were crystallized from MeOH to give a solid which was washed with Et_2O. Three crystallizations from Et_2O gave 0.75 g of **3**, mp 101–103°. It was identified by spectral comparison with an authentic sample.[4]

Fractions 38–52 were crystallized from MeOH to give 2 g of **1**, mp 201–202°. It was identical with authentic **1** previously prepared.

2-Hydroxyethyl 2,3-Bis(*p*-methoxyphenyl)indole-5-carboxylate (4).—A mixture of 29.1 g (0.16 mole) of *p*-carbethoxyphenylhydrazine[3] and 41.5 g (0.16 mole) of desoxyanisoin was stirred and heated at 160–170° (internal) for 10 min. Ethylene glycol (485 ml) was added and the mixture was refluxed for 22 hr. The solid obtained upon cooling and filtration was crystallized from EtOH to give 31.7 g (47%) of **4**, mp 209–210°, raised to 211–212° on recrystallization. *Anal.* ($C_{25}H_{23}NO_5$) C, H, N.

2,3-Bis(*p*-methoxyphenyl)indole-5-carboxylic Acid Acetone Solvate (5).—A mixture of 11 g of **4**, 20 g of KOH, 80 ml of H_2O, and 200 ml of EtOH was refluxed for 18 hr. The EtOH was evaporated. A solution of the residue in H_2O was extracted with Et_2O and was then acidified with concentrated HCl. The solid obtained was crystallized from Me_2CO–H_2O to give 9 g (79%) of **5**, mp 296–298° dec, raised to 297–298° by crystallization from Me_2CO–Skellysolve B. *Anal.* ($C_{23}H_{19}NO_4 \cdot C_3H_6O$) C, N; H: calcd, 5.84; found, 6.31.

Saponification of **1** also gave **5**.

5-Acetyl-2,3-bis(*p*-methoxyphenyl)indole (6).—A mixture of 1 g of **5**, 10 ml of $SOCl_2$, and 25 ml of C_6H_6 was refluxed for 1 hr and then evaporated to give the acid chloride. A solution of 6 ml of 3 *M* ethereal MeMgBr in 50 ml of Et_2O was added to a stirred suspension of 1.80 g of $CdCl_2$ in 20 ml of Et_2O. The resulting suspension was cooled in ice and a solution of the acid chloride in 25 ml of Et_2O was added. The mixture was refluxed for 4 hr, cooled in ice, treated with 50 ml of 2.5 *N* HCl, and extracted with CH_2Cl_2. The extract was washed with H_2O, 1 *N* NaOH, and H_2O and evaporated. The resulting solid was chromatographed on Florisil using 8% Me_2CO in Skellysolve B as the eluent. The solid fractions were crystallized twice from EtOAc to give 0.25 g (29%) of **6**, mp 222–223°. *Anal.* ($C_{24}H_{21}NO_3$) C, H, N.

(4) J. C. Irvine and D. McNicoll, *J. Chem. Soc.*, **93**, 1601 (1908).

Antimalarials. Chloroquine Analogs with the 1,2,3,6-Tetrahydropyridyl Function in the Side Chain

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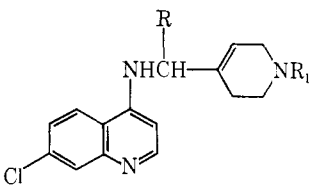
In a recent publication, Bailey[1] has reported "folded" chloroquine analogs of the structure **1** (saturated



1a, R = H; $R_1 = CH_3$
b, R = CH_3; $R_1 = CH_3$
c, R = CH_3; $R_1 = C_2H_5$

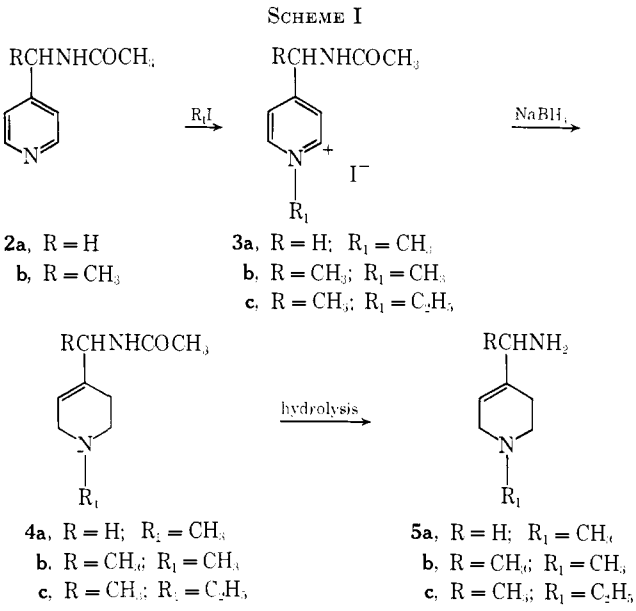
pyridyl ring) where R = H and CH_3 and $R_1 = C_2H_5$ and CH_2CH_2OH. This has prompted us to report a few similar compounds but with a double bond between C-4 and C-5 as shown in the generic structure **1** (see Table I).

(1) D. M. Bailey, *J. Med. Chem.*, **12**, 184 (1969).

The rationale for making such compounds was arrived at from several publications[2] in which a number of compounds containing the 1,2,3,6-tetrahydropyridyl moiety have been reported to exhibit promising pharmacological activity. Furthermore, we have found earlier[3] that the introduction of an unsaturation function such as the *cis* and *trans* double bond and an acetylenic triple bond in the chloroquine side chain significantly improved the antimalarial activity and lowered the toxicity when tested against *Plasmodium berghei* in mice. Thus, 1,2,3,6-tetrahydropyridyl moiety presented a unique feature containing a modified cyclic chloroquine side chain as well as one unsaturated center.

The tetrahydropyridylamines were made as outlined in Scheme I. The general procedures are described in

SCHEME I



the Experimental Section. It is well known that the reduction of pyridinium salts with KBH_4[4] and $NaBH_4$[5] gives 1,2,3,6-tetrahydropyridyl compounds. On the basis of this accumulated evidence, the amines have been assigned the structure as shown.

Biological Activity.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice. The screening was carried out by Dr. L. Rane of the University of Miami, Miami, Fla., according to the procedure published by Osdene, Russell, and Rane.[6] The activity figures are given in Table II.

Experimental Section

Acetylaminoalkylpyridines (2) were prepared by the reaction of excess Ac_2O with aminopyridines.

(2) J. H. Biel and H. B. Hopps, U. S. Patent 3,221,019 (1965); *Chem. Abstr.*, **64**, 5053*e* (1966); French Patent M3502 (1965); *Chem. Abstr.*, **64**, 2104*d* (1966); J. R. Geigy A.G., Netherlands Appl 6,408,219 (1965); *Chem. Abstr.*, **63**, 586*a* (1965); F. Hoffmann-La Roche & Co. A.G., Netherlands Appl 6,407,413 (1965); *Chem. Abstr.*, **63**, 1774*b* (1965), and Netherlands Appl 6,407,463 (1965); *Chem. Abstr.*, **62**, 16207*c* (1965).

(3) T. Singh, R. G. Stein, and J. H. Biel, *J. Med. Chem.*, **12**, 368 (1969).

(4) J. J. Panouse, *Compt. Rend.*, **233**, 260, 1200 (1951); *Chem. Abstr.*, **46**, 2542*i*, 6643*h* (1952).

(5) R. E. Lyle, E. F. Perlowski, H. J. Troscianiec, and G. G. Lyle, *J. Org. Chem.*, **20**, 1761 (1955); R. C. Elderfield, B. Fischer, and J. M. Lagowski, *ibid.*, **22**, 1376 (1957); E. Wenkert, R. A. Massey-Westrop, and R. G. Lewis, *J. Amer. Chem. Soc.*, **84**, 3732 (1962).

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

TABLE I

Compd	Bp (mm) or mp, °C[a]	Cryst solvent	Yield, %	Formula	Analyses[b]
1a	162–163.5	EtOAc	63.0	$C_{16}H_{18}ClN_3$	C, H, N
b	159–160	EtOAc	31.0	$C_{17}H_{20}ClN_3$	C, H, N
c	152–153	EtOAc	56.0	$C_{18}H_{22}ClN_3$	C, H, N
2a	87–89	CH_2Cl_2–Et_2O	89.0	$C_8H_{10}N_2O$	C, H, N
b	85–86.5	EtOAc	76.0	$C_9H_{12}N_2O$	C, H, N
3a	159–161		74.0	$C_9H_{13}IN_2O$	C, H, N
b	148–150	EtOH	82.0	$C_{16}H_{15}IN_2O$	C, H, N
c	Liquid		83.0	$C_{11}H_{17}IN_2O$	
4a	115–120 (0.7)		60.0	$C_9H_{16}N_2O$	
Oxalate	125–126.5	*i*-PrOH		$C_{11}H_{18}N_2O_5$	C, H, N
b	125–130 (0.05)		83.0	$C_{16}H_{18}N_2O$	
Oxalate	150–151	*i*-PrOH		$C_{12}H_{20}N_2O_4$	C, H, N
c	110–115 (0.3)		43.0	$C_{17}H_{20}N_2O$	N
5a	88–90 (17)		61.0	$C_7H_{14}N_2$	N
Phenylurea deriv	128–129	EtOAc		$C_{14}H_{19}N_3O$	C, H, N
b	93 (15)		50.0	$C_8H_{16}N_2$	
Phenylurea deriv	138–139	EtOAc		$C_{15}H_{21}N_3O$	C, H, N
c	98 (8)		36.0	$C_9H_{18}N_2$	
Phenylurea deriv	122–123	EtOAc		$C_{16}H_{23}N_3O$	C, H, N

[a] All melting points are uncorrected. [b] All analyses were within ±0.4% of the theoretical values except for **2a** (C: calcd, 63.98; found, 64.55).

TABLE II

Compd	Activity[a] D	C	TD	Increase in MST
1a	20	0	0	4.2
	40	0	0	4.6
	80	0	0	5.8
	160	0	0	9.2 (active)
	320	0	0	10.2 (active)
	640	2	1	... (curative, toxic)
1b	20	0	0	8.1 (active)
	40	0	0	8.7 (active)
	80	0	0	11.9 (active)
	160	0	0	18.7 (active)
	320	1	0	... (curative)
	640	4	0	... (curative)
1c	20	0	0	4.9
	40	0	0	6.5 (active)
	80	0	0	9.5 (active)
	160	0	0	14.1 (active)
	320	1	0	... (curative)
	640	3	0	... (curative)

[a] D, dose in mg/kg of body weight; C, cures; MST, mean survival time in days of the treated mice; TD, toxic death when the mice die within 2–5 days after infection which is attributed to drug toxicity. A compound is active if the increase in MST of the treated mice exceeds 6.3 days (MST of the control group) and curative if one or more mice live for 60 days or more post-infection.

4-Acetylaminopyridinium Alkyliodides (3).—A solution of 1 equiv of the acetylaminoalkylpyridine and 1 equiv of RI in Me_2CO was stirred at room temperature for 6–8 hr. A precipitate of the quaternary salt usually appeared which was removed by filtration. **3a** was pure enough at this stage to give satisfactory elemental analyses, **3b** was crystallized from EtOH, and **3c** was used as such for reduction.

1-Alkyl-4-acetylaminoalkyl-1,2,3,6-tetrahydropyridines (4).—A solution of 1 equiv of the 4-acetylaminoalkylpyridinium alkyliodide in MeOH was treated with 4 equiv of $NaBH_4$ with stirring. After 2 hr of additional stirring the solvent was evaporated under reduced pressure, the residual solid dissolved in a minimum amount of H_2O, strongly basified with NaOH, extracted with CH_2Cl_2, dried ($MgSO_4$), and solvent was removed under reduced pressure. The product was purified by distillation. **4a** and **4b** were converted to oxalates for identification.

1-Alkyl-4-aminoalkyl-1,2,3,6-tetrahydropyridines (5).—The Ac derivatives were hydrolyzed by refluxing with excess 4 *N* NaOH for 12 hr. The amines were hygroscopic and were converted to phenylureas for identification.

4-Substituted Amino-7-chloroquinolines (1).—A mixture of 1 equiv of 4,7-dichloroquinoline, 1.1 equiv of the 1-alkyl-4-aminoalkyl-1,2,3,6-tetrahydropyridine, and sufficient PhOH to give a clear solution was heated at 140–150° for 4 hr. The reaction mixture was cooled, poured into 2 *N* NaOH, and stirred. It was extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and evaporated to give solid product which was purified by recrystallization.

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N-Acyl- and N-Sulfonylcysteine Derivatives

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Additional work on N-acylcysteines[1–4] includes the synthesis of larger N-acyl, N-sulfonyl, and N-carbamoyl analogs as well as two dicysteine derivatives listed in Table I. The mucolytic activity[4,5] of representative sulfhydryl compounds is demonstrated (Table II). The biological activities of the compounds as potential

(1) T. A. Martin and C. W. Waller, U. S. Patent 3,184,505 (1965).

(2) T. A. Martin, J. R. Corrigan, and C. W. Waller, *J. Org. Chem.*, **30**, 2839 (1965).

(3) (a) T. A. Martin and A. L. Steffner, U. S. Patent 3,340,147 (1967); (b) T. A. Martin, D. H. Causey, A. L. Steffner, A. G. Wheeler, and J. R. Corrigan, *J. Med. Chem.*, **10**, 1172 (1967).

(4) T. A. Martin, D. H. Causey, and J. R. Corrigan, *ibid.*, **11**, 625 (1968).

(5) A. L. Steffner, *Ann. N. Y. Acad. Sci.*, **106**, 298 (1963); *Pharmacotherapeutica*, **1**, 46 (1965).