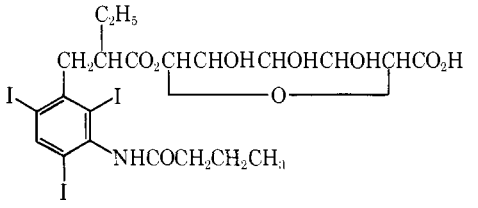
the gallbladder with the salt than with the free acid. The side effects observed with Na tyropanoate in the clinic were less than those seen with iopanoic acid.[18,20-22]

A crossover study in man by McChesney and Banks showed that 50% of a 4.5-g dose of Na tyropanoate is excreted in the urine in 108 hr while 37% of a 3-g dose of iopanoic acid was in the urine.[23] McChesney and Hoppe reported that iopanoic acid and Na tyropanoate are metabolized in the cat and man and that the biliary excretion is mostly as the glucuronic acid conjugates.[24-27] The suggested metabolite of Na tyropanoate is shown in 8.



8

Experimental Section[28]

α-Ethyl-3-formamido-2,4,6-triiodohydrocinnamic Acid (2), Na 3-Acetamido-α-ethyl-2,4,6-triiodohydrocinnamate (3, Na Salt), and Na α-Ethyl-2,4,6-triiodo-3-propionamidohydrocinnamate (4, Na Salt).—The preparation of the first two of these compounds by the acylation of iopanoic acid[5] is described elsewhere.[14] The acid **4** corresponding to the last of the above compounds is also described.[14] The Na salt of **4** was prepared by the method employed for Na tyropanoate and was obtained as colorless crystals, mp 199–210°. *Anal.* ($C_{14}H_{15}I_3NNaO_3$) C, H; I: calcd, 58.66; found, 58.06.

Tyropanoic Acid, 3-Butyramido-α-ethyl-2,4,6-triiodohydrocinnamic Acid (5, Acid).—A mixture of 50.0 g (0.0875 mole) of iopanoic acid[5] (1), 28.6 ml (0.175 mole) of butyric anhydride, 310 ml of $PrCO_2H$, and 5 drops of H_2SO_4 was heated on a water bath at 70–80° for 2 hr. A solution formed and was poured into H_2O. The solid which separated was collected and dried, 47.0 g (84%) of tan solid, neutralization equiv, 637; calcd for $C_{15}H_{18}I_3NO_3$: neutralization equiv, 641. Recrystallization from EtOAc gave very pale tan prisms, mp 182–184° (reported mp 172–185.5°[14]); neutralization equiv 640; uv max (95% EtOH) 237 mμ (ε 33,900); ir (3/4% KBr disc) 1660 (CONH), 1690 (COOH), 2500–2670 (broad H bonding), 2940 (CH), and 3220 cm^{-1} (NH).

Na Tyropanoate, [Na 3-Butyramido-α-ethyl-2,4,6-triiodohydrocinnamate (5)].—Tyropanoic acid (**5**, acid) was converted into its Na salt by the addition of a slight excess of methanolic NaOH to a suspension of **5** (acid) in MeOH. A solution was obtained and a gummy material separated when Et_2O was added. The addition of fresh Et_2O to the residue after the liquid layer was decanted and trituration produced a solid which was collected and dried. There was obtained a colorless solid, mp 208–210°. *Anal.* ($C_{15}H_{17}I_3NNaO_3$) C, H; I: calcd, 57.42; found, 56.6. Other samples of Na tyropanoate were recrystallized from H_2O and aq *i*-PrOH.

Na α-Ethyl-2,4,6-triiodo-3-valeramidohydrocinnamate (6, Na Salt).—The reaction of iopanoic acid[5] with valeric anhydride in the presence of valeric acid and H_2SO_4 in the manner described for tyropanoic acid (**5**, acid) gave α-ethyl-2,4,6-triiodo-3-valeramidohydrocinnamic acid (**6**). Recrystallization (EtOH) gave colorless prisms, mp 189–190.5°. *Anal.* ($C_{16}H_{20}I_3NO_3$) neutralization equiv: calcd., 655; found 652. The Na salt of **6** was obtained as colorless solid, mp 212–217° dec, from **6** in the manner described for Na tyropanoate. *Anal.* ($C_{16}H_{19}I_3NNaO_3$)C, H; I: calcd, 56.23, found, 56.75.

Na α-Ethyl-3-hexanamido-2,4,6-triiodohydrocinnamate (7).—The reaction of iopanoic acid[5] with hexanoyl anhydride and H_2SO_4 gave α-ethyl-3-hexanamido-2,4,6-triiodohydrocinnamic acid (**7**) as colorless prisms (EtOH), mp 196–198°. *Anal.* ($C_{17}H_{22}I_3NO_3$) C, H; I: calcd, 56.90; found, 56.01. The Na salt of **7** was prepared from the acid in the manner described for Na tyropanoate (**5**) and was obtained as a colorless solid, mp 170–190°. *Anal.* ($C_{17}H_{21}I_3NNaO_3$) C, H, I.

Acknowledgments.—Appreciation is expressed to Mr. John Romano, Mr. Chester Sapino, and Mr. Arnold Ludke for technical assistance. The authors wish to thank the Analytical and Physical Chemistry Departments at Sterling-Winthrop Research Institute for the analytical and spectral data. We also wish to thank Dr. H. P. Drobeck and Mr. L. Duprey for the acute toxicity studies.

(23) E. W. McChesney and W. F. Banks, Jr., *Proc. Soc. Exp. Biol. Med.*, **119**, 1027 (1965).

(24) E. W. McChesney and J. O. Hoppe, *Arch. Intn. Pharmacodyn.*, **99**, 127 (1954).

(25) E. W. McChesney and J. O. Hoppe, *ibid.*, **105**, 306 (1956).

(26) E. W. McChesney and J. O. Hoppe, *ibid.*, **142**, 562 (1963).

(27) E. W. McChesney, *Biochem. Pharmacol.*, **13**, 1366 (1964).

(28) When analyses are indicated only by symbols of elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were taken in a Hershberg-type apparatus and are corrected. The spectra were determined on a Cary 15 ultraviolet spectrophotometer and on a Perkin-Elmer 21 infrared spectrophotometer.

Isoquinolines. 2. 3-(Dialkylaminoalkylamino)isoquinolines as Potential Antimalarial Drugs[1,2]

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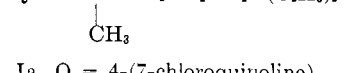
Received March 13, 1970

Because quinolines have played such an important role in malaria chemotherapy, we believed that the heretofore unexplored class of 3-aminoisoquinolines deserved further investigation. In our previous report[1] we presented the synthesis and biological activity of a number of 3-aminoisoquinolines which do not contain the usual dialkylaminoalkylamino side chain, a common feature of the active quinoline antimalarials such as chloroquine (Ia) or pamaquine (Ib).



Ia, Q = 4-(7-chloroquinoline)
Ib, Q = 8-(6-methoxyquinoline)

This report will present the synthesis and biological activity of such isoquinoline derivatives.

Chemistry.—The synthesis of the diamines (VI) was carried out by the sequence of reactions shown in Scheme I from the appropriately substituted aminoisoquinoline[1] (II). The attempted alkylation of the 3-chloropropionamide **27** with *N*-methylaniline yielded only the elimination product, *N*-(3-isoquinolyl)acrylamide.[4a] Such an elimination also occurred when the

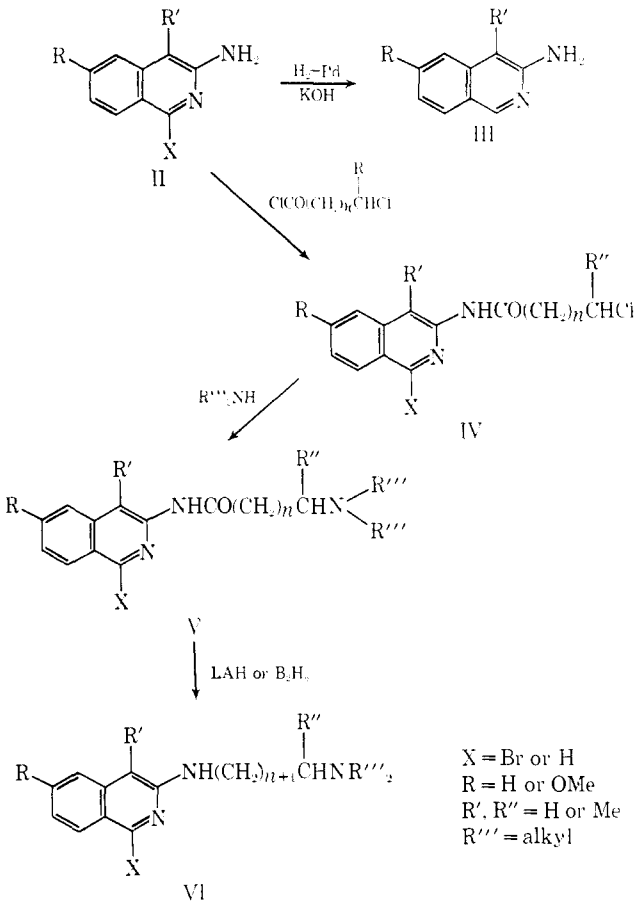
(1) Paper **1**: J. L. Neumeyer and K. K. Weinhardt, *J. Med. Chem.*, **13**, 613 (1970).

(2) This work was supported by the U. S. Army Medical Research and Development Command under Contract DA-49-193-MD-3023. This is Contribution No. 783 from the Army Research Program on Malaria. Presented in part at the 155th National Meeting of the American Chemical Society, Miami, Florida, 1968, N-28.

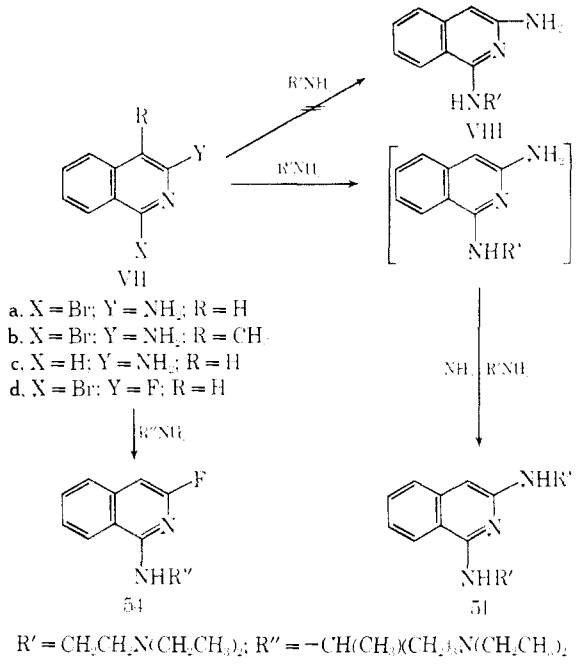
(3) To whom inquiries should be addressed at the Department of Medicinal Chemistry, College of Pharmacy, Northeastern University, Boston, Mass. 02115.

(4) (a) This compound was described in the previous paper (ref 1) and was designated as compound **14**; (b) This compound was described in the previous paper (ref 1) and was designated as compound **15**.

SCHEME I



SCHEME II



R' = $CH_2CH_2N(CH_2CH_3)_2$; R'' = $-CH(CH_3)(CH_2)_3N(CH_2CH_3)_2$

3-chlorobutyramide **28** was treated with *N,N*-dimethyl-*N'*-ethylenediamine in refluxing $CHCl_3$; *N*-(3-isoquinolyl)crotonamide[4b] was the product isolated in 50% yield. We observed that fusion of the 3-chloropropionamide (**27**) and the 3-chlorobutyramide (**28**) caused an intromolecular cyclization leading to the 3-oxo-1,2,3,4-tetrahydropyrimido[2,3-*b*]isoquinolin-11-ium system.[5]

The butyramides V bearing a labile Br in the 1 position (**42** and **43**) could be prepared best from II by acylation with 4-diethylaminobutyric acid hydrochloride[6] and DCC in DMF.

The reduction of the amides V with LAH[7] was successful by using the inverse addition technique. Partial hydrogenolysis of the labile halogen atom at the 1 position occurred, resulting in mixtures of products. Reduction of the amides with diborane in THF[8] was generally a more satisfactory method. In an attempt to prepare 3-amino-1-[(2-diethylaminoethyl)amino]-isoquinoline (VIII) by treatment of β-diethylaminoethylamine with 3-amino-1-bromoisoquinoline (VIIa), the unexpected disubstitution product **51** was isolated and characterized (Scheme II).

Halogen atoms at the 1 position of isoquinoline can be easily replaced by nucleophiles such as β-diethylaminoethylamine,[9] ethoxide,[10] or methoxide.[1] The displacement of 1- and 3-chloroisoquinolines has been studied, selective substitution occurring at the 1 position. In marked contrast to the 1-halo isomer, however, 3-chloroisoquinoline was unreactive toward β-diethylaminoethylamine.[9] When VIIb was similarly treated with an excess of β-diethylaminoethylamine, a slow evolution of NH_3 took place over a period of 15 hr. No single product could be isolated from the reaction mixture. The slow evolution of NH_3 and the failure to obtain the disubstitution product can be accounted for by the steric hindrance of the Me adjacent to the 3-amino group. Similarly, when 3-aminoisoquinoline (VIIc) was heated at reflux with an excess of β-diethylaminoethylamine for 7 days, only traces of NH_3 were liberated and 65% of the unreacted isoquinoline VIIc was recovered. This would suggest that nucleophilic displacement of the 3-amino group in VII by aliphatic amines can be achieved only if facilitated by an electron-rich substituent (*i.e.*, Br or NHR) at the 1 position.

Treatment of 1-bromo-3-fluoroisoquinoline[1] (VIId) with 2-amino-5-diethylaminopentane at 95° for 12 hr gave **54** in 35% yield.

Biological Activity.—All compounds reported in Tables I and II were tested for antimalarial activity against mice infected with *Plasmodium berghei*.[11] None of the compounds tested caused any increase in the mean survival time of more than 2 days in the mouse screen. The compounds tested were generally nonlethal to mice at the dosages tested. Only 2 compounds (**46** and **51**) were tested in the bird screen.[12] Compound **46** was inactive and caused no toxic deaths at 120 mg/kg, whereas **51** showed a mean survival time

(5) J. L. Neumeyer and K. K. Weinhardt, *Chem. Commun.*, 1423 (1967).

(6) F. F. Blicke, W. B. Wright, Jr., and M. F. Zienty, *J. Amer. Chem. Soc.*, **63**, 2488 (1941).

(7) N. G. Gaylord ["Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, p 555] reported several unsuccessful attempts to reduce 2- and 4-quinolyl-*N*-methylacetamide with LAH.

(8) Z. B. Papanastassiou and R. J. Bruni, *J. Org. Chem.*, **29**, 2870 (1964).

(9) R. D. Haworth and S. Robinson, *J. Chem. Soc.*, 1563 (1956).

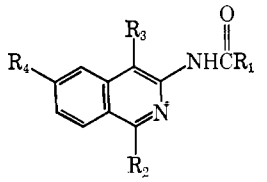
(10) N. B. Chapman and D. W. Russell-Hill, *ibid.*, 777 (1948).

(11) Tests were carried out in 5 mice infected with *P. berghei* at 40, 160, and 640 mg/kg in the screening facility of Dr. L. Rane of the University of Miami [T. S. Osdene, P. B. Russel, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)].

(12) Tests were conducted by Dr. L. Rane, University of Miami. Chicks were infected with *P. gallinaceum* fatal to 100% of untreated controls within 3–4 days. An increase of at least 100% survival time of treated animals was considered an active dose.

TABLE I

AMIDES OF 3-AMINOISOQUINOLINES

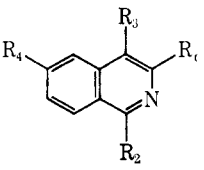


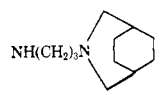
Compd	R_1	R_2	R_3	R_4	Mp, °C	Recrystn solvent	Formula	Analyses
27	CH_2CH_2Cl	H	H	H	159[a]	C_6H_6	$C_{12}H_{11}ClN_2O$	C, H, N, Cl
28	$CH_2CH(CH_3)Cl$	H	H	H	141.5–142.5	C_6H_6	$C_{13}H_{13}ClN_2O$	C, H, N
29	CH_2CH_2Cl	Br	H	H	185[b]	C_6H_6	$C_{12}H_{10}BrClN_2O$	C, H, N
30	$(CH_2)_3Cl$	H	H	H	127.5–129	C_6H_6	$C_{13}H_{13}ClN_2O$	C, H, N, Cl
31	$(CH_2)_3Cl$	Br	H	H	131–133	Et_2O	$C_{13}H_{12}BrClN_2O$	C, H, N
32	$(CH_2)_3Cl$	H	H	OCH_3	129.5–130	C_6H_6	$C_{14}H_{15}ClN_2O_2$	C, H, N, Cl
33	$(CH_2)_3Cl$	Br	CH_3	H	175[b]	THF	$C_{14}H_{14}BrClN_2O$	C, H, N, Cl
34	$(CH_2)_2N(Et)_2$	H	H	H	128–129[c]	EtOH	$C_{16}H_{23}Cl_2N_3O_9$	C, H, N
35	$(CH_2)_2N(CH_2)_4$	H	H	H	88–89.5	Hexane	$C_{16}H_{19}N_3O$	C, H, N
36	$(CH_2)_2N[(CH_2)_5CH_3]_2$	H	H	H	143.5–144.5[d]	EtOH[d]	$C_{36}H_{43}N_9O_{15}$[d]	C, H, N
37	$(CH_2)_2N(Et)(CH_2CH_2OH)$	H	H	H	124–125[e]	EtOH[e]	$C_{16}H_{23}BrN_3O_2$[e]	C, H, N, Br
					149–151[d]	EtOH[d]	$C_{28}H_{27}N_9O_{10}$	C, H, N
38	$CH_2CH(CH_3)N(CH_2)_4$	H	H	H	91.5–92.5	Hexane	$C_{17}H_{21}N_3O$	C, H, N
39	$(CH_2)_3N[(CH_2)_5CH_3]_2$	H	H	H	153–154[f]	C_6H_6–EtOH[f]	$C_{25}H_{40}IN_3O$	C, H, N, I
40	$CH_2CH_2N(Et)_2$	Br	H	OCH_3	86–87	Hexane		
41	$CH_2CH_2N(CH_2)_4$	Cl(Br)	H	OCH_3	118–120[g]	Hexane	$C_{17}H_{20}N_3ClO_2$	N
42	$(CH_2)_3N(Et)_2$	Br	CH_3	H	115–116	Et_2O–petr ether	$C_{18}H_{24}BrN_3O$	C, H, N
43	$(CH_2)_3N(Et)_2$	Br	H	OCH_3	200–202[e]	EtOH–Et_2O[e]	$C_{18}H_{26}BrN_3O_2$[e]	C, H, N

[a] When immersed in the oil bath at 157° compound melted and immediately resolidified. When immersed in the oil bath at 145° the compound slowly loses its crystalline structure, without melting up to 220°. For explanation, see ref 5. [b] Compound melts with resolidification. [c] Perchlorate salt. [d] Dipicrate salt. Biological evaluation was carried out on the free base, a light brown oil which could not be crystallized. *Anal.* C, H, N. [e] Dihydrobromide salt. [f] Dihydroiodide salt. [g] Analytical data (N: calcd 12.58, found 11.99) and the mass spectrum indicated the presence of small quantities of the 1-bromo derivative.

TABLE II

AMINOALKYL DERIVATIVES OF 3-AMINOISOQUINOLINES



Compd	R_1	R_2	R_3	R_4	Mp or bp, °C (mm)	Recrystn solvent	Formula	Analyses
44	$NH(CH_2)_3N(Et)_2$	H	H	H	155–158 (0.1)		$C_{16}H_{28}N_4$	C, H, N
45	$NH(CH_2)_3N(CH_2)_4CH_3$	H	H	H	195.5–196.5[a] 103–104.5	EtOH Hexane	$C_{28}H_{29}N_9O_{14}$ $C_{16}H_{21}N$	C, H, N C, H, N
46	$NH(CH_2)_3N(CH_2)_3CH_3$	H	H	H	170–174 (0.2)		$C_{17}H_{28}N_2$	C, H, N
47	$NH(CH_2)_3N[(CH_2)_5CH_3]_2$	H	H	H	197–200 (0.15)		$C_{24}H_{39}N_3$	C, H, N
					27–29			
					166–168[a]	EtOH	$C_{36}H_{43}N_9O_{14}$[a]	C, H, N
48		H	H	H	111–112.5	Petr ether	$C_{20}H_{21}N_3$	C, H, N
49	$NH(CH_2)_2CH(CH_3)N(CH_2)_4$	H	H	H	74–75	Hexane	$C_{17}H_{28}N_2$	C, H, N
					188–190[a]	EtOH[a]	$C_{29}H_{29}N_9O_{14}$[a]	C, H, N
50	$NH(CH_2)_3N(Et)_2$	Br	H	H	114–116[a]	EtOH		
					172–178 (0.1)[b]		$C_{16}H_{22}BrN_3$	C, H, N, Br
51	$NH(CH_2)_2N(Et)$	$NH(CH_2)_2N(Et)_2$	H	H	198–200[c]	95% MeOH	$C_{21}H_{38}Cl_3N_3$	C, H, N, Cl
52	$NH(CH_2)_4N(Et)_2$	Br	CH_3	H	90–95[d]	EtOH–Et_2O	$C_{18}H_{28}N_3Br$[d]	C, H, N, Br
53	$NH(CH_2)_4N(Et)_2$	Br	H	OCH_3	168–173[e]	MeCN	$C_{18}H_{28}Br_2N_3O$	C, H, N
54	F	$NHCH(CH_3)(CH_2)_3N(Et)_2$	H	H	230 (0.1)		$C_{18}H_{26}FN_3$	C, H, N

[a] Dipicrate. [b] $n^{25}D$ 1.6090. [c] Trihydrochloride. [d] Dihydrobromide; compound resolidifies, then again melts at 170–174°. [e] Decomposition, dihydrobromide salt.

of 0.8 days with no toxic deaths at 120 mg/kg and 5/5 toxic deaths at 240 mg/kg.

Experimental Section[13]

N-(3-Isoquinolyl)-3-chlorobutyramide (28).—A sample of 5 g (0.0345 mole) of 3-aminoisoquinoline[4] and 5.5 g (0.039 mole) of 3-chlorobutyryl chloride was heated at reflux temperature for 20 hr in 150 ml of dry C_6H_6. The cooled reaction mixture was diluted with 150 ml of $CHCl_3$ and washed with 200 ml of the following: 1.5 *M* Na_2CO_3, 0.1 *N* NaOH, H_2O, and saturated NaCl. The organic layer was filtered and dried ($MgSO_4$) in the presence of decolorizing charcoal. Stepwise concentration of the filtrate yielded three crops: 4.1 g, mp 141–142.5°; 1.3 g, mp 140.5–142°; and 0.55 g, mp 135–141° (total of 5.95 g, 69% yield) of **28** (Table I).

Similarly prepared from the appropriate 3-aminoisoquinoline and a chloroacyl chloride were **27, 29–33** (Table I).

N-(3-Isoquinolyl)-3-diethylaminopropionamide (34).—A sample of 2.3 g (0.01 mole) of *N*-(3-isoquinolyl)-3-chloropropionamide (**27**) and 6 ml of $HNEt_2$ in 75 ml of $CHCl_3$ was allowed to reflux for 3 hr. The solution was concentrated to near dryness and was then treated with *ca.* 100 ml of Et_2O. The insoluble $Et_2NH \cdot HCl$ was removed by filtration. The filtrate was concentrated and dried at 60° under vacuum. The light brown sirupy residue (2.2 g) was dissolved in *ca.* 100 ml of EtOH. The solution was warmed and was treated with 3.5 g of concentrated $HClO_4$. Slow cooling caused crystallization to occur to give 3.45 g, mp 65–70°, of crude product which was further purified by recrystallization from 100 ml of EtOH–*n*-BuOH (1:1), 2.7 g, mp 125–128°, and then from 70 ml of EtOH to give 2.2 g of **34**, mp 128–129°. Absorption bands of spectra (ir, nmr) were as expected.

The free base was isolated by dissolving the perchlorate salt in water and neutralizing with Na_2CO_3. The residual oil, extracted from Et_2O, slowly crystallized when stored at −5° for several weeks, mp 27–28°.

Similarly prepared from the appropriate chloroalkylamides and α-dialkylamine were the **3-dialkylaminoamides of 3-aminoisoquinoline** shown in Table I (**34–41**).

N-[3-(1-Bromo-4-methylisoquinolyl)]-4-diethylaminobutyramide (42).—A sample of 5 g (0.021 mole) of 3-amino-1-bromo-4-methylisoquinoline (VIIb)[1] was dissolved in 200 ml of molecular sieve dried DMF, together with 4.25 g (0.0218 mole) of 4-diethylaminobutyric acid · HCl[6] and 4.5 g (0.0218 mole) of DCC. The mixture was stirred for 4 days at room temperature and was then poured into 1.5 l. of H_2O that was acidified with 10 ml of concentrated HCl. The precipitated dicyclohexylurea was removed by filtration. The filtrate was made alkaline by addition of 20 ml of 50% sodium hydroxide and the product was extracted into five 100-ml fractions of Et_2O. The combined Et_2O extracts were washed with H_2O and then dried over Na_2SO_4 in the presence of some decolorizing charcoal. The solution was filtered and the filtrate was concentrated to 100 ml and treated with 200 ml of low-boiling petroleum ether. The amide **42** precipitated as an off-white solid, 4.5 g (56%), mp 113.5–114.5°. A 2-g sample was recrystallized from a mixture of 100 ml of low-boiling petroleum ether, 20 ml of Et_2O, and 2 ml of ethanol, to give 1.2 g, mp 115–116°, of pure **42** (Table I).

Absorption bands of spectra (ir, nmr) were as expected.

N-(3-Isoquinolyl)-3-diethylaminopropylamine (44).—A sample of 4.8 g (0.0177 mole) of the amide **34** was dissolved in 60 ml of dry Et_2O and added dropwise under nitrogen at room temperature to a stirred slurry of 0.7 g (0.0184 mole) of LAH in 80 ml of dry Et_2O. Stirring was continued after complete addition. The total reaction time was 6 hr. About 2 ml of H_2O was added slowly and the resulting precipitate was removed by filtration. The filtrate, a clear yellow solution that rapidly turned green when exposed to air, was evaporated and the residue was distilled at 0.1 mm. Two fractions were collected, the first one distilling at 135–154° (0.8 ml), and the second as a yellow oil at 155–158° (2 ml) ($n^{23}D$ 1.5872). This compound decolorized when exposed to air.

Absorption bands of spectra (ir, nmr) were as expected.

N-[3-(1-Bromo-4-methylisoquinolyl)]-4-diethylaminobutylamine Dihydrobromide (52·2HBr).—A sample of 4.2 g (0.011 mole) of the amide **42** was dissolved in 150 ml of dry THF and stirred in the presence of 15 ml of dry THF that was *ca.* 1 *M* in diborane. After 15 hr 10 ml of acetone was added and the mixture was concentrated to near dryness. The residue was dissolved in 150 ml of *ca.* 2% HCl, made alkaline with excess NaOH, and extracted into Et_2O. The Et_2O extract was washed with H_2O and then saturated NaCl solution, and concentrated to near dryness. The residue was taken up in a small amount of EtOH and a white, fluffy precipitate was removed by filtration. The filtrate was concentrated and dried overnight over concentrated H_2SO_4 and at *ca.* 0.1 mm to give 3.4 g of a very viscous, deep yellow oil. This oil was redissolved in EtOH (10 ml) and treated with 30 ml of the same solvent that contained *ca.* 3.3 g of HBr. The mixture was concentrated to *ca.* 15 ml and a small amount (*ca.* 0.5 g of a precipitate, mp 238–244°) was removed by filtration and discarded. When the mother liquor was treated with Et_2O, 1.2 g of **52**·2HBr, mp 90–95°, resolidification, second mp 170–174°, was observed (Table II).

The absorption bands of the spectra (ir and nmr) were as expected.

1-{[4-(Diethylamino)-1-methylbutyl]amino}-3-fluoroisoquinoline (54).—A sample of 2.5 g (0.011 mole) of 1-bromo-3-fluoroisoquinoline (VIId)[1] was added to 3.5 g (0.022 mole) of 2-amino-5-diethylaminopentane and the mixture heated at 95° in an oil bath for ~20 hr. The mixture was then dispersed between aq Na_2CO_3 and Et_2O. The Et_2O layer was washed (H_2O) and extracted into 2% HCl. The acidic layer was washed once with Et_2O, then made alkaline with excess Na_2CO_3, and extracted into Et_2O. After removal of Et_2O the residue was distilled twice at 0.1 mm using a Kugelrohr. The compound distilled when the oven temperature had reached 230°. Distillate (1.3 g, 39%) of **54** was collected.

Absorption bands of spectra (ir and nmr) were as expected.

1,3-Bis{[2-(diethylamino)ethyl]amino}isoquinoline Trihydrochloride (51·3HCl).—A 1.5-g sample of 3-amino-1-bromoisoquinoline (VIIa)[1] was dissolved in 10 ml of *N,N*-diethylethylenediamine together with a catalytic amount of KI. The solution was stirred and heated to 130°. After the initial reaction subsided, the oil bath was heated to 145° and the reaction mixture was kept at this temperature for about 1 hr. The deep brown liquid was poured into ice-water and extracted (Et_2O). The ether was evaporated and the oily residue was dried at 40° (3 mm) (P_2O_5) to yield 1.8 g of brown oil. This oil was dissolved in Et_2O and an Et_2O solution of HCl was added. The Et_2O was decanted from the resulting solid, which was then dissolved in approximately 40 ml of EtOH. The hydrochloride was induced to crystallize and the resulting crystals were collected, washed with a small amount of EtOH–Et_2O 1:1, and dried at 40° *in vacuo*. The yellow microcrystalline compound (1.75 g, 56%, mp 191–195°) was recrystallized twice from EtOH–Et_2O, mp 198–200° (immersed at 198°) (Table II).

The structure of the compound was confirmed by elemental analysis, mass, nmr, and ir spectra. The molecular weight was determined by mass spectroscopy as 357 (free base, calculated 357.53).

Antimalarial Agents. VI.[1] 5-Quinolinemethanols

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More than 200 4-quinolinemethanols, but only two of the 5 position isomers, have been screened

(13) All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The microanalyses were performed by Galbraith Laboratories, Inc. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(1) (a) Part V, *J. Heterocycl. Chem.*, **6**, 959 (1969); (b) this study was supported in part by the U. S. Army Medical Research and Development Command. The compounds were tested by Dr. L. Rane of the University of Miami, Florida (except for those antimalarials indicated later) and Col. W. E. Rothe of Walter Reed Army Institute for Research (phototoxicity results are mentioned later); (c) analyses are indicated by symbols of the elements, since analytical results obtained for these elements were within ±0.4% of the theoretical values.