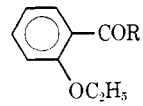
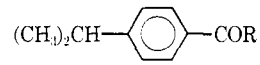
TABLE I
AMIDES OF *o*-ETHOXYBENZOIC ACID



No.	R	Mp or bp (mm), °C	Yield purified, %	Purification solvent[a]	Formula	—Carbon, %— Calcd	Found	—Hydrogen, %— Calcd	Found	—Nitrogen, %— Calcd	Found
1	NH-3-C_5H_4N[b]	66–68	33	A	$C_{14}H_{14}N_2O_2$	69.40	69.84	5.82	6.12	11.57	11.60
2	NHC_6H_5	70–71	50	A	$C_{15}H_{15}NO_2$	74.66	74.58	6.27	6.29	5.81	5.46
3	$N(C_2H_5)C_6H_5$	112–114 (0.2)	49	..	$C_{17}H_{19}NO_2$	75.81	75.73	7.11	7.28	5.20	5.15
4	$NH(CH_2)_2C_6H_5$	56–58	28	A	$C_{17}H_{19}NO_2$	75.81	76.09	7.11	7.25	5.20	5.09
5	$NHCH_2C_6H_4$-*p*-CH_3O	54–56	50	B	$C_{17}H_{19}NO_3$	71.59	71.60	7.07	6.69	4.92	4.80
6	$N(C_2H_5)CH_2C_6H_5$	133–135 (0.1)	33	..	$C_{18}H_{21}NO_2$	76.29	76.33	7.47	7.48	4.94	4.91
7	$N(C_6H_5)_2$	97–99	78	A	$C_{21}H_{19}NO_2$	79.47	79.79	6.03	6.09	4.42	4.49
8	$N(C_6H_{11})_2$[c]	170–172 (0.3)	32	..	$C_{21}H_{31}NO_2$	76.55	76.46	9.49	9.54	4.25	4.17

[a] A, isooctane; B, ethanol–water. [b] C_5H_4N represents the pyridyl radical. [c] C_6H_{11} represents the cyclohexyl radical.

TABLE II
AMIDES OF *p*-ISOPROPYLBENZOIC ACID



No.	R	Mp or bp (mm), °C	Yield purified, %	Purification solvent[a]	Formula	—Carbon, %— Calcd	Found	—Hydrogen, %— Calcd	Found	—Nitrogen, %— Calcd	Found
9	$N(C_2H_5)_2$[d]	97–100 (0.4)	25	..	$C_{14}H_{21}NO$	76.66	76.41	9.65	9.72	6.38	6.21
10	NH-3-C_5H_4N[b]	100–101	14	A	$C_{15}H_{16}N_2O$	74.97	75.12	6.71	6.77	11.66	11.47
11	$N(CH_2)_5$	60–61	37	A	$C_{15}H_{21}NO$	77.89	77.87	9.15	9.36	6.06	6.12
12	NHC_6H_5	129–131	43	B	$C_{16}H_{17}NO$	80.30	80.04	7.16	7.19	5.85	5.96
13	$N(CH_3)(C_6H_{11})$[c]	80–81	38	A	$C_{17}H_{25}NO$	78.71	78.98	9.72	9.95	5.40	5.35
14	$N(C_2H_5)(C_6H_5)$	124–127 (0.2)	36	..	$C_{18}H_{21}NO$	80.86	80.64	7.92	7.87	5.24	5.17
15	$NH(CH_2)_2C_6H_5$	110–112	19	B	$C_{18}H_{21}NO$	80.86	80.59	7.92	7.90	5.24	5.26
16	$NHCH_2C_6H_4$-*p*-MeO	119–121	33	B	$C_{18}H_{21}NO_2$	76.29	76.08	7.47	7.43	4.94	4.82
17	$N(C_2H_5)CH_2C_6H_5$	168–169 (0.4)	12	..	$C_{19}H_{23}NO$	81.10	80.99	8.24	8.49	4.98	4.81
18	$N(C_6H_{11})_2$[c]	170–172 (0.1)	43	..	$C_{22}H_{31}NO$	81.18	80.19	9.60	9.68	4.30	4.19

[a–c] See corresponding footnotes, Table I. [d] W. F. Barthel, J. Leon, and S. A. Hall, *J. Org. Chem.*, **19**, 485 (1954).

from the original filtrate was removed *in vacuo* and the residue was recrystallized or distilled.

Acknowledgment.—The authors wish to thank Mr. Charles E. Childs and his staff for the microanalytical data reported herein.

4-(1-Methyl-4-pyrrolidinobutylamino)-7-chloroquinoline and 4-(1-Methyl-4-morpholinobutylamino)-7-chloroquinoline as Potential Antimalarials

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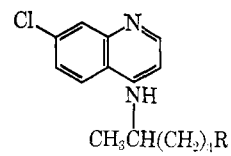
Increased interest in finding a prophylactic agent against drug-resistant *Plasmodium falciparum* and *Plasmodium vivax* has led to the synthesis of two new substituted quinolines, 4-(1-methyl-4-pyrrolidinobutylamino)-7-chloroquinoline (I) and 4-(1-methyl-4-morpholinobutylamino)-7-chloroquinoline (II) (Table I). 4-(1-Methyl-4-bromobutylamino)-7-chloroquinoline (III),[1] upon reaction with morpholine or pyrrolidine, gave I and II, respectively. Preliminary reports[2] show these compounds to be active against *Plasmodium berghei* infected mice.

(1) M. Carmack, H. Bullitt, Jr., G. Handrick, L. W. Kissinger, and I. Von, *J. Am. Chem. Soc.*, **68**, 1220 (1946).

TABLE I
ANTIMALARIAL TEST DATA

Compd	No. of mice[a]	Dose, mg/kg	Mean survival time, days[b]	Deaths
I	5	40	15.2	5
II	5	80	13.8	4
II	5	160	14.4	4

[a] Mice infected with *P. berghei*. [b] Treatment is withheld for 3 days after infection. Death occurs in untreated controls within 6–8 days.



I, R = pyrrolidino
II, R = morpholino

Experimental Section[3]

4-(1-Methyl-4-pyrrolidinobutylamino)-7-chloroquinoline (I).—4-(1-Methyl-4-bromobutylamino)-7-chloroquinoline (III)[1] (13.2

(2) We wish to thank Dr. Leo Rane, University of Miami, Miami, Fla., for the preliminary test data.

(3) Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus. The microanalyses were performed by Mr. Joseph Alicino, Metuchen, N. J. 08840.

g, 0.05 mole) and 35.6 g (0.5 mole) of freshly distilled pyrrolidine, each previously cooled, were combined and the mixture was permitted to warm to room temperature. After 48 hr the excess pyrrolidine was removed under reduced pressure. A solution of 17 g of K_2CO_3 in 350 ml of water was added and the free base was extracted with three 100-ml portions of chloroform. The extract obtained on evaporation of the solvent was dissolved in ethanol–water (1:1), and the pH was adjusted to 8.1 with 6 *N* HCl. Some 4-(2-methyl-1-pyrrolidyl)-7-chloroquinoline,[3] formed by ring closure of the starting material, was removed by adding water and extracting with three 50-ml portions of ether. The aqueous layer was made basic with 5 g of KOH in 10 ml of water, and the product was extracted with three 50-ml portions of chloroform. The crude I, 10 g, was purified on a base-washed silicic acid–charcoal (4:1) chromatographic column, and was eluted with benzene. Recrystallization from benzene gave 4.3 g (26.0%) of I, mp 107–108°.

Anal. Calcd for $C_{18}H_{21}ClN_3$: C, 68.01; H, 7.61; N, 13.22. Found: C, 68.41; H, 8.14; N, 13.25.

4-(1-Methyl-4-morpholinobutylamino)-7-chloroquinoline (II). Compound III (13.2 g, 0.05 mole) was treated by the above procedure with 43.6 g (0.5 mole) of morpholine to yield 16 g of II. Recrystallization from acetone gave 4.5 g (25.0%) of II, mp 153–154°.

Anal. Calcd for $C_{18}H_{24}ClN_3O$: C, 64.75; H, 7.25; N, 12.59. Found: C, 64.09; H, 7.54; N, 13.04.

Substituted N-Aminomethylisatins[1]

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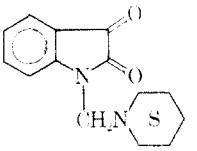
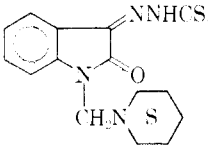
Received December 19, 1966

In a recent report[3] from this laboratory, we described the synthesis of several isatin N-Mannich bases (Table I). One compound of this series, N-piperidinemethylisatin (1), demonstrated a high order of antiviral activity[4] against poliomyelitis Type II, herpes simplex, measles, and parainfluenza 3 (HA-1) viruses. Initially, it was our plan to synthesize isatin-N-Mannich bases and then convert them to corresponding thiosemicarbazones. But because of the striking activity of 1 on one hand and considerably less activity demonstrated by N-piperidinomethylisatin-β-thiosemicarbazone[4] (11) on the other, we prepared additional isatin-N-Mannich bases for biological screening.



I



II

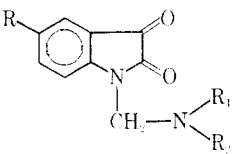
Experimental Section

Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were charted in Nujol mull on a Perkin-Elmer Model 137 Infracord spectrophotometer. Analyses are by Dr. Alfred Bernhardt, Max-Planck Institut, Mulheim (Ruhr), Germany; Micro-Analysis, Inc., Wilmington, Del.; and Galbraith Laboratories, Knoxville, Tenn.

Isatin N-Mannich Bases.—To a mixture of the appropriate substituted isatin (0.05 mole), ethanol (20 ml), and 37% aqueous formaldehyde solution (7.5 ml) there was added the desired secondary amine (0.05 mole) with stirring. Solid amines were dissolved in 10 ml of ethanol prior to addition. Dimethylamine was used as the 25% aqueous solution. After the additions were completed, the reaction mixture was warmed on a steam bath for 10–15 min. The product separated upon cooling or overnight refrigeration and was removed by filtration; it was recrystallized from ethanol or chloroform–petroleum ether (bp 60–80°). The new Mannich bases thus prepared are listed in Table I.

TABLE I

ISATIN N-MANNICH BASES



No.	NR$_1$R$_2$	R	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Infrared, μ C=O
1[a]	4-Methylpiperidino	H	102–103	47	$C_{15}H_{18}N_2O_2$	69.74	7.02		69.51	7.01		5.80
2[a]	3-Methylpiperidino	H	101–103	54	$C_{15}H_{18}N_2O_2$	69.74	7.02		69.53	6.93		5.76
3[a]	2,6-Dimethylmorpholino	H	122–124	37	$C_{15}H_{18}N_2O_3$	65.68	6.61		65.15	6.60		5.77
4[a]	4-Phenylpropylpiperidino	H	81–82	72	$C_{23}H_{26}N_2O_2$	76.21	7.23		76.13	7.18		5.78
5[a]	Pyrrolidino	H	106–107	61	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	67.71	6.17	12.07	5.80
6[a]	AZBN[c]	H	103–105	68	$C_{17}H_{20}N_2O_2$	71.81	7.09	9.85	72.45	7.43	9.61	5.81
7[a]	Dimethylamino	Br	137–139	86	$C_{11}H_{11}BrN_2O_2$	46.65	3.91	9.89	46.55	3.79	9.44	5.78
8[b]	AZBO[d]	Br	180	80	$C_{16}H_{17}BrN_2O_2$	55.00	4.90	8.02	55.01	4.97	7.69	5.76
9[a]	Morpholino	Br	143–146	61	$C_{12}H_{13}BrN_2O_3$	48.02	4.03	8.64	48.04	3.90	8.46	5.79
10[a]	Hexamethyleneimino	Br	135–137	50	$C_{15}H_{17}BrN_2O_2$	53.42	5.08	8.31	53.47	5.27	8.22	5.76

[a] Recrystallized from ethanol. [b] Recrystallized from chloroform–petroleum ether (bp 60–80°). [c] 3-Azabicyclo[3.2.2]nonane moiety. [d] 3-Azabicyclo[3.2.1]octane moiety.

(1) This work was supported in part by Grant No. AI 04701 from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.

(2) Author to whom inquiries should be addressed.

(3) R. S. Varma and W. Lewis Nobles, *J. Heterocyclic Chem.*, **3**, 462 (1966).

(4) R. S. Varma and W. L. Nobles, unpublished work. Other compounds are being screened.