorobenzo(g)quinoline reported by Koeberle and Ploetz.[3] This compound was proved to be 5,10-dichlorobenzo(g)quinoline by its oxidation to the known benzo(g)quinoline-5,10-dione.[5]

Experimental

Preparation of Naphthalene Intermediates.—(I), (II), (III) and (IV) were prepared by the direct chlorination of the corresponding acetamidonaphthalene derivative in acetic acid according to the procedure of Franzen and Stäuble,[4] the resulting compounds being recrystallized from ethanol, forming white needles.

1-CHLORO-X-NITRO-2-ACETAMIDONAPHTHALENE, $C_{12}H_9ClN_2O_3$

X	M. p., °C.	Yield, %	Percentage composition Carbon Calcd.	Found		Hydrogen Calcd.	Found	
5	183–185	80	54.45	54.28	54.66	3.43	3.48	3.46
6[a]	221–223	76	54.45	54.55	54.48	3.43	3.40	3.47
8	188–190	65	54.45	54.59	54.63	3.43	3.57	3.66

[a] Pale yellow.

Treatment of (I) with fuming nitric acid (d. 1.49) at −10° gave a mixture of (II) and (IV) which was separated by fractional crystallization from ethanol. No depression in melting point resulted when samples of (II) obtained by nitration and by chlorination were mixed; mixtures of samples of (IV) from the two sources also exhibited no melting point depression.

The action of fuming nitric acid (d. 1.49) on a solution of (I) in glacial acetic acid at room temperature resulted in some (III). Samples of (III) prepared by nitration and by chlorination exhibited no depression in melting point when mixed.

10-Chlorobenzo(g)quinoline (V).—Sulfuric acid, glycerol, arsenic acid and (I) were heated according to the procedure of Koeberle and Ploetz.[3] The crude product was extracted with acetone, the extract treated with charcoal and added dropwise to water with rapid stirring. (V) was obtained as cream-colored crystals; m. p. 138–140°; yield, 34%.

6-Nitro-10-chlorobenzo(g)quinoline (VI).—To 10 ml. (0.23 mole) of fuming nitric acid (d. 1.49) cooled to −18° in a snow–hydrochloric acid bath was added 2 g. (0.01 mole) of (V) in small portions. After fifteen minutes the solution was poured into 200 ml. of water. The precipitate which separated was filtered, washed with sodium bicarbonate solution to remove oxides of nitrogen, and extracted with 100 ml. of boiling ethanol. The extract was set aside (see preparation of (VIII) below) and the residue recrystallized from ethanol to give (VI) as fluffy yellow needles; m. p. 211–212°; yield, 1 g. (45%).

Anal. Calcd. for $C_{13}H_7ClN_2O_2$: C, 60.36; H, 2.72. Found: C, 60.29, 60.31; H, 2.44, 2.73.

(VI) was also prepared by subjecting (II) to the same Skraup procedure used to prepare (V). The two samples of (VI) exhibited no depression in melting point when mixed.

7-Nitro-10-chlorobenzo(g)quinoline (VII).—A mixture of 32 g. (0.12 mole) of (III), 50 ml. (0.66 mole) of glycerol and 100 ml. of 70% sulfuric acid (1.6 mole) was heated to gentle reflux by means of an oil-bath. A solution of 30 g. (0.13 mole) of arsenic acid in 75 ml. of 70% sulfuric acid (1.2 mole) was added in the course of thirty minutes. Heating was continued for another thirty minutes and the cooled mixture poured into 800 ml. of water and allowed to stand a few hours. The solution was filtered through a cellite pad and the filtrate neutralized with dilute sodium hydroxide. The crude product was extracted with acetone, the extract treated with charcoal and slowly poured into water. The resulting yellow solid was recrystallized three times from ethanol; yellow needles; m. p. 243–245°; yield, 1.2 g. (4%).

Anal. Calcd. for $C_{13}H_7ClN_2O_2$: C, 60.36; H, 2.72. Found: C, 60.60, 60.36; H, 2.90, 2.81.

9-Nitro-10-chlorobenzo(g)quinoline (VIII).—See preparation of (VI), above. Upon cooling, the alcoholic extract of the nitration product deposited a yellow solid; yellow crystals from ethanol; m. p. 209–211°; yield, 0.3 g. (12%).

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[1] Parke, Davis and Company Fellow.

[2] Clem and Hamilton, THIS JOURNAL, **62**, 2349 (1940); Utermohlen and Hamilton, *ibid.*, **63**, 156 (1941); Barnum and Hamilton, *ibid.*, **64**, 540 (1942); Mueller and Hamilton, *ibid.*, **65**, 1017 (1943).

[3] Koeberle and Ploetz, U. S. Patent 2,003,596 (1935).

[4] Franzen and Staüble, *J. prakt. Chem.*, [2] **103**, 381 (1922).

[5] Phillips, *Ber.*, **27**, 1925 (1894); Braun and Gruber, *ibid.*, **55B**, 1711 (1922).

Anal. Calcd. for $C_{13}H_7ClN_2O_2$: C, 60.36; H, 2.72. Found: C, 60.46, 60.61; H, 2.86, 2.92.

A mixture of some of this material and (VI) melted from 161–190°. However, these yellow crystals did not lower the melting point of the product obtained by subjecting (IV) to the same Skraup procedure used to prepare (V).

10-Morpholinobenzo(g)quinoline (IX).—In a sealed tube 2 g. (0.01 mole) of (V), 15 ml. (0.17 mole) of morpholine, and a few crystals of potassium iodide were heated at 150° for thirty-six hours. The reaction mixture was poured into 100 ml. of water and the resulting gummy precipitate dissolved in 5% hydrochloric acid. The acid solution was treated with charcoal and dilute sodium hydroxide added until the solution was barely acid. The unreacted (V) was removed by filtration and the filtrate made alkaline. The greenish-yellow solid was recrystallized twice from ethanol; bright yellow prisms; m. p. 160–161°; yield, 0.15 g. (6%).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10. Found: C, 77.10, 77.34; H, 6.19, 6.16.

10-Piperidinobenzo(g)quinoline (X).—In a sealed tube 2 g. (0.01 mole) of (V) and 12 ml. (0.13 mole) of piperidine were heated at 150° for thirty-six hours. The reaction mixture was treated as in the preparation of (IX). Recrystallization of the product from ethanol gave bright-yellow needles; m. p. 97–99°; yield, 0.2 g. (8%).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.42; H, 6.91. Found: C, 82.27, 82.22; H, 7.07, 7.01.

5,10-Dichlorobenzo(g)quinoline (XI).—According to the procedure of Koeberle and Ploetz,[3] 3 g. of (V) was dissolved in chloroform and chlorine slowly bubbled in. The precipitate formed was treated with ammonium hydroxide and recrystallized twice from ethanol; yellow needles; m. p. 213–215°; yield, 2.5 g. (71%).

Anal. Calcd. for $C_{13}H_7Cl_2N$: C, 62.92; H, 2.84. Found: C, 62.86; H, 2.91.

In their patent[3] Koeberle and Ploetz neither characterized this chlorination product nor proved its structure. Refluxing (XI) with chromium trioxide in glacial acetic acid gave a tan solid which was recrystallized from benzene as tan needles; m. p. 278–280°. This product did not contain chlorine and its melting point agreed with that reported[5] for benzo(g)quinoline-5,10-dione. Hence, the chlorination product was 5,10-dichlorobenzo(g)quinoline.

6-Nitrobenzo(g)quinoline-5,10-dione (XII).—A mixture of 0.6 g. (0.002 mole) of (VI), 0.2 g. (0.002 mole) of chromium trioxide and 20 ml. of glacial acetic acid was refluxed for twenty-five hours. The reaction mixture was poured into water and the precipitate recrystallized twice from ethanol; pale tan crystals; m. p. 243–245°; yield, 0.25 g. (42%).

Anal. Calcd. for $C_{13}H_6N_2O_4$: C, 61.42; H, 2.34. Found: C, 61.52, 61.37; H, 2.35, 2.54.

6-Amino-10-chlorobenzo(g)quinoline (XIII).—Five grams (0.019 mole) of (VI), 3.2 g. (0.057 mole) of reduced iron powder, 80 ml. of glacial acetic acid, and 25 ml. of water were refluxed one hour. The mixture was diluted with about twice its volume of water, made alkaline, and extracted with three 100-ml. portions of chloroform. The combined extracts were washed with two 50-ml. portions of 5% hydrochloric acid and the acid solution treated with charcoal and neutralized with dilute sodium hydroxide. The precipitate was recrystallized from ethanol as orange needles; m. p. 181–183°; yield, 1.3 g. (30%).

Anal. Calcd. for $C_{13}H_9ClN_2$: C, 68.22; H, 3.97. Found: C, 68.09, 68.07; H, 3.94, 4.06.

6-Nitro-10-morpholinobenzo(g)quinoline (XIV).—One gram (0.004 mole) of (VI), 10 ml. (0.11 mole) of morpholine, and a pinch of copper bronze were refluxed five hours. The reaction mixture was poured into 300 ml. of water and the crude precipitate dissolved in 30 ml. of 5% hydrochloric acid. The acid solution was treated with charcoal and dilute sodium hydroxide added. The greenish precipitate which first appeared was rejected; the addition of more alkali to the filtrate precipitated a red solid. Recrystallization from ethanol gave red needles; m. p. 156–158°; yield, 0.06 g. (5%).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.02; H, 4.88. Found: C, 66.25; H, 4.73.

7-Nitro-10-morpholinobenzo(g)quinoline (XV).—A mixture of 0.5 g. (0.002 mole) of (VII), 6 ml. (0.07 mole) of morpholine and a pinch of copper bronze was refluxed six hours. The reaction was worked up just as in the preparation of (XIV). The product was recrystallized from ethanol as tan platelets; m. p. 202–204°; yield, 0.02 g. (3%).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.02; H, 4.88. Found: C, 66.24; H, 4.64.

Summary

10-Chlorobenzo(g)quinoline was condensed with morpholine and with piperidine. Nitration of 10-chlorobenzo(g)quinoline was found to give chiefly 6-nitro-10-chlorobenzo(g)quinoline, together with a small amount of 9-nitro-10-chlorobenzo(g)quinoline.

6-Nitro-, 7-nitro- and 9-nitro-10-chlorobenzo(g)quinoline were prepared from the new naphthalene intermediates, 1-chloro-5-nitro-, 1-chloro-6-nitro- and 1-chloro-8-nitro-2-acetamidonaphthalene, respectively.

6-Nitro- and 7-nitro-10-chlorobenzo(g)quinoline were condensed with morpholine. 6-Nitro-10-chlorobenzo(g)quinoline was reduced to 6-amino-10-chlorobenzo(g)quinoline.

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