A New Approach to Synthesis of Dihalogenated 8-Quinolinol Derivatives

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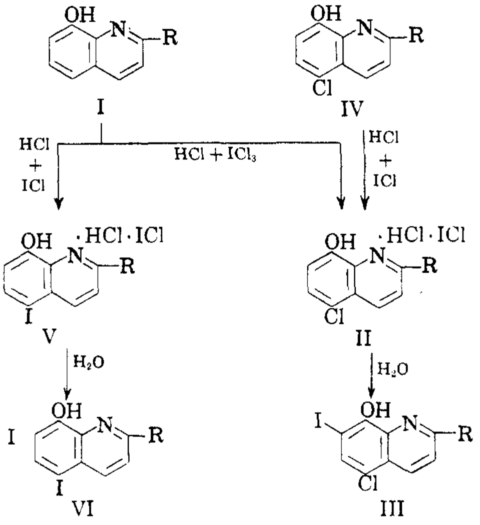
Of the halogenated 8-quinolinols, 5-chloro-7-iodo (IIIa) and 5,7-diiodo-8-quinolinols (VIa), commonly known as Vioform and Diodoquin respectively, have proved very useful in the treatment of intestinal amoebiasis. Among the recently prepared amoebicidal compounds containing the quinoline group, 5-chloro-7-diethylaminomethyl-8-quinolinol showed considerable promise in laboratory animals according to the preliminary results reported by Burckhalter and Edgerton.[2]



a, R = H; b, R = CH_3

Various methods of preparing IIIa from 5-chloro-8-quinolinol have been reported.[3-5] Certain patents[6,7] claim its preparation from 8-quinolinol (Ia) and iodine trichloride; however, the product isolated by Lasker and Ghosh[8] by a similar reaction was VIa. The authors prepared IIIa and VIa[9] most conveniently by the treatment of Ia in hydrochloric acid with iodine trichloride and iodine monochloride to give the respective iodine chloride-addition compounds; these were then decomposed with water to give IIIa and VIa. By the action of iodine monochloride in 15% hydrochloric acid, Papesch and Burtner[10] obtained VIa directly but in a less pure state as is evident from the low melting point. This compound has also been reported by Zeifman[11] using iodine and potassium iodate as the iodinating agent.

The preparation of dihalogenated 8-quinolinols described in this paper has resulted from our study of the reactions of iodine trichloride and iodine monochloride on Ia in a variety of media. In view of the recent report that 5,7-dichloro-2-methyl-8-quinolinol possesses stronger bactericidal properties than the di-halogenated 8-quinolinols,[12] the authors also prepared the Vioform and Diodoquin analogs of 2-methyl-8-quinolinol (Ib) by similar reactions for pharmacological studies against amoebiasis.

We have observed that the reaction of iodine trichloride or iodine monochloride with Ia in hydrochloric acid, IIIa or VIa is not formed directly, but through the respective iodine chloride-addition compounds. Probably iodine trichloride, as a strong chlorinating agent, chlorinates the 5-position of Ia liberating one molecule of iodine monochloride *in situ* which, instead of iodinating the 7-position directly, immediately forms an iodine chloride-addition compound of 5-chloro-8-quinolinol hydrochloride (IIa). This compound on treatment with water or very dilute acetic acid effects iodination of the 7-position. The formation of IIIa through IIa has been confirmed by its synthesis from 5-chloro-8-quinolinol (IVa) as shown in the experimental section. Similarly, VIa is not formed directly but through the iodine chloride-addition compound of 5-iodo-8-quinolinol hydrochloride (Va), which on subsequent decomposition with water yields VIa. This mechanism is supported by the fact that under similar conditions, by using one molecular equivalent of iodine monochloride or less, Va has always been obtained[13] instead of the expected mono-iodo derivative.[14] Similar addition compounds have not been observed when the reactions were conducted in glacial acetic acid and other solvents, *e.g.*, chloroform and ethanol. The direct formation of VIa by the action of iodine monochloride on Ia in ethanol is described in the Experimental part.

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[2] J. H. Burckhalter and W. H. Edgerton, *J. Am. Chem. Soc.*, **73**, 4837 (1951).

[3] Basler, German Patent 117767.

[4] M. K. Vose, *J. Indian Chem. Soc.*, **22**, 169 (1945).

[5] R. Sengupta, *J. Indian Chem. Soc.*, **22**, 171 (1945).

[6] F. Boedecker and L. Cassel, German Patent 697,731 (1940); *Chem. Abstr.* **35**, 6603 (1941).

[7] S. L. Mukherji, Indian Patent, 34380 (1948).

[8] S. L. Lasker and T. N. Ghosh, *Science and Culture (India)*, **10**, 58 (1944).

[9] Albert David Limited, Indian Patent 43579 (1951).

[10] V. Papesch and R. Burtner, *J. Am. Chem. Soc.*, **58**, 1314 (1936).

[11] V. Zeifman, *Trans. Inst. Pure Chem. Reagents (U.S.S.R.)*, No. 16, 80–2 (1939); *Chem. Abstr.*, **34**, 3745 (1940).

[12] Emil Senn, Switzerland, U.S. Patent, 2,411,670 (1946); *Chem. Abstr.*, **41**, 6024 (1947).

[13] Unreacted 8-quinolinol has been recovered from the filtrate after neutralization.

[14] K. Glue and W. Jageman, *J. prakt. Chem.*, **145**, 257–264 (1936).

The preparation of the Vioform and Diodoquin analogs of Ib through their iodine chloride compounds is described, and their structures have been assigned by analogy to the related derivatives of 8-quinolinol.

EXPERIMENTAL[15]

Iodine chloride addition compound of 5-chloro-8-quinolinol hydrochloride (IIa).[16]

A. To a solution of Ia[17] (30 g.) in concd. hydrochloric acid (150 ml.) was gradually added a solution of iodine trichloride (48 g.) in 300 ml. of concd. hydrochloric acid with stirring; a deep yellow crystalline solid precipitated out instantaneously. Stirring was continued for 0.5 hr. after the last addition of iodine trichloride. The addition compound was then filtered under suction, washed with glacial acetic acid followed by dry ether to give 74 g. (95%) of the product, m.p. 144–145° after desiccation over night. Repeated recrystallization from glacial acetic acid gave yellow prismatic crystals, m.p. 148–149°.

Anal. Calcd. for $C_9H_7ONICl_3$: N, 3.69; total halogen, 61.69. Found: N, 3.46; total halogen, 60.82.

B. To A solution of iodine monochloride (17 g.) in 150 ml. of concd. hydrochloric acid was added with stirring 15 g. of 5-chloro-8-quinolinol hydrochloride[18] suspended in 150 ml. of concd. hydrochloric acid. After standing for 0.5 hr., the deep yellow crystalline compound was collected on a filter and sucked dry to yield 21 g. (80%) of dry product. Recrystallized from glacial acetic acid, it melted at 149–150°. Its admixture with IIa, A did not depress the melting point.

Anal. Calcd. for $C_9H_7ONICl_3$: N, 3.69. Found: N, 3.81.

5-Chloro-7-iodo-8-quinolinol (IIIa). The crude addition compound, 38 g. (IIa,A) was decomposed by being added to water with vigorous mechanical stirring. The precipitate was filtered, washed with water, and then with 2% sodium bisulfite solution to give a brownish white powder, 28.1 g. (90%), m.p. 178°. On recrystallization from glacial acetic acid it yielded long brownish silky needles, m.p. 181°. Admixture with an authentic sample,[4] m.p. 178–179°, gave no depression of melting point.

Anal. Calcd. for C_9H_5ONICl: Cl, 11.62; I, 41.57. Found: Cl, 11.45; I, 41.03.

IIa,B was similarly decomposed and the precipitate recrystallized from glacial acetic acid, m.p. 180–181°. The iodine and the chlorine values agreed with those of IIIa, and it showed no depression of melting point on admixture with IIIa.

Iodine chloride addition compound of 2-methyl-5-chloro-8-quinolinol hydrochloride (IIb). *A.* A solution of iodine trichloride (5 g.) in concd. hydrochloric acid (40 ml.) was gradually added to a solution of Ib[19] (3.3 g.) in 2 ml. of concd. hydrochloric acid with stirring. The crystalline yellow compound was filtered and dried to give 6.3 g. (80%) of product which on recrystallization from glacial acetic acid melted at 146°.

Anal. Calcd. for $C_{10}H_9ONICl_3$: N, 3.56; total halogen, 59.49. Found: N, 3.60; total halogen, 60.02.

B. To a suspension of 2-methyl-5-chloro-8-quinolinol hydrochloride[20] (17 g.) in 100 ml. of concd. hydrochloric acid was gradually added a solution of iodine monochloride (17 g.) in concd. hydrochloric acid (100 ml.) with constant stirring. The crystalline yellow compound was filtered on a Buchner funnel and dried. The desiccated addition compound, 22.3 g. (77%) on recrystallization from glacial acetic acid melted at 148°.

Anal. Calcd. for $C_{10}H_9ONICl_3$: N, 3.56; total halogen, 59.49; Found: N, 3.35; total halogen, 58.92.

Admixture with IIb, A gave no depression of melting point.

2-Methyl-5-chloro-7-iodo-8-quinolinol (IIIb). The decomposition of 6.1 g. of crude iodine chloride addition compound (IIb, A) was carried out as for IIIa and IIIb. The product was collected as a brownish white powder, 3.5 g. (70%) which on repeated recrystallization from ethanol yielded light brown needles, m.p. 125–126°.

Anal. Calcd. for $C_{10}H_7ONICl$: Cl, 11.11; I, 39.74. Found: Cl, 10.82; I, 39.90.

The addition compound (IIb, B) was decomposed by stirring into water. The compound obtained after repeated recrystallization from ethanol, m.p. 124–125°, was identified as IIIb by analyses and mixed melting point.

Iodine chloride addition compound of 5-iodo-8-quinolinol hydrochloride (Va). Ia (20.4 g.) in 100 ml. of concd. hydrochloric acid reacted with a solution of iodine monochloride (47 g.) in 50 ml. of concd. hydrochloric acid under constant stirring to give a yellow crystalline mass. The solid mass was filtered under suction, washed, and dried as usual to give 62.7 g. (95%) of the product. On repeated recrystallization from glacial acetic acid, it melted at 172°.

Anal. Calcd. for $C_9H_7ONI_2Cl_2$: N, 2.97; total halogen, 69.14. Found: N, 2.72; total halogen, 70.05.

5,7-Diiodo-8-quinolinol (VIa). *A.* The crude Va (65 g.) was decomposed in water and the product collected as a yellowish brown powder, 52.1 g. (94%), m.p. 207–208°. Recrystallization from benzene gave pale yellow microcrystals, m.p. 213–214° (m.p. reported[11] 208–210°). Admixture with an authentic sample did not depress the melting point.

Anal. Calcd. for $C_9H_5ONI_2$: I, 63.97. Found: I, 64.00.

B. A solution of iodine monochloride, prepared by carefully adding 32.5 g. to 50 ml. of ice cold ethanol, was added to a solution of Ia (14.5 g.) in 100 ml. ethanol with stirring. There was an immediate separation of light brown crystalline needles which were collected under suction and washed with ethanol until the washings were colorless. The washings combined with the mother liquor afforded further crystalline material. The light brown microcrystalline needles, 35.7 g. (90%) melted at 211–212°. Recrystallization from benzene caused no elevation of the melting point, and there was no depression of melting point upon admixture with the above specimen.

Anal. Calcd. for $C_9H_5ONI_2$: I, 63.97. Found: I, 63.5.

Iodine chloride addition compound of 2-methyl-5-iodo-8-quinolinol hydrochloride (Vb). A solution of iodine monochloride (7 g.) in 10 ml. of concd. hydrochloric acid was stirred into a solution of Ib (3.2 g.) in 30 ml. of concd. hydrochloric acid. After some time the yellow crystalline mass was filtered and washed as usual to give 7.3 g. (76%) of the product. A sample crystallized from glacial acetic acid melted at 140–142°.

Anal. Calcd. for $C_{10}H_9ONI_2Cl_2$: N, 2.89; total halogen, 67.14. Found: N, 2.64; total halogen, 67.30.

5,7-Diiodo-2-methyl-8-quinolinol (VIb). Vb (5.1 g.) was decomposed in water under vigorous mechanical stirring. The diiodo-derivative was obtained as 2.8 g. (64%) of a brown powder. Repeated recrystallization from ethanol gave the pure compound, m.p. 147–148°.

Anal. Calcd. for $C_{10}H_7ONI_2$: I, 61.80. Found: I, 62.53.

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(15) All melting points are uncorrected.

(16) All the addition compounds were made using hydrochloric acid of sp. gr. 1.07 and 1.15.

(17) A. Das and S. L. Mukherji, *Science and Culture (India)*, 16, 477–478 (1951).

(18) T. N. Ghosh, *et al.*, *J. Indian Chem. Soc.*, 21, 354 (1944).

(19) O. Doebner and W. v. Miller, *Ber.*, 14, 2812 (1881).

(20) Prepared by the general procedure of the Doebner and Miller reaction.