#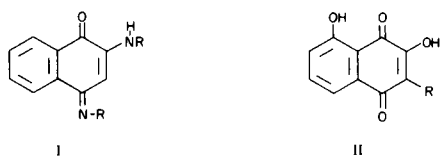 7-Amino-5-imino-8(5H)-quinolones, 6-Amino-8-imino-5(8H)-quinolones and 7-Alkyl-4,6-dihydroxy-5,8-quinolinediones as Potential Antiprotozoal Agents (1,2)

F. J. Bullock and J. F. Tweedie

Arthur D. Little, Inc.

Oxidation of 7-amino-8-hydroxyquinoline-5-sulfonic acid with silver oxide in dimethylformamide and in the presence of arylamines provided a series of 7-amino-5-arylimino-8(5H)-quinolones (VIIIb). Reaction of 8-dialkylamino-5,6-quinolinediones with triethyloxonium tetrafluoborate gave a series of unstable but synthetically useful enol ethers. These reacted with amines to give 6-amino-8-imino-5(8H)-quinolones, isolated and characterized as tetrafluoborate salts (XIa). Proton magnetic resonance studies showed these to be vinylogous amidinium salts, analogous to those previously obtained with 2-amino-1,4-naphthoquinone imines. 4,6-Dihydroxy-5,8-quinolinedione underwent free radical alkylation to give a 7-alkyl-4,6-dihydroxy-5,8-quinolinedione. Evaluation of the new compounds against various *Plasmodium* species in rodents, birds and mosquitoes revealed no significant antimalarial activity.

Previous studies (2,3) have shown the naphthoquinone derivatives I and II to have antimalarial and/or coccidiostat activity. We report here new syntheses and results of biological evaluation of the chemically related quinolones VIII and XI and a 5,8-quinolinedione XIV.

7-Amino-5-imino-8(5H)-quinolones (VIII).

Chlorination of 8-quinolinol proceeded to good yield to the unstable trichloroquinolone (VII) (4) which reacted smoothly with a variety of aryl amines at ordinary temperature to give VIIIa (5) (XIX-XXIII in Table I). We were unable to isolate any pure products when VII was reacted with benzylic or aliphatic amines under the same conditions, or at low temperatures.

The silver oxide oxidation of 7-amino-8-hydroxyquinoline-5-sulfonic acid (IV) in the presence of aryl amines in dimethylformamide provided a ready synthesis for the heretofore unknown quinolones (VIIIb) (XV-XVIII in Table I). This reaction is envisioned (Scheme A) as proceeding by way of the quinone imine (V) to the bisulfite adduct VI, which then readily decomposes to give VIIIb. In our hands, the reaction was successful only with aryl amines. The preparation of IV in 83% overall yield from commercial 8-hydroxyquinoline-5-sulfonic acid (see Ex-
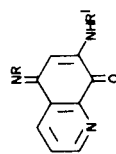
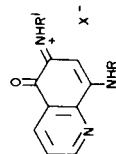perimental section) represents a substantial improvement over a previous method (6).

SCHEME A
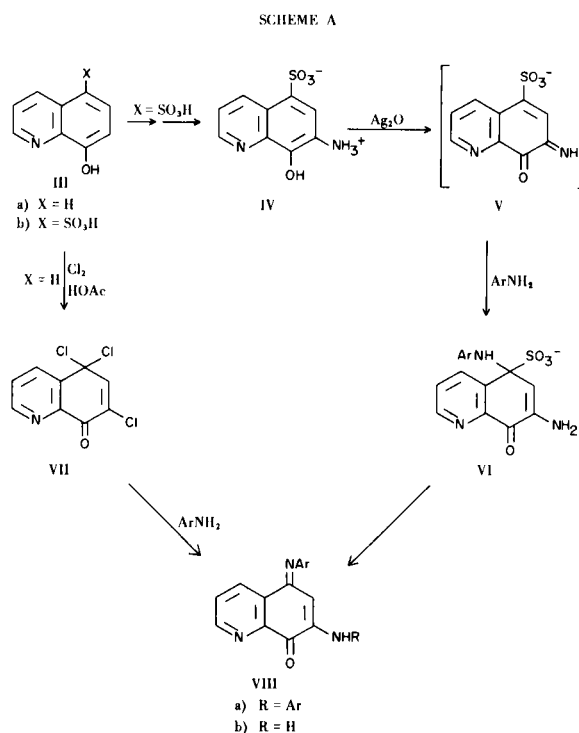
6-Amino-8-imino-5(8H)-quinolones (XI).

Our approach to this previously undescribed series was based on earlier experience in the preparation of 2-amino-1,4-naphthoquinone imines (7). 8-Dialkylamino-5,6-quinolinediones IXa and IXb (8) were converted to the

TABLE I

7-Amino-5-imino-8(5H)-quinolones and 6-Amino-8-imino-5(8H)-quinolones

No.	R	R^1	Crystallization Solvent	M.p. °C	Yield %	Formula		Carbon %	Analyses Hydrogen %	Nitrogen %
XV	C$_6$H$_5$	H	DMF/H$_2$O	264-265	26	C$_{15}$H$_{11}$N$_3$O	Calcd., Found,	72.27 72.38	4.45 4.52	16.86 16.79
XVI	C$_6$H$_4$OCH$_3$-p	H	CHCl$_3$/Hexane	183-184	31	C$_{16}$H$_{13}$N$_3$O$_2$	Calcd., Found,	68.80 68.39	4.69 4.93	15.05 15.26
XVII	C$_6$H$_4$Cl-p (a)	H	EtOH	245-247	24	C$_{15}$H$_{10}$N$_3$ClO	Calcd., Found,	63.53 63.77	3.55 3.59	14.82 14.72
XVIII	C$_6$H$_3$-3,4-Me$_2$	H	CHCl$_3$/Hexane	229-230	35	C$_{17}$H$_{15}$N$_3$O	Calcd., Found,	73.63 73.27	5.45 5.77	15.15 15.33
XIX	C$_6$H$_3$-3,4-Me$_2$	C$_6$H$_3$-3,4-Me$_2$	EtOH/HOAc	213-214.5	29	C$_{25}$H$_{23}$N$_3$O	Calcd., Found,	78.71 78.27	6.08 5.88	11.01 10.71
XX	C$_6$H$_4$OCH$_3$-p	C$_6$H$_4$OCH$_3$-p	EtOH/HOAc	193-195	38	C$_{23}$H$_{19}$N$_3$O$_3$	Calcd., Found,	71.67 71.47	4.97 4.94	10.90 10.85
XXI	C$_6$H$_4$Cl-p (b)	C$_6$H$_4$Cl-p	HOAc	271-273	58	C$_{21}$H$_{13}$N$_3$Cl$_2$O	Calcd., Found,	63.97 64.14	3.33 3.36	10.66 10.73
XXII	C$_6$H$_4$CO$_2$C$_2$H$_5$-p	C$_6$H$_4$CO$_2$C$_2$H$_5$-p	EtOH/HOAc	236-238	56	C$_{27}$H$_{23}$N$_3$O$_5$	Calcd., Found,	69.07 69.02	4.94 5.05	8.95 8.91
XXIII	(3-methylpyridyl)	(3-methylpyridyl)	MeOH	207-209	20	C$_{19}$H$_{13}$N$_5$O	Calcd., Found,	69.71 69.44	4.00 4.05	21.40 21.17
XXIV	COCH$_3$	COCH$_2$ (c)	CHCl$_3$/EtOH	256-259	67	C$_{13}$H$_{11}$N$_3$O$_3$	Calcd., Found,	— —	— —	— —
XXV	C$_6$H$_5$	C$_6$H$_5$ (d)	EtOH/HOAc	215-216	20	C$_{21}$H$_{15}$N$_3$O	Calcd., Found,	77.52 77.19	4.65 4.94	12.92 12.64

No.	R	R¹	X	Crystallization Solvent	M.p. °C	Yield %	Formula		Analyses		
									Carbon %	Hydrogen %	Nitrogen %
XIb	$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	Pamoate	DMF/H_2O	189-190 dec.	100	$C_{40}H_{39}N_3O_7$	Calcd.,	71.30	5.84	6.24
								Found,	71.34	6.30	6.42
XIc	H	$(CH_2)_3CH_3$	Maleate	EtOH/Et_2O	179.5-180.5	71	$C_{17}H_{19}N_3O_5$	Calcd.,	59.12	5.55	12.17
								Found,	58.92	5.66	12.24
XXVI	$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	BF_4^-	EtOAc	135-136	24	$C_{17}H_{24}N_3O \cdot BF_4$	Calcd.,	54.71	6.48	11.26
								Found,	55.09	6.04	11.30
XXVII	$(CH_2)_4C_6H_{11}$	$(CH_2)_4C_6H_{11}$	BF_4^-	EtOAc/EtOH/Et_2O	176-177	63	$C_{29}H_{44}N_3O \cdot BF_4$	Calcd.,	64.80	8.25	7.82
								Found,	64.97	8.27	7.74

(a) Calcd. for Cl, 12.68. Found, 12.51. (b) Calcd. for Cl, 17.98. Found, 17.84. (c) Prepared by the procedure of Y. T. Pratt and N. L. Drake, *J. Am. Chem. Soc.*, 79, 5025 (1957); ν potassium bromide 3270, 1700 (s), 1680 cm⁻¹; λ max (ethanol) 355 nm (log ε 3.41) 295 (s)(4.0), 265 (4.16), lit. m.p. 265°. (d) Lit. (4), m.p. 222°.

unstable enol ethers Xa and Xb, respectively, by triethyloxonium tetrafluoborate in methylene chloride. These ethers, similarly prepared in the 4-amino-1,2-naphthoquinone series (7), reacted with two moles of amine under the conditions described (see Experimental section) to give the salts XI (XXVI, XXVII in Table I). The fact that the same compound XI may be obtained from both IXa and IXb further supports the proposed course of these reactions as that of Scheme B. In view of the instability found here and previously (7) for enol ethers such as X, it is, in retrospect, not surprising that early efforts (9) to prepare XII by direct oxidation of the 8-amino-6-methoxyquinoline failed. The quinolone XII has long been of interest in connection with formation of the presumed biologically active quinonoid metabolites of the antimalarial 8-amino-6-methoxyquinolines (10).

The assignment of structure XI to the aminoquinolone salts is made by analogy with a study of the protonation of related 2-amino-1,4-naphthoquinone imines I (7). The pmr spectrum of the tetrafluoborate (XXVII, Table I) in deuteriochloroform showed the resonance of the α-methylene protons of the R groups (δ = 218 Hz, 231 Hz from internal TMS) as an overlapping doublet of triplets (J_{CHCH} = 7 Hz, J_{NHCH} = 7 Hz) which collapsed to a pair of overlapping triplets (δ = 218 Hz, 231 Hz from internal TMS, J_{CHCH} = 7 Hz) on deuterium exchange. This is consistent only with a single proton on N_6 and N_8 and excludes protonation on the ring nitrogen. This is completely analogous to what was observed on protonation of I (7).

From several unsuccessful attempts to convert the stable salts XIa to the pure parent quinolone, we conclude that the free bases are much less stable than the corresponding 2-amino-1,4-naphthoquinone imines (I). The fact that tetrafluoborates were isolated from the reaction mixture under conditions which previously gave directly the unprotonated 2-amino-1,4-naphthoquinone imines (7) seems to indicate that the parent quinolones of XI are also stronger bases than their carbocyclic analogs. No direct comparison of pK's of these two series has been carried out, however.

In one case, 8-amino-5,6-quinolinedione (IXc) (9) was converted to the quinolone imine (isolated as its maleate salt XIc) by direct condensation with n-butylamine. While the introduction of a single alkyl group was confirmed by the pmr spectrum, attempts to make more general use of this reaction were not successful.

It is also of interest with regard to the structure of the salts XIa that they show the carbonyl absorption at 1690 cm⁻¹ (potassium bromide), which is identical to the absorption of the 4-amino-1,2-naphthoquinones and 8-dialkyl-5,6-quinolinediones. This is significantly different

from the carbonyl absorption of the 1,4-naphthoquinone imines and 1,4-naphthoquinones which is ordinarily found in the range of 1660-1670 cm⁻¹.
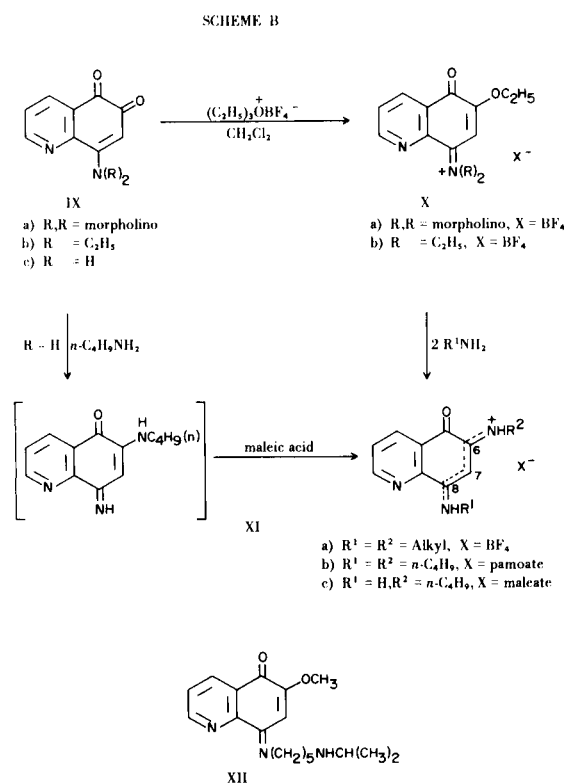
SCHEME B

7-Alkyl-4,6-dihydroxy-5,8-quinolinediones (XIV).

The quinolinedione (XIV) was accessible by free radical alkylation of XIII prepared by the sequence of Scheme C (11), using thermal decomposition of diacylperoxide in a way analogous to other syntheses of 3-alkyl-4-hydroxy-1,4-naphthoquinones (12). Quinolinedione (XIV) is a nitrogen analog of a class of coccidiostat in the series II shown to be useful at 0.01-0.03 weight percent in poultry feed (3). It was evaluated as a coccidiostat against *Eimeria tenella* in chickens and found to be completely inactive at a level of 0.035 percent of drug added to the feed (13). For this reason, the series was not further explored.

The compounds of Table I were evaluated (14) in *Plasmodium berghei*-infected mice, *Plasmodium gallinaceum*-infected chicks and against the sexual phase of *P. gallinaceium* in mosquitoes (*Aedes Aegypti*). The quinolones XV-XXV were inactive and nontoxic in all three primary screens. The salts XIb, XIc, XXVI and XXVII showed no significant activity in infected mice and birds. An indication of the high toxicity in this series is the fact that even the relatively insoluble pamoate salt XIb was

toxic in both mice and birds. The maleate salt XIc showed partial sporozoite suppression at 0.01 percent in the mosquito screen, but high toxicity in other tests.

EXPERIMENTAL (15)

8-Hydroxy-7-phenylazoquinoline-5-sulfonic Acid, Sodium Salt (16).

This compound was prepared based on the procedures of Matsumura (6). Benzene diazonium chloride was prepared by adding dropwise a solution of sodium nitrite (106 g., 1.56 mole) in water (525 ml.) to a stirred mixture of aniline (150 g., 1.61 mole), ice (*ca.* 800 g.) and concentrated hydrochloric acid (294 ml.) with the temperature being maintained from 0 to 5°. This diazo solution was then added rapidly (*ca.* 1 minute) to a stirred solution (0°) of 8-hydroxyquinoline-5-sulfonic acid monohydrate (352 g., 1.65 mole) in 2 N sodium hydroxide (2.5 liters) (17). The resulting reaction mixture was cooled for 2 hours by addition of ice and the red gelatinous product was filtered, washed (cold water) and used directly in a moist condition.

7-Amino-8-hydroxyquinoline-5-sulfonic Acid (IV) (16).

To a suspension of the 8-hydroxy-7-phenylazoquinoline-5-sulfonic acid sodium salt in warm water (9 liters) was added with stirring 3.2 N sodium hydroxide (825 ml.). This red-orange solution was then treated in a well-vented hood at 25° by the rapid addition of solid sodium hyposulfite (554 g., 3.19 mole). After additional sodium hyposulfite (554 g.) was added the dark claret solution was cooled to 15° by addition of ice and neutralized with concentrated hydrochloric acid (220 ml.). The light orange solid was collected, washed (acetone) and dried to give 311 g. of product (83% overall yield). The material effloresced at high temperature without melting; ν potassium bromide 3565 cm⁻¹, 3425 cm⁻¹, 3340 cm⁻¹, 2500-3000 (broad) cm⁻¹, 1625 cm⁻¹, 1595 cm⁻¹; λ max (water) 285 nm (log ε 4.02), 252 (4.35) (lit. no melting up to 310°).

Preparation of 7-Amino-5-imino-8(5H)-quinolones.

7-Amino-5-Arylimino-8(5H)-quinolones (XV-XVIII).

A solution of 7-amino-8-hydroxyquinoline-5-sulfonic acid (4 g., 16 mmoles) in DMF (50 ml.) was stirred with the aryl amine (19 mmoles) and commercial silver oxide (8 g.) at 25° for 2 hours. During the first 15 minutes the temperature rose to 30-35°, but gradually subsided to 25°. After filtration and thorough washing of the filter cake with DMF, the filtrate was evaporated *in vacuo*. The dark tarry residue was then extracted several times with 2 N hydrochloric acid (100 ml. portions), decanted, and the extract filtered through glass fiber paper. Careful neutralization with solid sodium carbonate gave, after filtration and crystallization (charcoal), the desired compounds. Quinone XVIII was chromatographed on neutral alumina (chloroform elution) prior to crystallization. These compounds had the expected spectral properties; ν potassium bromide 3415-3450 cm⁻¹ (NH), 1665-1670 cm⁻¹ (C=O), 1610-1620 cm⁻¹ (C=C); λ max (ethanol) (visible) XV = 445 nm (3.82), XVI = 490 nm (3.75), XVII = 455 nm (3.86), XVIII = 465 nm (3.80). Pmr spectra recorded in deuteriochloroform were consistent with the assigned structures.

7-Arylamino-5-arylimino-8(5H)-quinolones (XIX-XXI).

Using essentially the procedure of Hebebrand (5), a steady stream of chlorine was passed through a stirred solution of 8-quinolinol (5 g., 35 mmoles) in acetic acid (50 ml.) for 1 hour with the temperature maintained at 15-20°. The resulting heavy

SCHEME C
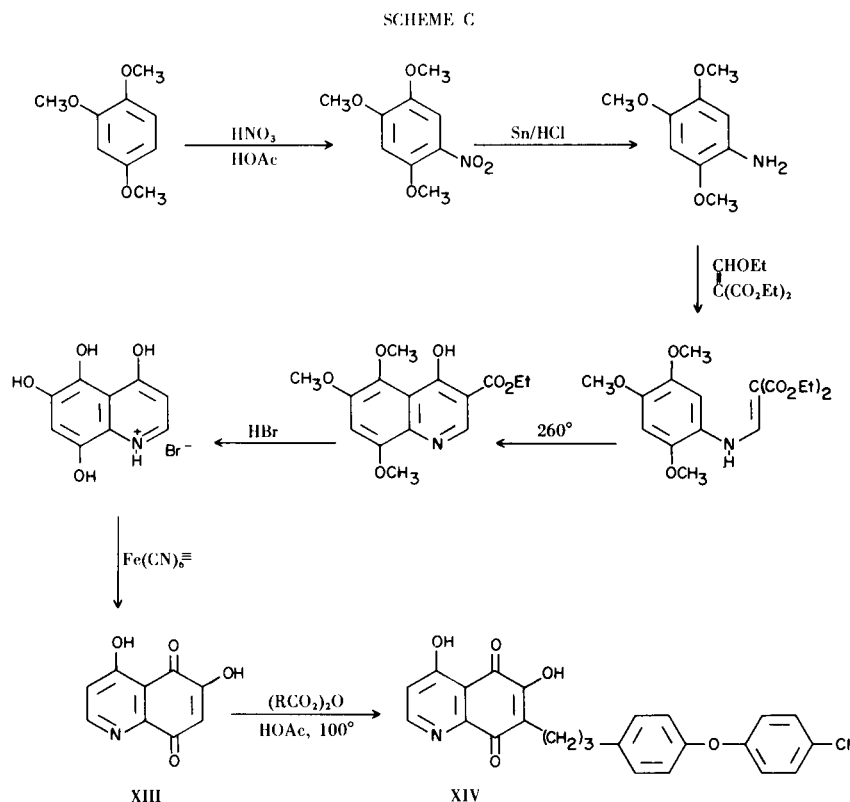
precipitate (the trichloroquinolone VII) was filtered, washed thoroughly with acetic acid, dried by pressing between pieces of filter paper and used immediately.

A solution of VII, obtained as above, in ethanol (200 mL) at $0°$ was treated with excess aryl amine (165 mmoles) in ethanol (200 ml.) and the resulting red reaction mixture was stirred at $0°$ for 15 hours. In some cases, the product precipitated immediately. Filtration and crystallization gave the quinones as red solids. Compound XXIII was chromatographed on neutral alumina (chloroform elution) prior to crystallization. Typically, ν potassium bromide 3300-3450 cm^{-1} (NH), 1660-1680 cm^{-1} (C=O), 1595-1510 cm^{-1} (C=C); λ max (ethanol) (visible) XIX = 496 nm (3.56), XXI = 478 nm (3.88), XXV = 478 nm (3.76), XX = 510 nm (3.88), XXII = 470 nm (3.94), XXIII = 460 nm (3.72).

6-Amino-8-imino-5(8H)-quinolone Tetrafluoborates (XXVI-XXVII).

A stirred solution of 8-dialkylamino-5,6-quinolinedione (7,18) (16 mmoles) in dry methylene chloride (300 ml.) at $25°$ was treated by adding rapidly $(C_2H_5)_3OBF_4^-$ (19) (ca. 5 g.) in dry methylene chloride (50 ml.). After the mixture was stirred for 1.5 hours at $25°$, excess alkylamine (8-10 ml.) was then added and the resulting deep red solution was stirred for an additional 15 minutes. The reaction mixture was filtered (charcoal) and the filtrate was evaporated in vacuo. Trituration of the residue with ether-ethyl acetate gave after filtration the orange-hellow product; λ max (ethanol) XXVII = 435 nm (3.83).

The pamoate salt (XIb) was obtained by pouring a solution of XXVI (1.2 g., 3 mmoles) in DMF (7 mL) into a stirred solution of monosodium pamoate (1.28 g., 3 mmoles) in DMF (7 mL). After stirring for 5 minutes, water (4-5 ml.) was added. The mixture was then filtered and the red product was washed several times

with water, ethanol, and finally with ether; λ max (ethanol) XIb = 462 nm (3.84), 298 nm (4.20), 287 nm (S) (4.30), 277 nm (4.31), 236 nm (5.10).

γ-[p-(p-Chlorophenoxy)phenyl]butyric Acid.

p-Chlorophenyl phenyl ether (20) was acylated with succinic anhydride in benzene using aluminum chloride and a procedure analogous to that of Huang-Minlon (21). β-[p-(p-Chlorophenoxy)-benzoyl]propionic acid obtained in this way was crystallized from benzene-petroleum ether (b.p. $30-60°$) and had m.p. $141-142°$. The butyric acid was obtained by Huang-Minlon reduction (21) and purified by recrystallization from benzene-petroleum ether (charcoal). It had a m.p. $98.5-99°$.

Anal. Calcd. for $C_{16}H_{15}ClO_3$: C, 66.09; H, 5.20; Cl, 12.19. Found: C, 66.20; H, 5.37; Cl, 12.10.

7-[3-(4-(4-Chlorophenoxy)phenyl)propyl]-4,6-dihydroxy-5,8-quinolinedione (XIV).

γ-[p-(p-Chlorophenoxy)phenyl]butyric acid (10.38 g., 35.4 mmoles) was converted to the acid chloride with thionyl chloride and the diacylperoxide prepared using the pyridine method described previously (12). The ether solution of peroxide was washed with 0.5 N hydrochloric acid, ice water, then dried (sodium sulfate) and used immediately in the alkylation step. For the alkylation, 4,6-dihydroxy-5,8-quinolinedione (XIII, 3.4 g., 18 mmoles) (11) was dissolved in hot acetic acid (1.2 liters, a small amount of the insoluble material being removed by filtration) and to this solution held at $100±5°$, the ethereal solution of diacylperoxide was added dropwise during 2 hours, the ether being permitted to flash distill out. The reaction mixture was then stirred for 1 hour at $100°$, then cooled. It was stirred overnight before workup. The solvent was evaporated in vacuo and the

brown solid, obtained by trituration of the oily residue with methanol, filtered. The material was recrystallized from benzene (charcoal)-hexane, then from ethanol to give 0.6 g. of yellow solid, m.p. 203-205°; ν potassium bromide 3600 cm^{-1} (w), 1661 (s), 1610 (s), 1540 (s), 1390 (s), 1240 (s).

Anal. Calcd. for $C_{24}H_{18}ClNO_5$: C, 66.13; H, 4.16; Cl, 8.14; N, 3.21. Found: C, 66.41, 66.83; H, 4.30, 4.16; Cl, 8.23; N, 3.18.

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(1) This work was supported in large part by the U. S. Army Medical Research and Development Command under Contract DA-49-193-MD-2880. This paper is Contribution No. 848 from the Army Research Program on Malaria and much of the work was the subject of a preliminary report at the First Northeast Section Meeting of the American Chemical Society, Boston, Mass., October, 1968.

(2) For the previous paper in this series, see F. J. Bullock and J. F. Tweedie, *J. Med. Chem.*, 13, 550 (1970).

(3) For a report on the biological activity of II, see Merck and Co., Inc., Netherlands patent application 6,612,826; *Chem. Abstr.*, 67, 73443q (1967).

(4) The trichloroquinolone is formulated as VII for convenience. The alternative structure 5,7,7-trichloro-8(7H)-quinolone cannot be excluded as was appreciated by early workers (5).

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(6) K. Matsumura, *J. Am. Chem. Soc.*, 49, 810 (1927).

(7) F. J. Bullock, J. F. Tweedie and D. D. McRitchie, *J. Chem. Soc.* (C), 1799 (1969).

(8) F. J. Bullock and J. F. Tweedie, *J. Med. Chem.*, 13, 261 (1970).

(9) N. L. Drake and Y. T. Pratt, *J. Am. Chem. Soc.*, 73, 544 (1951).

(10) For a recent succinct review of the background to this problem, see E. F. Elslager, M. P. Hutt, L. M. Werbel, *J. Heterocyclic Chem.*, 6, 99 (1969).

(11) E. Biekert and W. Shäfer, *Ber.*, 93, 642 (1960).

(12) F. J. Bullock, *J. Med. Chem.*, 11, 419 (1969) and references therein.

(13) Biological evaluation was carried out by Dr. R. G. Strout, University of New Hampshire, using an oral dose of 200,000 sporulated oocysts for infection and the scoring system described by Cuckler *et al.*, [*Proc. Soc. Exptl. Biol. Med.*, 98, 167 (1958); *ibid.*, 117, 488 (1964)]. Drug was administered at a level of 0.035% in the feed, beginning two days before infection. Amprolium was used as a positive control during evaluation of candidate compounds.

(14) Biological evaluations were made as part of the Walter Reed Army Institute of Research malaria program using methods detailed previously, F. J. Bullock, J. F. Tweedie, D. D. McRitchie and M. A. Tucker, *J. Med. Chem.*, 13, 97 (1970).

(15) Melting points, ir, uv, nmr, and elemental analyses were recorded or obtained as described previously (14).

(16) We wish to thank Dr. G. R. Handrick and R. Proverb for large-scale preparation of these compounds.

(17) Because of the volume of solution and temperature control needed, it was more convenient to carry out the coupling reaction simultaneously in two equal portions.

(18) The morpholino compound (IXa) is used with greatest advantage here because of its easy preparation.

(19) H. Meerwein, in "Organic Syntheses," Vol. 46, E. J. Corey, Ed., John Wiley and Sons, Inc., New York, N. Y., 1966, p. 113.

(20) C. M. Sutter and F. O. Green, *J. Am. Chem. Soc.*, 59, 2578 (1937).

(21) Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2487 (1946).