[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF KANSAS, SCHOOL OF PHARMACY]

A New Type of 8-Quinolinol Amebacidal Agent

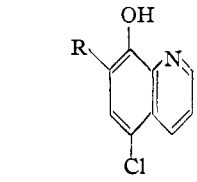
BY J. H. BURCKHALTER AND WILLIAM H. EDGERTON[1]

Various halogenated quinolinols were converted by the Mannich reaction to such compounds as Ic and VI with the object of improving the amebacidal effectiveness and solubility of a well known class of drugs, one of which is Vioform (Ib). Animal studies indicate considerable promise for 5-chloro-7-diethylaminomethyl-8-quinolinol (Ic) in intestinal amebiasis.

Discussion

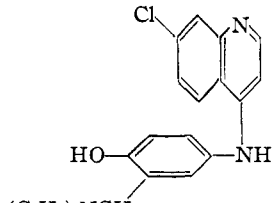
Dysentery and malaria were the tropical diseases of greatest occurrence among the armed forces of the United States during World War II. Through the use of modern suppressive and curative drugs, there is no reason why malaria should be so serious in the future. However, because amebiasis, which is caused by the organism *Endameba histolytica*, is at present difficult to detect and to treat, it remains a widespread chronic ailment as indicated by its prevalence in a surprising 20% of the population of this country.[2]

Our object has been to improve the effectiveness and solubility of one of the principal classes of amebacidal agents,[3] the halogenated quinolinols, through the introduction of the dialkylaminomethyl grouping. Thus, the replacement of the iodine in the well known drug, Vioform (Ib), by this basic grouping would give Ic. Interest in



R =
a, H c, $CH_2N(C_2H_5)_2$
b, I d, $CH_2CH=CH_2$

I

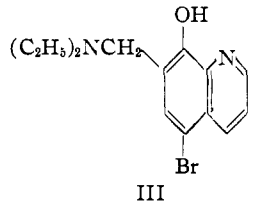


II

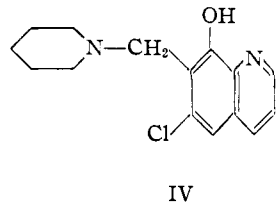
the introduction of this particular grouping is based upon its successful use in the valuable antimalarial Camoquin (II),[4] and upon the reports of promising use of certain antimalarial agents in the treatment of amebiasis.[5]

Further reason for the introduction of such a radical into the chloroquinolinols was supplied by a report which came to our attention after these syntheses had been completed. 5-Chloro-8-quinolinol (Ia) and 7-allyl-5-chloro-8-quinolinol (Id) were shown by Schönhöfer to possess high *in vitro* activity against *Endameba histolytica*. However, such agents failed to offer promise because of inadequate physical properties.[6]

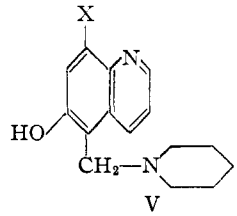
Ic was isolated as the dihydrochloride in 74% yield from the reaction between Ia, paraformaldehyde and diethylamine.[7] III and IV were similarly prepared from the appropriate halogenated 8-quinolinol.[8] Three compounds, Va, b and c, were similarly prepared as an extension of the study of effects of position isomerization upon biological activity.



III

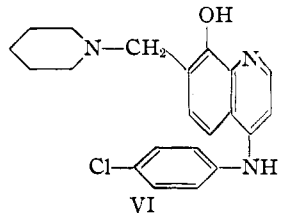


IV

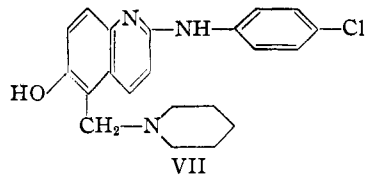


X
a, Cl
b, Br
c, I

V



VI



VII

A compound of structure VI was desirable because of its relationship to Camoquin (II),[9] and because of the *p*-chloroanilino group, which is present in the novel antiparasitic drug chloroguanide.[10] To obtain VI, 4-chloro-8-methoxyquinoline was demethylated by heating with dilute sulfuric acid, giving 4-chloro-8-quinolinol in 88% yield. 4-Chloro-8-quinolinol was condensed with *p*-chloroaniline by the method of Banks[11] to give 4-(4-chloroanilino)-8-quinolinol hydrochloride in 71% yield. The latter intermediate then was converted to VI in 62% yield by means of the Mannich reaction. VII, which is an isomer of VI, was similarly prepared.

Pharmacological Results.—Ic and its relatives have been studied by Dr. Paul E. Thompson, of

(1) Parke, Davis and Company Fellow.

(2) Editorial, *J. Am. Med. Assoc.*, **142**, 343 (1950).

(3) For a recent review, see Anderson and Hansen, *Pharmacological Reviews*, **2**, 402 (1950).

(4) Burckhalter, Tendick, E. Jones, P. Jones, Holcomb and Rawlins, THIS JOURNAL, **70**, 1363 (1948).

(5) Private communication: Drs. Paul E. Thompson and A. M. Moore, Parke, Davis and Company, Detroit, Michigan.

(6) Office of Publication Board Reports, Department of Commerce, Washington, D. C., PB 85033, 1948, pp. 85–95.

(7) This method is commonly referred to as the Mannich reaction. See the review by F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 10.

(8) The structure IV was assigned by analogy with related compounds.

(9) VI is actually a position isomer of the Camoquin analog, SN 11,636.[4]

(10) Curd and Rose, *J. Chem. Soc.*, 729 (1946).

(11) Banks, THIS JOURNAL, **66**, 1127 (1944).

Parke, Davis and Company, Detroit, Michigan. Ic appears to be more active *in vitro* than the established halogenated 8-quinolinol drugs. Also, animal studies indicate a superiority of Ic over related agents, and therefore suggest for it considerable promise in the treatment of intestinal amebiasis. Further, the absence of iodine from this compound eliminates the problem of iodine absorption by the host, a condition encountered with well known related agents.

The objective of obtaining high activity against extraintestinal amebiasis with Ic appears to have been only partially achieved since the compound possesses only slight oral activity in the hamster against hepatic amebiasis.

Experimental[12]

5-Chloro-7-diethylaminomethyl-8-quinolinol (Ic) Dihydrochloride.—A mixture of 8 g. (0.045 mole) of 5-chloro-8-quinolinol,[13] 1.4 g. (0.045 mole) of paraformaldehyde, 5 ml. (0.05 mole) of diethylamine and 500 ml. of alcohol was heated at reflux temperature for 90 minutes. A small amount of insoluble dark solid was removed by filtration from the cooled solution. The filtrate was concentrated under reduced pressure to a thick oily residue which was dissolved in ether. A stream of dry hydrogen chloride precipitated from the solution 11.2 g. (74% yield) of a yellow solid, m.p. 195–196° dec. Recrystallization from alcohol gave an elevation to 197–198° dec.

Anal. Calcd. for $C_{14}H_{17}ClN_2O \cdot 2HCl$: Cl, 21.00. Found: Cl, 21.08.

5-Bromo-7-diethylaminomethyl-8-quinolinol (III) Dihydrochloride.—Using 5-bromo-8-quinolinol[14] in the foregoing procedure, a 51% yield of a golden crystalline product (III dihydrochloride) was obtained, m.p. 182–183° dec. Several recrystallizations from alcohol changed the melting point to 197–198° dec.

Anal. Calcd. for $C_{14}H_{17}BrN_2O \cdot 2HCl$: C, 44.00; H, 5.01. Found: C, 43.71; H, 5.02.

6-Chloro-7-(1-piperidylmethyl)-8-quinolinol (IV) Dihydrochloride.—Using 6-chloro-8-quinolinol[15] in the procedure of Ic gave 72% yield of a gray solid, m.p. 190–192° dec. Several recrystallizations from isopropyl alcohol yielded an off-white solid, m.p. 198–199° dec.

Anal. Calcd. for $C_{15}H_{17}ClN_2O \cdot 2HCl \cdot {}^3/_4H_2O$: C, 49.60; H, 5.65. Found: C, 49.67; H, 5.89.

8-Chloro-6-quinolinol.—A solution of 5 g. (0.026 mole) of 8-chloro-6-methoxyquinoline[16] and 50 ml. of 48% hydrobromic acid was heated at reflux temperature for six hours. The solution was cooled, and enough 20% sodium hydroxide solution was added to dissolve the solid hydrobromide which had separated. The filtered solution was neutralized with 10% hydrochloric acid. The precipitated product was collected on a filter, washed with water and dried; 4.5 g. (96% yield), m.p. 236–237° dec. Recrystallization from alcohol gave m.p. 237–238° dec.

Anal. Calcd. for C_9H_6ClNO: C, 60.18; H, 3.37. Found: C, 60.08; H, 3.49.

8-Chloro-5-(1-piperidylmethyl)-6-quinolinol (Va) Dihydrochloride.—Using 8-chloro-6-quinolinol in the procedure of Ic gave 88% yield of light tan Va dihydrochloride, m.p. indefinitely above 220°. It was recrystallized from alcohol for analysis.

Anal. Calcd. for $C_{15}H_{17}ClN_2O \cdot 2HCl \cdot 1{}^1/_2H_2O$: Cl, 18.82. Found: Cl, 18.82.

8-Bromo-6-quinolinol was obtained from 8-bromo-6-methoxyquinoline[17] in 95% yield by the foregoing demethylation procedure, m.p. 242–243° dec. A sample was purified by vacuum sublimation at 0.2–0.3 mm. and several recrystallizations from alcohol, m.p. 245° dec.

Anal. Calcd. for C_9H_6BrNO: C, 48.24; H, 2.70. Found: C, 48.96; H, 2.81.

8-Bromo-5-(1-piperidylmethyl)-6-quinolinol (Vb).—Using 8-bromo-6-quinolinol in the procedure of Ic, Vb was isolated as the crystalline free base after removal of the volatile solvent. The yield was 70% of the solid; m.p. 137° dec. Recrystallization from alcohol changed melting point to 139° dec.

Anal. Calcd. for $C_{15}H_{17}BrN_2O$: C, 56.08; H, 5.34. Found: C, 55.86; H, 5.47.

8-Iodo-6-quinolinol was obtained from 8-iodo-6-methoxyquinoline[16] in 89% yield by the customary demethylation procedure, m.p. 246–248° dec. A sample was purified by vacuum sublimation at 0.2–0.3 mm. and by recrystallization from alcohol, m.p. 259–260° dec.

Anal. Calcd. for C_9H_6INO: C, 39.88; H, 2.23. Found: C, 40.57; H, 2.48.

8-Iodo-5-(1-piperidylmethyl)-6-quinolinol (Vc).—Using 8-iodo-6-quinolinol in the procedure of Ic, the product was isolated after removal of the solvent from the reaction mixture in 86% yield as a tan crystalline solid, m.p. 171–172° dec. Recrystallization from alcohol raised the m.p. to 178° dec.

Anal. Calcd. for $C_{15}H_{17}IN_2O$: C, 48.92; H, 4.66. Found: C, 49.23; H, 4.85.

4-Chloro-8-quinolinol.[18]—A solution of 9.5 g. (0.049 mole) of 4-chloro-8-methoxyquinoline, 61 ml. of concentrated sulfuric acid and 36 ml. of water was heated at reflux temperature for 5.5 hours. The solution was then poured over cracked ice and neutralized with ammonium hydroxide to precipitate a green solid. The material was collected on a funnel and stirred well for two hours with 500 ml. of 2% sodium carbonate solution. Collected, washed and dried, 8.2 g. (88% yield) of greenish colored product was obtained, m.p. 139–141° dec. For analysis a sample was sublimed *in vacuo* and recrystallized from alcohol as white crystals, m.p. 142–143°.

Anal. Calcd. for C_9H_6ClNO: C, 60.18; H, 3.37. Found: C, 59.98; H, 3.36.

4-(4-Chloroanilino)-8-quinolinol Hydrochloride.—A solution of 7.2 g. (0.04 mole) of 4-chloro-8-quinolinol and 5.2 g. (0.04 mole) of *p*-chloroaniline in 400 ml. of alcohol was heated to boiling for three hours. The solution was concentrated and diluted with ether to separate 8.8 g. (71% yield) of green solid, m.p. 289–292° dec. A portion was recrystallized with difficulty from isopropyl alcohol, m.p. 306–307° dec.

Anal. Calcd. for $C_{15}H_{11}ClN_2O \cdot HCl \cdot {}^1/_2H_2O$: C, 57.16; H, 4.16. Found: C, 56.96; H, 4.83.

4-(4-Chloroanilino)-7-(1-piperidylmethyl)-8-quinolinol (VI).—To a previously heated solution of 0.2 g. (0.0067 mole) of paraformaldehyde and 1.3 ml. (0.013 mole) of piperidine in alcohol, 2 g. (0.0066 mole) of 4-(4-chloroanilino)-8-quinolinol hydrochloride was added. The mixture was heated to boiling for 25 minutes and then evaporated to dryness *in vacuo*. The green residue was extracted with ether in a Soxhlet apparatus. Evaporation of the ether extract left 1.6 g. (62%) of a yellow powder, m.p. 179–181° dec. It was recrystallized from alcohol, m.p. 206–207° dec.

Anal. Calcd. for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03. Found: C, 68.48; H, 6.06.

2-Chloro-6-quinolinol.—A solution of 30 g. (0.155 mole) of 2-chloro-6-methoxyquinoline[19] and 100 ml. of 48% hydrobromic acid was heated at reflux temperature for six hours. After water was added to dissolve a small quantity of solid, the solution was cooled, made alkaline with 20%

(12) All except the last three analyses were determined by Mr. C. W. Beazley, Skokie, Illinois.

(13) Supplies were kindly furnished by Dr. N. G. Phillips, Cincinnati Chemical Works; Dr. Robert M. Delcamp, University of Cincinnati; and Dr. W. F. Ringk, Benzol Products Company, Newark, N. J.

(14) Claus and Howitz, *J. prakt. Chem.*, [2] **44**, 444 (1891).

(15) Hoffmann, *Bull. soc. chim.*, [5] **14**, 969 (1947).

(16) Price, Snyder and Van Heyningen, THIS JOURNAL, **68**, 2589 (1946).

(17) Reported by Berkenheim and Antik, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 537 (1941); *C. A.*, **35**, 6962 (1941). However, better yields were obtained by adaptation of the method used by Price, *et al.*,[16] for the analogous chloride.

(18) The general procedure of Ramsey and Cretcher, THIS JOURNAL, **69**, 1660 (1947), was used.

(19) Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

sodium hydroxide solution and poured through a sintered glass filter. Neutralization with glacial acetic acid precipitated 26.1 g. (93% yield) of brown solid, m.p. 187–188°.[20] Recrystallized from acetone, it melted at 192°

Anal.[21] Calcd. for C_9H_6ClNO: Cl, 19.74. Found: Cl, 19.45.

2-(4-Chloroanilino)-6-quinolinol Hydrochloride.—A solution of 6 g. (0.03 mole) of 2-chloro-6-quinolinol and 4 g. (0.031 mole) of *p*-chloroaniline in 150 ml. of butyl alcohol was heated at reflux temperature overnight. The solution was concentrated to about 40 ml. of residue which was treated first with ether and then with acetone to give 7.4 g. (74% yield) of yellow crystals, m.p. 223–225° dec. A sample was recrystallized from isopropyl alcohol, m.p. 227–228° dec.

Anal.[21] Calcd. for $C_{15}H_{11}ClN_2O \cdot HCl \cdot 1^1/_4H_2O$: C, 54.64; H, 4.43; Cl, 21.51. Found: C, 54.51; H, 3.79; Cl, 21.51.

2-(4-Chloroanilino)-5-(1-piperidylmethyl)-6-quinolinol (VII).—The procedure of compound VI was applied. After three hours at reflux temperature, the solution was evaporated to about 50 ml. whereupon cooling gave 2.7 g. (88% yield) of white crystals, m.p. 192–193°. Purification by means of ether in a Soxhlet extractor and recrystallization from alcohol raised the melting point to 199–200°.

Anal.[21] Calcd. for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03. Found: C, 68.65; H, 6.30.

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(20) Edinger, *Ber.*, **30**, 2420 (1897), reported 187° for which is presumed to be the same compound.

(21) By Mr. Charles Childs and staff, of Parke, Davis and Company.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE DEFENSE RESEARCH LABORATORY OF THE UNIVERSITY OF TEXAS]

The Compressibility of Pentene-1

BY H. O. DAY[1] WITH W. A. FELSING

The compressibility of pentene-1 has been determined over the temperature range of 80° to 225°. The data presented are accurate to 0.1–0.2%, except at the highest temperatures (200° and 225°); evidence of decomposition at these temperatures was found.

Introduction

This Laboratory has been interested for a number of years in the determination of some of the thermodynamic properties of pure, saturated hydrocarbons.[2] The present investigation presents data on the compressibility of an unsaturated hydrocarbon, pentene-1, for which no previous accurate compressibility data existed in the literature. The vapor pressures of this substance were presented in a recent publication.[3] It was hoped at the initiation of this problem that critical data could be determined for this substance; however, the polymerization rate at 200° or above becomes too great to allow for an accurate determination of a series of isotherms in the immediate vicinity of the critical point (near 201°).[3]

Method and Apparatus.—All compressibility data were determined by means of a dead-weight piston gage described elsewhere,[4] being a modification of the M. I. T. unit described by Beattie.[5]

TABLE I

COMPRESSIBILITY OF PENTENE-1

Specific volume, ml./g.	Pressure, atmospheres	Specific volume, ml./g.	Pressure, atmospheres
80.00°		1.6213	259.372
1.7466	5.616	1.6046	311.814
1.7404	13.518		
1.7346	21.414	125.00°	
1.7273	31.918	1.9637	11.681
1.7165	49.025	1.9597	13.530
1.6871	101.529	1.9543	16.158
1.6621	154.075	1.9442	21.426
1.6404	206.705	1.9260	31.930
1.9003	49.036	1.8230	13.529
1.8386	101.539	1.8149	21.423
1.7940	154.084	1.8045	31.927
1.7583	206.714	1.7893	49.033
1.7286	259.381	1.7488	101.537
1.7032	311.822	1.7160	154.083
175.00°		1.6889	206.711
2.5135	27.094	1.6661	259.378
2.5052	27.476	1.6467	311.819
2.4269	31.930	150.00°	
2.3413	39.826	2.1566	18.541
2.2738	49.032	2.1427	21.439
2.1554	75.274	2.1012	31.953
2.0816	101.531	2.0496	49.048
1.9842	154.075	1.9479	101.550
1.9195	206.704	1.8822	154.095
1.8691	259.370	1.8344	206.724
1.8290	311.810	1.7968	259.391
225.00°		1.7644	311.832
7.1296	43.280	200.00°	
5.7037	47.306	7.1296	36.415
4.7531	50.543	5.7037	38.151
4.0741	53.600	4.7531	39.090
3.5648	57.144	4.0741	39.772
3.1687	62.144	3.5648	40.680
2.8519	71.502	3.1687	42.458
2.5926	87.225	2.8519	46.718
2.3765	114.483	2.5926	57.124
2.1937	159.762	2.3765	78.066
2.0370	231.852	2.1937	117.323
1.9262	311.712	2.0370	185.302
100.00°		1.9012	288.570
1.8297	7.203	1.8775	311.790

The thermostat temperatures were controlled to ±0.005° by means of a platinum resistance thermometer in conjunction with a Mueller bridge and a photoelectric relay. The actual thermostat temperature was simultaneously determined by the resistance thermometer (calibrated by the National Bureau of Standards). The method of manipulation was described elsewhere.[4]

(1) Chemistry Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.; formerly Research Assistant, Defense Research Laboratory, The University of Texas.

(2) Felsing, Cuellar and Newton, THIS JOURNAL, **69**, 1972 (1947), reference 1.

(3) Day and Nicholson with Felsing, *ibid.*, **70**, 1784 (1948).

(4) Kelso with Felsing, *ibid.*, **62**, 3132 (1940); *Ind. Eng. Chem.*, **34**, 161 (1942).

(5) Beattie, *Proc. Am. Acad. Arts and Sci.*, **69**, 389 (1934).