of 5-carboxyuracil. The yield was increased to 61% when the "active" MnO_2 was washed with 15% HNO_3, followed by washing with distilled water to pH 5 (*cf.* ref 14).

Attempted Oxidation of 3',5'-Diacetylthymidine.—This compound could not be oxidized to 3',5'-diacetyl-5-carboxy-2'-deoxyuridine with "active" MnO_2, $KMnO_4$, or CrO_3.

(14) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

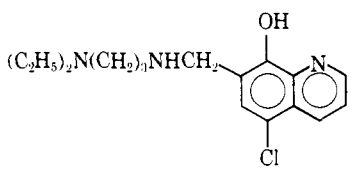
Preparation and Properties of Clamoxyquin Pamoate,[1] an Antiamebic and Antidiarrheal Agent

EDWARD F. ELSLAGER AND DONALD F. WORTH

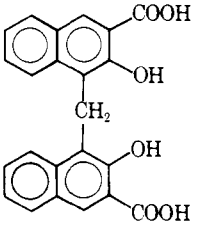
Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan

Received March 25, 1967

A wide variety of substituted 8-quinolinols has been examined in these laboratories for antiamebic and antibacterial properties.[2-4] Among them, 5-chloro-7-({[3-(diethylamino)propyl]amino}methyl)-8-quinolinol dihydrochloride (clamoxyquin hydrochloride, Ia)[3] has shown a particularly interesting degree of antiamebic activity in experimental animals.[3-5] Clamoxyquin hydrochloride formulated in gelatin capsules was



Ia, ·2HCl



b, ·pamoic acid

pamoic acid

tolerated well in man following daily 15-mg/kg doses for 5–10 days and was highly effective against various forms of intestinal amebiasis.[6,7]

Tablet and suspension formulations of clamoxyquin were of special interest for expanded clinical studies. In order to find a salt form of clamoxyquin whose taste would be more acceptable for use in aqueous suspensions for oral pediatric use, a series of salts was prepared (Table I). Among them, clamoxyquin pamoate (Ib), a salt of clamoxyquin with 1 formula weight of 4,4'-methylenebis(3-hydroxy-2-naphthoic acid), appeared to be of particular interest and was selected for extensive chemical and biological evaluation.

Clamoxyquin pamoate as the anhydrous salt contains 45.3% clamoxyquin base. The compound is relatively insoluble in water (0.004%) and is tasteless, making it well suited for use in oral pediatric suspensions.

A comparison of the antiamebic properties of clamoxyquin hydrochloride and pamoate indicated that the potent antiamebic activity of the hydrochloride salt is retained by the pamoate.[4,8] Thus, both salts were active against *Entamoeba histolytica* (200 strain) in rats when administered in the diet in dose levels of 160–679 mg/kg day for 7 days or by gavage in doses of 75–600 mg/kg day for 4 days. When dogs infected with *E. histolytica* were treated orally for 10 days, both the hydrochloride and pamoate salts were active, the cure rate being dependent upon the dosage in the range of 3.13–50 mg/kg/day and 12.5–25 mg/kg/day, respectively. These doses were well tolerated as judged by gross examination.[4]

Toxicologic studies with clamoxyquin hydrochloride and pamoate were carried out in mice, rats, dogs, and monkeys.[8,9] Acute oral LD_{50} values in albino mice were much higher for the pamoate (>2500 mg/kg) than for the hydrochloride (891.3 ± 33.7 mg/kg).[9] In chronic oral-tolerance studies in albino rats, both salts were tolerated well for 28 days at average daily drug-diet doses of 25 mg/kg; at greatly exaggerated daily doses of 200 mg/kg over the same period, the pamoate was clearly better tolerated than was the hydrochloride salt, although in neither case was evidence of organ damage observed.[9]

The two salts were also compared in subacute rising-dose-tolerance trials in dogs and monkeys.[9] Dogs tolerated up to 525 mg/kg of clamoxyquin pamoate by the end of a 35-day dosing period with manifestations similar to, but much less severe than, the gastrointestinal irritation that was seen during the administration of 250–275 mg/kg of the hydrochloride salt during 24–25 days. In monkeys, a maximum dose of 1100 mg/kg of clamoxyquin pamoate was dictated only by the bulk of drug required to deliver the dose. At this level, signs of intolerance were modest compared with those produced by similar doses of the hydrochloride salt. Therefore, in all species of animals studied to date, clamoxyquin pamoate was uniformly better tolerated than the hydrochloride salt.[9]

In definitive clinical trials, clamoxyquin pamoate formulated as compressed tablets or as a suspension was compared with iodochlorhydroxyquin[10] in the treatment of diarrheal disease.[11] Clamoxyquin pamoate was administered in a dose of 16 mg of clamoxyquin base/kg of body weight daily, in divided doses, for 5 days. Iodochlorhydroxyquin was given at the recommended dosage regimen, namely 1500 mg (500 mg tid) daily for 10 days. Clamoxyquin pamoate was tolerated well and was equal to iodochlorhydroxyquin in reducing the daily number of stools, in improving stool consistency, and eliminating fetid odor. Both drugs were effective in eliminating blood and mucus in stools. Clamoxyquin pamoate was usually better than iodochlorhydroxyquin in ameliorating subjective gastrointestinal symptoms and was superior or equal to iodochlorhydroxyquin in eliminating *E. histolytica*, *Giardia lamblia*, and *Shigella*.[7,11]

(1) Clamoxyquin pamoate is the generic name for 5-chloro-7-({[3-(diethylamino)propyl]amino}methyl)-8-quinolinol salt with 1 formula weight of 4,4,-methylenebis(3-hydroxy-2-naphthoic acid) (Clamoxyl®).

(2) P. E. Thompson, J. W. Reinertson, A. Bayles, D. A. McCarthy, and E. F. Elslager, *Am. J. Trop. Med. Hyg.*, **4**, 224 (1955).

(3) J. H. Burckhalter, W. S. Brinigar, and P. E. Thompson, *J. Org. Chem.*, **26**, 4070 (1961).

(4) P. E. Thompson, A. Bayles, P. McClay, and J. E. Meisenhelder, *J. Parasitol.*, **51**, 817 (1965).

(5) R. Cavier and F. Glaudon, *Therapie*, **18**, 1153 (1963).

(6) R. H. Hugonot, E. Granotier, and J. P. Farges, *ibid.*, **20**, 329 (1965).

(7) K. O. Courtney, personal communication, 1967.

(8) Drug concentrations and doses are expressed in terms of the free base content.

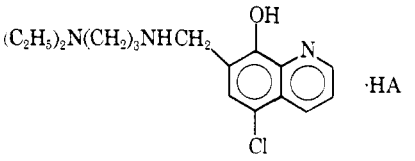
(9) D. H. Kaump, R. A. Fisken, J. E. Fitzgerald, J. A. Lucas, T. F. Reutner, D. E. Roll, and J. L. Schardein, personal communication, 1967.

(10) Entero-Vioform®.

(11) F. Fernandez, *Semana Med. Mexico*, **49**, 328 (1966).

TABLE I

CLAMOXYQUIN SALTS



Compd no.	HA	Mp, °C	Yield, purified, %	Purification solvent[a]	Formula $C_{16}H_{24}ClN_3O$	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Water, %[b] Calcd	Water, %[b] Found
1	Salicylic	108–110	72	A	$\cdot 2C_7H_6O_3$	62.25	61.91	6.07	6.33	7.03	6.70		
2	8-Hydroxy-7-iodoquinoline-5-sulfonic	145 dec	77	B	$\cdot 2C_9H_6INO_4S \cdot 1.5H_2O$	40.00	40.34	3.74	3.69	6.66	6.54	2.57	2.25
3	Naphthalene-1,5-disulfonic	238–240 dec	67	B	$\cdot C_{10}H_8S_2O_6 \cdot 0.25H_2O$	52.76	52.66	5.33	5.59	6.83	6.41	0.73	0.40
4	1-Hydroxy-2-naphthoic	95–97	63	C	$\cdot 2C_{11}H_8O_3 \cdot H_2O$	65.40	65.37	5.91	5.95	5.87	5.85	2.51	2.28
5	3-Hydroxy-2-naphthoic	142–143	60	D	$\cdot 2C_{11}H_8O_3$	67.09	67.02	5.77	5.96	6.02	5.76		
6	2,2′-Thiobis(4,6-dichlorophenol)	108–110	92	B	$\cdot 2C_{12}H_6Cl_4O_2S$	47.62	47.33	3.51	3.54	4.06	3.89		
7	2,2′-Methylenebis(3,4,6-trichlorophenol)	125 dec	77	E	$\cdot 2C_{13}H_6Cl_6O_2$	45.47	45.14	3.20	3.26	3.70	3.54		
8	4,4′-Methylenebis(3-hydroxy-2-naphthoic)	150 indef	93	F	$\cdot C_{23}H_{16}O_6 \cdot 0.5H_2O$	66.79	66.39	5.75	5.74	5.84	5.88	1.25	1.08

[a] A, acetone–ether; B, methanol–water; C, ethanol–water; D, ethanol; E, acetonitrile–ethanol; F, not recrystallized. [b] Water determinations are by the Karl-Fischer method.

Experimental Section[12]

General Procedure.—Aqueous or methanol solutions of 0.01–0.1 mole of 5-chloro-7-({[3-(diethylamino)propyl]amino}methyl)-8-quinolinol dihydrochloride[3] (clamoxyquin hydrochloride) were added at 25° to aqueous or methanol solutions of stoichiometric amounts of the sodium salts of the requisite acids or phenols (Table I). If the salt precipitated, it was collected and recrystallized from the solvent indicated. If not, the reaction mixture was refrigerated until crystallization occurred.

Clamoxyquin Pamoate.—A solution of 39.5 g (0.1 mole) of 5-chloro-7-({[3-(diethylamino)propyl]amino}methyl)-8-quinolinol dihydrochloride[3] (clamoxyquin hydrochloride) in 500 ml of distilled H_2O was poured slowly with vigorous stirring at 25° into a solution of 45.0 g (0.1 mole) of 4,4′-methylenebis(3-hydroxy-2-naphthoic acid) disodium salt monohydrate (sodium pamoate) in 800 ml of distilled H_2O. The resulting thick slurry was diluted to 3 l. with distilled H_2O and stirred briefly. The precipitate was collected by filtration and slurried twice with 3-l. portions of distilled H_2O. The off-white solid was collected and dried *in vacuo* at 45° for 48 hr; yield 66.0 g (93%), melting point indefinite beginning at approximately 150°.

The clamoxyquin pamoate thus obtained ranged from 1–5 μ in particle size with aggregates up to 300 μ. The X-ray diffraction pattern indicates that this material is amorphous. The compound exhibits the ultraviolet absorption maxima shown in Table II.

TABLE II

Abs methanol λ, mμ	Abs methanol $E^{1\%}_{1cm}$	0.1 *N* NaOH λ, mμ	0.1 *N* NaOH $E^{1\%}_{1cm}$
362	96	364	135
300	125	300	96
289	164	288	153
278	140	236	1526
238	1685		

The solubility of clamoxyquin pamoate in pH 7 0.1 *M* phosphate buffer is 0.012%. Solutions of this drug (0.01%) in methanol or pH 7 phosphate buffer are stable for more than 2 weeks.

Acknowledgment.—The authors wish to express their appreciation to Dr. Loren M. Long for encouragement in this investigation and to Dr. Paul E. Thompson, Dr. D. H. Kaump, and co-workers for the biological evaluation of these compounds. We are also indebted to Mr. Charles E. Childs and associates for the microanalyses and to Dr. J. M. Vandenbelt and associates for the physical-chemical data.

(12) Melting points (corrected) were taken in open capillary tubes in a Thomas–Hoover capillary melting point apparatus.

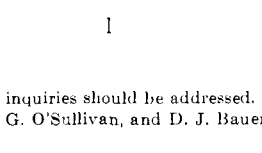
Synthesis and Antiviral and Antibacterial Activity of Certain N-Dialkylaminomethylisatin β-Thiosemicarbazones

RAJENDRA S. VARMA and W. LEWIS NOBLES[1]

Department of Pharmaceutical Chemistry, School of Pharmacy, The University of Mississippi, University, Mississippi 38677

Received March 14, 1967

Thiosemicarbazones of different carbonyl compounds have shown antiviral[2–8] and tuberculostatic[9–15] activity, including the activity of isatin 3-thiosemicarbazone (I) against the pox group of viruses in human beings and type 2 polio in ERK cells.[16] Bauer and Sadler[7] in-



I

(1) Author to whom inquiries should be addressed.

(2) P. W. Sadler, D. G. O'Sullivan, and D. J. Bauer, *Antibiot. Chemotherapy*, **2**, 403 (1963).

(3) D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 2032 (1963).

(4) R. Slack, K. R. H. Wooldridge, J. A. McFadzean, and S. Squires, *Nature*, **204**, 587 (1964).

(5) R. L. Thompson, S. A. Minton, J. A. Officer, and G. H. Hitchings, *J. Immunol.*, **70**, 229 (1953).

(6) E. Campaigne, R. L. Thompson, and J. E. Van Werth, *J. Med. Pharm. Chem.*, **1**, 577 (1959).

(7) D. J. Bauer and P. W. Sadler, *Brit. J. Pharmacol.*, **15**, 101 (1960).

(8) D. Hamre, J. Bernstein, and R. Donovick, *Proc. Soc. Exptl. Biol. Med.*, **73**, 275 (1950).

(9) G. Domagk, *Naturwissenschaften*, **33**, 315 (1946).

(10) R. Behnisch, F. Mietzsch, and H. Schmidt, *Angew. Chem.*, **60**, 113 (1948).

(11) N. P. Buu-Hoi, M. Welsch, G. Dechamps, H. L. Bihan, F. Binon, and N. D. Xuong, *J. Org. Chem.*, **18**, 121 (1953).

(12) R. S. Varma, *J. Indian Chem. Soc.*, **43**, 558 (1966).

(13) W. L. Nobles, *J. Am. Chem. Soc.*, **77**, 6675 (1955).

(14) H. C. Caldwell and W. L. Nobles, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 729 (1956).

(15) D. Dodgen, Jr., and W. L. Nobles, *ibid.*, **46**, 437 (1957).

(16) H. E. Whipple, *Ann. N. Y. Acad. Sci.*, **130**, 71 (1965).