electrostatic binding to a DNA phosphate group. Loss of correlation found with the parameters associated with the diamino side chain in series III when series I and III were combined suggests that perhaps different substituents at position 7 dictate different drug–DNA orientations which therein alter the manner in which the 4-diamino side chain is able to interact with the DNA backbone.

Antimalarials. 7-Chloro-4-(substituted amino)quinolines

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Forty-one derivatives of 7-chloro-4-substituted quinolines were made and tested for their antimalarial activity against *Plasmodium berghei* in mice. Twenty-seven showed activity.

We have previously prepared[1] many substituted 7-chloroquinolines incorporating several novel features in the side-chain amines attached at position 4. The derivatives described in the present paper do not fall into a single class as did the compounds previously reported, but cover a wide variation of substitutional features in the side chain (Table I).

Compounds **24**, **26–28**, and **37** have been described by Carmack, *et al.*[2] The alcohol **24** was used as a key intermediate. We have also used this alcohol for the preparation of **29–36**, using their procedure with slight modification. Similarly, we have used the alcohol **9** as starting material for many derivatives, but in this case, we were able to isolate the comparatively more stable bromo derivative **11** and use it for reaction with various amines.

The acetates **10** and **25** were obtained in our attempted oxidation of the alcohols **9** and **24** with DMSO in Ac_2O according to the procedure described by Burdon and Moffat.[3] No oxidation took place even when the variation described by Albright and Goldman[4,5] was used.

Some of the amines required for this work were made by using literature procedures, *e.g.*, benzylcyclopropylamine,[6] 3,4,5-trimethoxybenzylmethylamine,[7] and indanylpropargylamine.[8] The reduction of the benzylidene intermediate was carried out with $NaBH_4$ instead of using catalysts as prescribed in the literature procedures. 3,4,5-Trimethoxybenzylcyclopropylamine was prepared in the same way. Preparation of the indanylpropargylamine by the literature procedure, *i.e.*, by the alkylation of indanylamine with propargyl bromide, gave a very poor yield of the monopropargylamine. However, this difficulty was solved by formylating the indanylamine and then alkylating it with propargyl bromide. The resulting formyl derivative was hydrolyzed by treating with 3 *N* HCl.

Biological Tests.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice, by Dr. L. Rane, *et al.*,[9] by a procedure reported by them. The active compounds and their activity figures are listed in Table II. All others were found to be inactive.

Experimental Section

Preparation of 1, 2, 6, 7, 39, and 40.—A mixt of a 1 *M* portion of 4,7-dichloroquinoline and 2 *M* portions of the amine (or the amine·HCl as in **6**, **7**, and **39**, in which excess of anhyd K_2CO_3 was also added) in ethoxyethanol was refluxed for 24 hr. The mixt was cooled and filtered (to remove K_2CO_3 if any), and ethoxyethanol was removed under reduced pressure. The residue was mixed with H_2O, basified with NaOH soln, and extd with Et_2O or CH_2Cl_2, and the ext was dried (K_2CO_3) and concd. The residue was either distd or crystd.

For **40**, a 10 *M* excess of piperazine was used which was later distd off after the removal of ethoxyethanol, and the residue was worked up as usual.

Preparation of 5, 9, and 24.—A modification of procedure A of Surrey and Hammer[10] was used. After the mixt was heated at 150–165° for 6–8 hr, the excess amine was removed by distn under reduced pressure, and the residue cooled and triturated with dil NaOH soln. The product, which generally solidified at this stage, was then purified by crystn.

Preparation of 3, 4, 38, and 41.—A modification of procedure B of Surrey and Hammer[10] was used. After the phenol soln of 4,7-dichloroquinoline and 1–2 *M* portions of the amine was heated at 150–165° for 4–8 hr, the mixt was cooled and poured into 20% soln of NaOH. After stirring and triturating the product generally solidified, and was then purified by crystn. For **41**, a slight excess of 4,7-dichloroquinoline was used to eliminate the formation of the monoproduct.

7-Chloro-4-(3-bromo-1-methylpropylamino)quinoline (11).—To a soln of 44 ml of concd H_2SO_4 in 125 ml of 48% HBr, maintained at 0°, was slowly added 25.0 g (0.1 mole) of **9**. The mixt was then heated to boiling and maintained at boiling till (*ca.* 10 min) a turbidity was formed. After further boiling for 3 min, the mixt was cooled to room temp and extd with $CHCl_3$. The ext was washed with 10% NaOH and then with H_2O. It was dried ($MgSO_4$), filtered, and concd. The product was purified by crystn.

7-Chloro-4-[3-(*N*-phthalimido)-1-methylpropylamino]quinoline (12).—A suspension of **11** (30.0 g, 0.096 mole) and K phthalimide (22.0 g, 0.12 mole) in 500 ml of DMF was heated at 70–80° for 18 hr. The mixt was cooled, dild with 1 l. of H_2O, and extd with

(1) T. Singh, R. G. Stein, and J. H. Biel, *J. Med. Chem.*, **12**, 368 (1969); T. Singh, R. G. Stein, H. H. Koelling, J. F. Hoops, and J. H. Biel, *ibid.*, **12**, 524 (1969); T. Singh, R. G. Stein, and J. H. Biel, *ibid.*, **21**, 801 (1969); *ibid.*, **12**, 949 (1969).

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

(3) M. G. Burdon and J. G. Moffat, *ibid.*, **88**, 5855 (1966).

(4) J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965).

(5) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965).

(6) British Patent 913,898; *Chem. Abstr.*, **59**, 509e (1963).

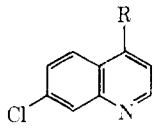
(7) A. Sonn, *Ber.*, **58**, 1105 (1925).

(8) C. F. Huebner, Belgian Patent 633,762; *Chem. Abstr.*, **61**, 3046a (1964).

(9) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(10) A. R. Surrey and H. F. Hammer, *J. Amer. Chem. Soc.*, **68**, 116 (1946).

TABLE I



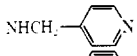
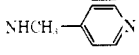
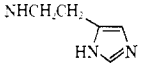
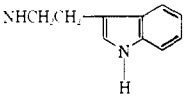
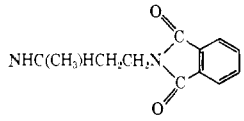
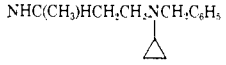
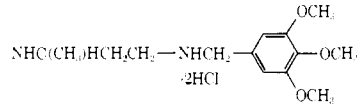
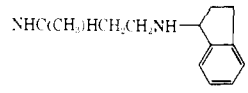
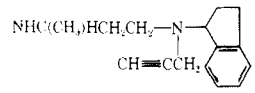
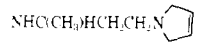
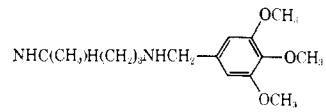
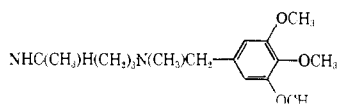
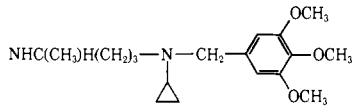
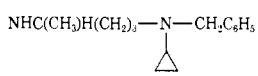
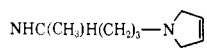
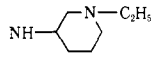
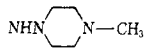
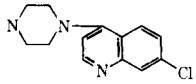
No.	R	Yield, %	Crystn solvent	Mp or bp, °C (mm)[a]	Formula[b]	Analyses
1	$NHCH_2CH(OC_2H_5)_2$	43.3		150 (0.01)	$C_{15}H_{19}ClN_2O_2$	N
2	$NHC(CH_3)HCH_2CH(OCH_3)_2$	46.2	CH_2Cl_2–heptane	138–141	$C_{15}H_{19}ClN_2O_2$	C, H, N
3		33.0	EtOH–H_2O	196–197.6	$C_{15}H_{12}ClN_3$	N
4		30.0	EtOAc	165	$C_{16}H_{14}ClN_3$	N
5	$NHCH_2CH_2C_6H_5$	40.0	MeOH–cyclohexane	136–139	$C_{17}H_{15}ClN_2$	C, H, N
6		26.4	EtOAc	211–213	$C_{14}H_{13}ClN_4$	C, H, N
7		31.0	EtOAc	211–213	$C_{19}H_{16}ClN_3$	C, H, N
8	$NHC(CH_3)HCH_2N(CH_3)CH_2C_6H_5$	52.0		140–150 (3×10^{-4})	$C_{20}H_{22}ClN_3$	C, H, N
9	$NHC(CH_3)HCH_2CH_2OH$	45.2	Me_2CO–$CHCl_3$	174–176	$C_{13}H_{15}ClN_2O$	C, H, N
10	$NHC(CH_3)HCH_2CH_2O_2CCH_3$		Et_2O	130–132	$C_{15}H_{17}ClN_2O_2$	C, H, N
11	$NHC(CH_3)HCH_2CH_2Br$	77.0	Et_2O–heptane	148–150	$C_{13}H_{14}BrClN_2$	C, H, N
12		74.0	EtOAc–Et_2O	150–152	$C_{21}H_{18}ClN_3O_2$	C, H, N
13	$NHC(CH_3)HCH_2CH_2NH_2$	61.2		150–160 (4×10^{-3})	$C_{13}H_{16}ClN_3$	C, H, N
14	$NHC(CH_3)HCH_2CH_2ONH_2$	53.0	EtOAc	141–142	$C_{13}H_{16}ClN_3O$	N
15	$NHC(CH_3)HCH_2CH_2N(CH_3)CH_2C_6H_5$	53.0	Cyclohexane	132–133	$C_{21}H_{24}ClN_3$	C, H, N
16		71.5	Et_2O	138–140	$C_{23}H_{26}ClN_3$	C, H, N
17	$NHC(CH_3)HCH_2CH_2N(CH_3)_2CH_2CH_2C_6H_5$	43.5	Cyclohexane	63–66	$C_{22}H_{26}ClN_3$	C, H, N
18	$NHC(CH_3)HCH_2CH_2NCH(CH_3)_2)CH_2C_6H_5$	39.5	Cyclohexane	78–80	$C_{23}H_{28}ClN_3$	C, H, N
19	$NHC(CH_3)HCH_2CH_2N(CH_2C{\equiv}CH)CH_2C_6H_5$	62.1	Purified by chromatography		$C_{23}H_{24}ClN_3$	C, H, N
20		33.0	*i*-PrOH–EtOAc	232–234	$C_{23}H_{30}Cl_3N_3O_3$	N
21		61.1		180–190 (5×10^{-4})	$C_{22}H_{24}ClN_3$	C, H, N
22		57.8	Purified by chromatography		$C_{25}H_{26}ClN_3$	N
23		79.0		190 (0.01)	$C_{17}H_{20}ClN_3$	C, H, N
24	$NHC(CH_3)H(CH_2)_3OH$	70.0	EtOH	178–180	$C_{14}H_{17}ClN_2O$	
25	$NHC(CH_3)H(CH_2)_3O_2CCH_3$		C_6H_6	97–99	$C_{16}H_{19}ClN_2O_2$	C, H, N
26	$NHC(CH_3)H(CH_2)_3NH_2$	72.0		139–141; 150–160 (0.3)	$C_{14}H_{18}ClN_3$	N
27	$NHC(CH_3)H(CH_2)_3NHCH_3$	57.0		160–170 (0.4)	$C_{15}H_{20}ClN_3$	
28	$NHC(CH_3)H(CH_2)_3NHC_2H_5$	63.0		170–180 (0.02)	$C_{16}H_{22}ClN_3$	
29	$NHC(CH_3)H(CH_2)_3NHCH_2C_6H_5$	22.0		185–190 (0.15)	$C_{21}H_{24}ClN_3$	C, H, N
30	$NHC(CH_3)H(CH_2)_3N(CH_3)CH_2C_6H_5$	33.0	*i*-PrOH	151–153	$C_{22}H_{26}ClN_3$	C, H, N
31	$NHC(CH_3)H(CH_2)_3N(C_2H_5)CH_2C_6H_5$	10.0	Cyclohexane	99–100	$C_{23}H_{28}ClN_3$	N
32		27.0		170–185 (7×10^{-3})	$C_{24}H_{30}ClN_3O_3$	N
33			Et_2O	106–107	$C_{25}H_{32}ClN_3O_3$	C, H, N

TABLE I (*Continued*)

No.	R	Yield, %	Crystn solvent	Mp or bp, °C (mm)[a]	Formula[b]	Analyses
34		8.0	Purified by chromatography		$C_{27}H_{34}ClN_3O_3$	N
35		16.0	THF-petrether	135–136	$C_{24}H_{28}ClN_3$	N
36		19.0	Cyclohexane	122–123	$C_{18}H_{22}ClN_3$	C, H, N
37				158 (0.03)	$C_{14}H_{15}ClN_2$	
38		41.0	Cyclohexane	124–125	$C_{16}H_{20}ClN_3$	N
39		24.6	EtOAc	223–225	$C_{14}H_{17}ClN_4$	C, H, N
40		83.0	Cyclohexane	113–115	$C_{13}H_{14}ClN_3$	C, H, N
41		50.0	C_6H_6	262–264	$C_{22}H_{18}Cl_2N_4$	N

[a] All melting points are uncorrected. [b] Compds **24, 27,** and **28,** having already been described, were not analyzed. Compds **1, 3, 4, 14, 20, 22, 26, 31, 32, 34, 35, 38,** and **41** were analyzed for N. All others were analyzed for C, H, and N. All analyses were within ±0.4% of the calcd values.

$CHCl_3$. The $CHCl_3$ ext was washed with H_2O, dried ($MgSO_4$), filtered, and concd. The residual oil solidified when triturated with Et_2O.

7-Chloro-4-(3-amino-1-methylpropylamino)quinoline (13).—A soln of **12** (25.0 g, 0.066 mole) and hydrazine hydrate in 500 ml of EtOH was refluxed for 3 hr. The pptd solid was removed by filtration, the filtrate treated with 200 ml of 6 *N* HCl, and EtOH evapd under reduced pressure. The cloudy soln was filtered, and the filtrate was evapd to dryness under reduced pressure. The residue was treated with 10% NaOH and extd with CH_2Cl_2, and the ext dried ($MgSO_4$) and evapd. The residue was distd to give the product as a light yellow oil.

3-(7-Chloro-4-quinolylamino)-3-methylpropyloxyamine (14).—A soln of **11** (6.26 g, 0.03 mole), *N*-hydroxyphthalimide (3.26 g, 0.03 mole), and Et_3N (2.02 g, 0.03 mole) in 75 ml of MeCN was refluxed for 4 hr. It was concd to a semisolid and treated with H_2O. The crude phthalimide derivative was removed by filtration, mixed with 98% hydrazine (0.7 ml) in 100 ml of EtOH, and refluxed for 1 hr. EtOH was removed under reduced pressure, and the residue was basified with 10% NaOH and extd with CH_2Cl_2. The combined ext was dried (K_2CO_3), filtered, and evapd to leave behind the product.

Preparation of 15–19, and 21–23.—A mixt of **11** (0.03 mole) and the required amine (0.06 mole) in 100 ml of EtOH was refluxed for 8 hr. EtOH was removed under reduced pressure, and the residue was basified with NaOH soln and extd with C_6H_6. The ext was dried (K_2CO_3), filtered, and evapd to leave behind the product. At this stage, the last traces of the excess amine could be removed by vacuum distn after which the product was purified either by distn or by crystn.

7-Chloro-4-(2-benzyl-*N*-methyl-1-methylethylamino)quinoline (8) was prepd starting from 7-chloro-4-(2-chloro-1-methylethylamino)quinoline[11] and *N*-benzyl-*N*-methylamine by the procedure described for **15–19.**

7-Chloro-4[3-(3,4,5-trimethoxybenzylamino)-1-methylpropylamino]quinoline (20).—A soln of **13** (5.0 g, 0.02 mole), 3,4,5-trimethoxybenzaldehyde, and *p*-TsOH (0.2 g) in 250 ml of PhMe was refluxed for 18 hr, using a H_2O separator. The mixt was cooled to room temp and shaken with a 50 ml of a concd soln of K_2CO_3, and the PhMe layer was sepd, dried (K_2CO_3), and evapd *in vacuo* to dryness. The residue was dissolved in 125 ml of EtOH and reduced with $NaBH_4$ in the usual manner. The product was converted into the HCl salt.

The same procedure was used for **32,** starting from the amine **26,** but the product was isolated as a free base and purified by distn.

Preparation of 29–31, 33–36.—The procedure described by Carmack[2] was used. **31** was distd and then chromatographed on basic alumina using Et_2O–petr ether (5:95) as eluting solvent. Then it was crystd from cyclohexane. Similarly, **35** had to be chromatographed for purification. **34** could not be obtained in sufficient purity even after exhaustive chromatography. Its elemental analyses were not satisfactory, except for the titrable N (calcd, 5.60: found, 5.36). It was possibly contaminated with 3,4,5-trimethoxyphenylcyclopropylamine.

3,4,5-Trimethoxybenzylcyclopropylamine.—A mixt of 3,4,5-trimethoxybenzaldehyde (64.0 g, 0.33 mole), cyclopropylamine (20.0 g, 0.35 mole), and 300 ml of MeOH was stirred for 8 hr. To this was added 18.9 g (0.5 mole) of $NaBH_4$ in portions with stirring in 0.5 hr. The mixt was stirred for 2 hr more. The solvent was evapd *in vacuo*, the residue was treated with H_2O and extd with Et_2O, and the ext was worked up as usual: yield, 24.4 g (30.0%); bp 115–120° (1 mm). *Anal.* ($C_{13}H_{19}NO_3$) C, H, N.

1-Formamidoindan.—A mixt of 1-aminoindan (26.65 g, 0.2 mole) and ethyl formate (50 ml) was refluxed for 2 hr. The product crystd on cooling: yield, 25.0 g (78.0%). The anal. sample was recrystd from ethyl formate, mp 105–106°. *Anal.* ($C_{10}H_{11}NO$) C, H, N.

1-(*N*-Formyl-*N*-propargylamino)indan.—To a suspension of NaH (4.8 g, 0.2 mole) in 100 ml of DMF was added 1-formamidoindan (29.0 g, 0.18 mole) in small portions with stirring over a period of 10 min. The mixt was then warmed at 65–70° for 1 hr and cooled in an ice–water bath, and propargyl bromide (26.2 g, 0.22 mole) was added through a dropping funnel in about 0.5 hr. The color changed from blue to off-white. After stirring at room temp for 16 hr, DMF was removed under vacuum (bath temp about 60°). The viscous residue solidified to give 30.0 g (83.3%) of the product. An anal. sample was crystd from petr ether, mp 68–70°. *Anal.* ($C_{13}H_{13}NO$) N.

1-(*N*-Propargylamino)indan.—A suspension of 1-(*N*-formyl-*N*-propargylamino)indan (52.0 g of the crude material) in 200 ml of

(11) Rhone-Poulenc, S. A., Belgian Patent 612,207; *Chem. Abstr.*, **58**, 9099*b* (1963).

TABLE II

No.[a]	Antimalarial activity[b]				
	D	*C*	*TD*	*T* − *C*	Remarks[c]
6	40	0	0	1.3	
	160	0	0	5.5	
	640	2	0	...	Curative
8	40	0	0	4.5	
	160	0	0	11.7	Active
	640	3	0		Curative
13	20	0	0	9.1	Active
	80	0	0	12.1	Active
	320	3	0		Curative
14	40	0	0	0.3	
	160	0	0	1.1	
	640	0	0	6.9	Active
15	20	0	0	4.5	
	80	0	0	11.7	Active
	320	3	0		Curative
16	10	0	0	0.2	
	40	0	0	9.8	Active
	160	0	0	12.2	Active
17	20	0	0	4.7	
	80	0	0	8.1	Active
	320	0	3		Toxic
18	20	0	0	9.5	Active
	80	0	0	15.7	Active
	320	3	0		Curative
19	10	0	0	0.4	
	40	0	0	6.4	Active
	160	1	0		Curative
20	40	0	0	3.1	
	160	0	5		Toxic
	640	0	5		Toxic
21	40	0	0	5.4	
	160	0	2	6.8	Toxic
	320	2	3		Curative; toxic
22	40	0	0	3.8	
	160	0	0	11.0	Active
	640	5	0		Curative
23	40	0	0	8.1	Active
	160	0	0	13.7	Active
	640	4	1		Curative; toxic
26	20	0	0	9.1	Active
	80	0	0	12.1	Active
	320	3	0		Curative
27	40	0	0	4.4	
	160	0	0	7.0	Active
	640	1	0		Curative
28	160	0	0	5.8	
	320	1	2		Curative; toxic
	640	2	3		Curative; toxic
29	40	0	0	7.2	Active
	80	0	4	9.8	Toxic
	160	0	5		Toxic
30	40	3	0		Curative
	160	5	0		Curative
	640	4	1		Curative; toxic
31	40	0	0	8.7	Active
	160	0	3	17.4	Active; toxic
	640	0	5		Toxic
32	20	0	0	0.6	
	80	0	0	4.2	
	320	0	0	6.2	Active
33	40	0	0	4.3	
	160	0	0	11.9	Active
	640	1	2	25.9	Curative; toxic
34	40	0	0	0.2	
	160	0	0	1.0	
	640	0	0	6.6	Active
35	40	0	0	4.4	
	160	0	0	12.8	Active
	640	3	0		Curative
36	40	0	0	14.1	Active
	160	4	0		Curative
	640	3	2		Curative; toxic
38	20	0	0	9.7	Active
	40	0	0	11.5	Active
	80	3	0		Curative
	160	5	0		Curative
	320	5	0		Curative
	640	5	0		Curative
39	40	3	0		Curative
	160	4	0		Curative
	640	5	0		Curative
40	40	0	0	0.4	
	160	0	3		Toxic
	640	0	5		Toxic
41	40	0	0	5.8	
	160	0	0	9.8	Active
	640	0	5		Toxic

[a] Numbers refer to those in Table I. [b] *D*, dose in mg/kg; *C*, cures; *TD*, toxic deaths when mice die 2–5 days post infection, attributed to drug toxicity; *T* − *C*, increase in mean survival time of the treated mice over the control group. [c] A compd is active if the *T* − *C* exceeds 6.1 days, and curative if one or more mice live for 60 days or more post infection.

3 *N* HCl was refluxed with vigorous stirring till the soln became clear (about 1 hr). The mixt was cooled and neutralized with K_2CO_3. The brown oil was extd and the Et_2O ext worked out as usual: bp 86–88° (0.45 mm); yield, 34.0 g (76.4%). A portion was converted into the HCl salt and crystd twice from EtOH, mp 183–185°. *Anal.* ($C_{12}H_{14}NCl$) C, H, N, Cl.

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