TABLE I

CHEMICAL AND PHYSICAL PROPERTIES OF AMINE DERIVATIVES (RNH_2) OF 2-CHLORO-1,4-NAPHTHOQUINONE

Amine deriv	Mp, °C[a]	Formula[b]
Methyl	101	$C_{11}H_8ClNO_2$
Propyl	110–112	$C_{13}H_{12}ClNO_2$
Isopropyl	117	$C_{13}H_{12}ClNO_2$
Allyl	149–150	$C_{13}H_{10}ClNO_2$
Butyl	112	$C_{14}H_{14}ClNO_2$
Isobutyl	113	$C_{14}H_{14}ClNO_2$
sec-Butyl	82–83	$C_{14}H_{14}ClNO_2$[c]
t-Butyl	112–113	$C_{14}H_{14}ClNO_2$
Pentyl	97–98	$C_{15}H_{16}ClNO_2$
Heptyl	91	$C_{17}H_{20}ClNO_2$
n-Octyl	86	$C_{18}H_{22}ClNO_2$
Nonyl	96	$C_{19}H_{24}ClNO_2$
Dodecyl	89	$C_{22}H_{30}ClNO_2$
Hexadecyl	88–92	$C_{26}H_{38}ClNO_2$
Octadecyl	98	$C_{28}H_{42}ClNO_2$
Methoxyethyl	86	$C_{13}H_{12}ClNO_3$
Methoxypropyl	79	$C_{14}H_{14}ClNO_3$
Methoxyisopropyl	75–76	$C_{14}H_{14}ClNO_3$
3-*n*-Butoxypropyl	46–47	$C_{17}H_{20}ClNO_3$
$3\text{-}Me_2N(CH_2)_3$	55	$C_{15}H_{17}ClN_2O_2$
$H_2N(CH_2)_3NH$	99–101	$C_{23}H_{16}Cl_2N_2O_4$
$H_2N(CH_2)_6NH$	170–171	$C_{26}H_{22}Cl_2N_2O_4$
Ethoxyethoxyethyl	79–80	$C_{16}H_{18}ClNO_4$
Ethoxyethoxypropyl	45–46	$C_{17}H_{20}ClNO_4$
Ethoxyethoxyethoxypropyl	73	$C_{19}H_{24}ClNO_5$
Di(methoxyethyl)	92–95	$C_{16}H_{18}ClNO_4$
Di(ethoxyethyl)	51–53	$C_{18}H_{22}ClNO_4$
n-Aminopropyldiethanol	62–65	$C_{17}H_{21}ClN_2O_4$
Dicyclopentyl	65–68	$C_{20}H_{22}ClNO_2$
Di-*n*-hexyl	160–162	$C_{22}H_{30}ClNO_2$
Di-*n*-decyl	159	$C_{30}H_{46}ClNO_2$
Di-*n*-dodecyl	171	$C_{34}H_{54}ClNO_2$
Methyliminobispropyl	115	$C_{27}H_{25}Cl_2N_3O_4$
3,3′-Iminobispropyl	68	$C_{38}H_{26}Cl_3N_3O_6$
Benzyl	245–247	$C_{17}H_{12}ClNO_2$
p-Anisidine	205	$C_{17}H_{12}ClNO_3$
Phenetidine	239–241	$C_{18}H_{14}ClNO_3$
Thymyl	254	$C_{20}H_{18}ClNO_2$
p-Aminobenzenesulfonic acid	>300	$C_{16}H_{10}ClNO_5S$
Sulfanilamide	>300	$C_{16}H_{14}ClN_3O_4S$
Sulfapyridine	260	$C_{21}H_{17}ClN_4O_4S$
4,4′-Diaminodiphenyl sulfone	192–194	$C_{32}H_{18}Cl_2N_2O_6S$
n-Aminomorpholine	132	$C_{14}H_{13}ClN_2O_3$
n-Aminopropylmorpholine	159	$C_{17}H_{19}ClN_2O_3$
2,6-Dimethylmorpholine	126–129	$C_{16}H_{16}ClNO_3$
Piperazine	250	$C_{34}H_{16}Cl_2N_2O_4$
1-Methylpiperazine	220–225	$C_{15}H_{15}ClN_2O_2$
n-Aminoethylpiperazine	240	$C_{26}H_{21}Cl_2N_3O_4$
Bis(aminopropyl)piperazine	200–204	$C_{36}H_{30}Cl_2N_4O_4$
2-Hydrazino-5-nitropyridine	220	$C_{13}H_9ClN_4O_4$
2-Aminopyridine	275	$C_{15}H_9ClN_2O_2$
2-Aminothiazole	165–168	$C_{13}H_7ClN_2O_2S$
α-Naphthyl	170	$C_{20}H_{12}ClNO_2$
8-Aminoquinoline	289	$C_{19}H_{11}ClN_2O_2$
Furfuryl	134–136	$C_{15}H_{10}ClNO_3$
Imidazole	191–193	$C_{13}H_7ClN_2O_2$
2-Hydrazinobenzothiazole	204	$C_{17}H_{10}ClN_3O_2S$
Glutaric dihydrazide	170–173	$C_{25}H_{18}Cl_2N_4O_6$
1,4-Dihydrazinophthalazine	192–194	$C_{28}H_{16}Cl_2N_6O_4$
5-Aminoindazole	267–270	$C_{17}H_{10}ClN_3O_2$
6-Aminoindazole	252–255	$C_{17}H_{10}ClN_3O_2$
2-Aminoethylphosphonic acid	198	$C_{12}H_{10}ClNO_5P$
Glycine	174	$C_{12}H_8ClNO_4$
Hydrazine	>300	$C_{20}H_{10}Cl_2N_2O_4$

[a] All melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus. [b] All compounds were analyzed for C, H, N (±0.3% limit), except where indicated otherwise. [c] H: calcd, 5.35; found, 5.61.

TABLE II

ANTIMALARIAL ACTIVITY OF CERTAIN DERIVATIVES OF 2-CHLORO-1,4-NAPHTHOQUINONE AGAINST *Plasmodium berghei* IN MICE

Compd	Dose, mg/kg	Mean survival time, days[a]	Increase in survival time, days	Mortality	Remarks
I	20	14.4	7.1	5/5	
	40	24.8	17.5	4/5	1 mouse survived 60 days
	80	44.4	37.1	2/5	3 mice survived 60 days
	160			2/5	2 toxic deaths,[b] 1 mouse survived 22 days, 2 mice survived 60 days
	320			4/5	4 toxic deaths, 1 mouse survived 60 days
	640			4/5	4 toxic deaths, 1 mouse survived 60 days
II	40	13.4	7.2	5/5	
	80	15.8	9.6	5/5	
	160	16.4	10.2	5/5	
	320	14.0	7.8	1/5	4 mice survived 60 days
	640			0/5	5 mice survived 60 days
	1280			1/5	1 toxic death, 4 mice survived 60 days
Chloroquine diphosphate	40	11.0	4.0	5/5	
	80	12.8	5.8	5/5	
	160	17.0	10.0	5/5	
	320	24.0	17.0	5/5	2 toxic deaths
	640		0	5/5	5 toxic deaths

[a] Mean survival time of controls: 7.3 for I, 6.2 for II, and 7.0 for chloroquine diphosphate. [b] Deaths due to toxicity of drug occur in 3–5 days. Mice surviving 60 days are considered cures.

four mice, respectively, surviving in each group for 60 days with no evidence of toxicity. The results of the antimalarial activity of the two active compounds and of the control drug chloroquine diphosphate, supplied by Dr. David P. Jacobus of the Walter Reed Army Institute of Research, are summarized in Table II. Initial blood studies in normal white mice have indicated that the chemical structures of these complex molecules made them difficult to cleave, since no detectable amounts of the original components were found present in the blood.

Synthesis of Potential Antineoplastic Agents. XX. Compounds Related to the 3-*o*-Nitrophenylhydrazone of Isatin[1]

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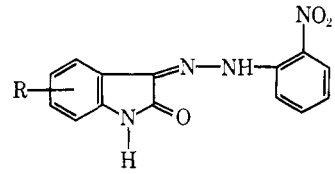
Received August 19, 1968

In connection with other work in progress in this laboratory we synthesized the title compound (I) by the condensation of isatin and *o*-nitrophenylhydrazine.

(1) (a) Part XIX: F. P. Silver, F. D. Popp, A. C. Casey, D. P. Chakraborty, E. Cullen, W. R. Kirsch, J. E. McCleskey, and B. Sinha, *J. Med. Chem.*, **10**, 986 (1967). (b) Supported by a research grant (CA 10345) from the National Cancer Institute.

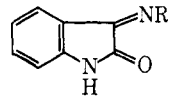
TABLE I



R	Mp,[a] °C	Yield, %	Formula	Analyses[b]	Activity[c] (dose, mg/kg) WM[d]	Activity[c] (dose, mg/kg) LE[e]
H	294–295	96	$C_{14}H_{10}N_4O_3$	C, H, N	25 (400)	102 (100)
1-CH_3	240–241	92	$C_{15}H_{12}N_4O_3$	C, H	83 (400)	95 (100)
1-$COCH_3$	238–239	86	$C_{16}H_{12}N_4O_4$	C, H	81 (400)	98 (400)
4-CF_3	304–305	91	$C_{15}H_9F_3N_4O_3$	C, H		103 (100)
5-Br	338–340	99	$C_{14}H_9BrN_4O_3$	C, H		113 (400)
5-Cl	339–340	92	$C_{14}H_9ClN_4O_3$	C, H		95 (400)
5-F	313–314	92	$C_{14}H_9FN_4O_3$	C, H		
5-CH_3O	301–302[f]	65	$C_{15}H_{12}N_4O_4$	C, H		
5-CH_3	317–319	96	$C_{15}H_{12}N_4O_3$	C, H		
5-NO_2	349–350[f]	89	$C_{14}H_9N_5O_5$	C, H		105 (400)
5-SO_3H	219–220	81	$C_{14}H_{10}N_4O_6S \cdot 2.5H_2O$	C, H, N, S		100 (400)
7-Cl	324–325[f]	75	$C_{14}H_9ClN_4O_3$	C, H		100 (200)
7-CH_3	336–337	95	$C_{15}H_{12}N_4O_3$	C, H		113 (400)
4-Cl-7-CH_3O	330–332	91	$C_{15}H_{11}ClN_4O_4$	C, H		
6-Cl-5-CH_3O	326–327[f]	95	$C_{15}H_{11}ClN_4O_4$	C, H		
4-Cl-7-CH_3	320–321	90	$C_{15}H_{11}ClN_4O_3$	C, H		
5-Cl-7-CH_3	>360	97	$C_{15}H_{11}ClN_4O_3$	C, H		
6-Cl-7-CH_3	>360	91	$C_{15}H_{11}ClN_4O_3$	C, H		
4,7-Cl_2	342–344	91	$C_{14}H_8Cl_2N_4O_3$	C, H		
5,7-Cl_2	338–340[f]	96	$C_{14}H_8Cl_2N_4O_3$	C, H		105 (100)
4,7-$(CH_3)_2$	>360[f]	92	$C_{16}H_{14}N_4O_3$	C, H		97 (400)
5,7-$(CH_3)_2$	344–345[f]	95	$C_{16}H_{14}N_4O_3$	C, H		
6,7-$(CH_3)_2$	339–340	98	$C_{16}H_{14}N_4O_3$	H; C[g]		

[a] Recrystallized from EtOH unless otherwise noted. [b] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Analyses for the elements indicated were within ±0.25% of the theoretical values. [c] Expressed as T/C. [d] Walker carcinosarcoma 256 (intramuscular)(T/C based on tumor weight). [e] L1210 lymphoid leukemia (T/C based on survival time). [f] Recrystallized from dioxane. [g] C: calcd, 61.93; found, 61.55.

TABLE II



RNH_2	Mp, °C[a]	Yield, %	Formula	Analyses[b]	Activity[c] WM[d]	Activity[c] LE[e]
Pentafluorophenylhydrazine	232–233	58	$C_{14}H_6F_5N_3O$	C, H		94 (400)
o-Chlorophenylhydrazine	269–270	64	$C_{14}H_{10}ClN_3O$	C, H		105 (400)
o-Methoxyphenylhydrazine	248–250	81	$C_{15}H_{13}N_3O_2$	C, H		102 (400)
o-Methylphenylhydrazine	241–242	93	$C_{15}H_{13}N_3O$	C, H		96 (400)
2-Hydrazinopyridine	293–294	86	$C_{13}H_{10}N_4O$	C, H, N	75 (100)	104 (400)
2-Hydrazino-4-methyl-6-hydroxypyrimidine	316–318	98	$C_{13}H_{11}N_5O_2$	C, H		
Ethyl carbazate	200–202	52	$C_{11}H_{11}N_3O_3$	C, H		92 (400)
Indole-3-acetic acid hydrazide	251–254	99	$C_{18}H_{14}N_4O_2$	C, H, N	89 (400)	102 (100)
o-Nitrobenzhydrazide	250–251	90	$C_{15}H_{10}N_4O_4$	C, H	63 (400)	96 (400)
p-Fluoroaniline	220–221	75	$C_{14}H_9N_2OF$	C, H		98 (100)
o-Phenylaniline	223–224	82	$C_{20}H_{14}N_2O$	C, H		104 (400)
5-Aminoquinoline	298–299	87	$C_{17}H_{11}N_3O$	C, H		100 (400)
Cyclopentylamine	145–148	36	$C_{13}H_{14}N_2O$	C, H		100 (400)
3-Aminocarbazole	318–320	87	$C_{20}H_{13}N_3O$	C, H, N	89 (400)	97 (400)
3-Amino-4-ethylcarbazole	266–267	95	$C_{22}H_{17}N_3O$	C, H	80 (400)	98 (100)
o-Aminobenzhydrazide[f]	277–278	96	$C_{15}H_{12}N_4O_2$	C, H, N	84 (400)	94 (400)

[a] Recrystallized from EtOH unless otherwise noted. [b] Analyses by Spang Microanalytical Lab., Ann Arbor, Mich. Analyses for the elements indicated were within ±0.25% of the theoretical value. [c] Expressed as T/C (mg/kg). [d] Walker carcinosarcoma 256 (intramuscular) (T/C based on tumor weight). [e] L1210 lymphoid leukemia (T/C based on survival time). [f] Condensation takes place at amine rather than at hydrazide.

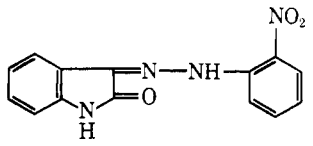
This compound was routinely sent to CCNSC[2] for screening and was found to be active[3] intramuscularly against Walker carcinosarcoma 256. In view of this activity we have synthesized a number of analogs of I. Table I includes compounds prepared by the condensation of *o*-nitrophenylhydrazine with a variety of substituted isatins while Table II includes compounds prepared by the condensation of isatin with a variety

(2) Cancer Chemotherapy National Service Center. We would like to thank the CCNSC for the screening results included in this paper.

(3) In the screening system used a compound is considered active if T/C ≦ 53%. At last report this compound had passed stage 2 (product of two T/C ± 0.19).

of hydrazines, hydrazides, amines, and related compounds.

Although screening data on all of the compounds have not yet become available, the representative results listed in Tables I and II indicate that the intramuscular activity of I against Walker carcinosarcoma 256 does not extend to the related derivatives. I was subsequently found to be inactive against L1210 lymphoid leukemia.



I

Experimental Section

Condensation Reactions.—Equimolar quantities of isatin and the hydrazine (in several cases the HCl salt was used) or related compounds were dissolved in warm EtOH and heated on the steam bath for 20–40 min. After standing for approximately 24 hr at room temperature the products described in Tables I and II were collected by filtration. The compounds exhibited ir peaks (KBr) at 3.12 ± 0.11, 5.80 ± 0.11, and 6.14 ± 0.04 (and at 2.95 ± 0.05 in compounds containing =NNH–).

Quinoline Antimalarials. Folded Chloroquine

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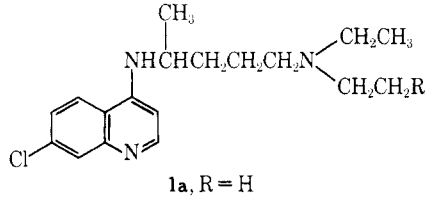
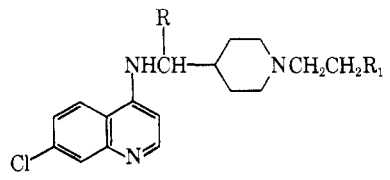
Chloroquine[1a] (**1a**) and hydroxychloroquine[1b] (**1b**)



1a, R = H
b, R = OH

have been widely used in the treatment of malaria and collagen diseases.[2] In an effort to increase the magnitude or duration of activity and/or reduce the toxicity of this class of compounds, we have examined the effect of "folding" the side chain to give compounds of structure **2**.[3] The syntheses of these compounds were accomplished by the interaction, at elevated temperatures, of 4,7-dichloroquinoline and the appropriate side-chain diamine[4] (see Experimental Section).



2a, R = CH_3; R_1 = H
b, R = H; R_1 = H
c, R = H; R_1 = OH

Biological Activity.—None of the new compounds showed any advantage over **1a** or **1b**. When tested in Swiss mice against blood-induced infections with two species of rodent malaria, *i.e.*, *Plasmodium berghei* and *Plasmodium vinckei*, **2a** and **2b** were found to have antimalarial activity comparable to chloroquine, having oral minimum curative doses[5] of about 10 and 5 mg/kg/day, respectively, for 5 days compared with about 5 mg/kg/day for 5 days for chloroquine. Against NK65 strain of *P. berghei*, **2c** cleared all animals of parasitemia during a 4-week postinfection period at a dose of 12.5 mg/kg/day for 5 days but was ineffective at a similarly administered dose of 6.25 mg/kg/day.

In the carrageenan edema test[6] at a dose of 100 mg/kg *po*, **2a–c** reduced the average edema weight by 42, 37, and 36%, respectively. Hydroxychloroquine (**1b**) reduced edema by 29% at the same dose.

The acute oral toxicities are given in Table I.

TABLE I
ACUTE ORAL TOXICITY IN MICE

Compd	Oral LD_{50}, mg/kg[a] 24 hr	7 day
1a	580 ± 114	580 ± 114
1b	2340 ± 384	1240 ± 170
2a	1240 ± 294	1090 ± 220
2b	1050 ± 200	770 ± 144
2c	2040[b]	1040[b]

[a] As free base. [b] ALD_{50}.

Experimental Section[7]

4-(1-Aminoethyl)-1-ethylpiperidine.—4-Acetyl-1-ethylpyridinium iodide oxime[8] (149 g) was hydrogenated in 350 ml of absolute EtOH over 1.5 g of PtO_2 at an initial pressure of 57.5 kg/cm² and an initial temperature of 23° followed by a 4-hr heating period at 80–90°. The uptake was 85% of theory. The catalyst was filtered off and most of the solvent was removed through a short column. The pot residue was digested with 1 equiv of dry $NaOCH_3$. Et_2O was added and the precipitated salts were removed by filtration. Concentration of the filtrate and fractionation of the residue gave 29.9 g (37.6%) of product, bp 91–94° (7 mm), $n^{25}D$ 1.4654–1.4662. *Anal.* Calcd for $C_9H_{20}N_2$: N, 17.93. Found: N, 17.46.

4-Aminomethyl-1-ethylpiperidine.—The N-acetyl derivative of 4-cyanopiperidine prepared from 45 g of amine,[9] and 150 ml of Ac_2O was added as a slurry over a period of 4 hr to a stirred suspension of 24 g of $LiAlH_4$ in 600 ml of THF. The mixture was refluxed for 16 hr, decomposed by the dropwise addition of 74.4 g of ethylene glycol in 400 ml of THF, and filtered through Filter-cel. Distillation of the filtrate gave 23.9 g (41% from 4-cyanopiperidine) of product, bp 87.5–90.1° (6–7 mm).

4-Aminoethyl-1-(2-hydroxyethyl)piperidine.—A mixture containing 55 g of 4-cyanopiperidine,[9] 26.4 g of ethylene oxide, and 0.2 g of *p*-toluenesulfonic acid was stirred at 60° for 13 hr. Fractionation of the reaction mixture gave a 13% recovery of starting amine, bp 56–64° (1 mm), and 47.1 g (61%) of 4-cyano-1-(2-hydroxyethyl)piperidine, bp 122–123° (1 mm), $n^{25}D$ 1.4890.

(1) (a) Aralen®; (b) Plaquenil®.

(2) For a discussion see I. M. Rollo "The Pharmacological Basis of Therapeutics," 3rd ed, L. S. Goodman and A. Gilman, Ed., The Macmillan Co., New York, N. Y., 1965, p 1091 ff.

(3) For related structures see H. C. Scarborough, Y. H. Wu, and R. F. Feldkamp, U. S. Patent 3,184,462 (1965), and Regents, University of Michigan, British Patent 1,113,804 (1968).

(4) H. Andersag, S. Breitner, and H. Jung, U. S. Patent 2,233,970 (1941); *Chem. Abstr.*, **35**, 3771 (1941).

(5) Dose required to produce parasite-free blood in more than 50% of the tested animals, 46 days postinoculation.

(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(7) Melting points were taken in a Mel-Temp apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

(8) J. Druey and K. Schenker, U. S. Patent 3,004,979 (Oct 17, 1961).

(9) T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.*, **22**, 984 (1957).