Chemistry of Thienopyridines. VIII. Substitution Products Derived from Thieno[2,3-*b*]pyridine 7-Oxide (I)

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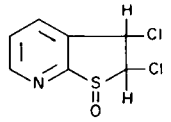
Thieno[2,3-*b*]pyridine (I) was concerted to the *N*-oxide (II, 53%) by means of hydrogen peroxide and acetic acid. Nitration of II in sulfuric acid gave 4-nitrothieno[2,3-*b*]pyridine 7-oxide (III, 50%), while nitration in acetic acid formed the isomeric 5-nitrothieno[2,3-*b*]pyridine 7-oxide (IV, 54%). Compounds III and IV were reduced to the corresponding 4- and 5-aminothieno[2,3-*b*]pyridines, respectively. Treatment of III with acetyl chloride gave 4-chlorothieno[2,3-*b*]pyridine 7-oxide (XI, 81%), convertible in two steps to 4-(*N*-substituted amino)thieno[2,3-*b*]pyridines (especially of the 4-dialkylaminoalkylamino type) for screening as potential antimalarial drugs. 4-Aminothieno[2,3-*b*]pyridine reacted with aromatic aldehydes to give Schiff's bases and other products. Mechanisms for some of the reactions are suggested. NMR spectral data are reported for various 4-substituted thieno[2,3-*b*]pyridine compounds.

Limited previous studies (4) have shown that thieno[2,3-*b*]pyridine (I) undergoes electrophilic substitution at C-3 (preferentially) and C-2 in the thiophene ring while nucleophilic substitution occurs (*via* addition to the C=N moiety) at C-6 in the pyridine ring. Direct substitution at C-4 or C-5 was not found to occur under these conditions. However, the 4-amino derivative and a variety of 5-substituted compounds were obtained (5) by transformations on 5-acetylthieno[2,3-*b*]pyridine, readily available by a one-step synthesis from a 2-aminothiophene salt. The present paper describes the synthesis and nitration of thieno[2,3-*b*]pyridine 7-oxide (II) as an alternative route to 4- and 5-substituted compounds (see Scheme 1).

Treatment of I with glacial acetic acid and 30% hydrogen peroxide at 55° produced II, isolated either as a dihydrate or in the anhydrous form. These reaction conditions are closely similar to those used for *N*-oxidation of pyridine and quinoline (6,7) but somewhat warmer than those for usual conversion of sulfides to sulfoxides and sulfones (8,9). The assignment of an *N*-oxide rather than a sulfoxide structure to II is based on the following considerations. First, II shows a strong, positive Katritsky test (10) for the presence of an *N*-oxide function. Second, anhydrous II exhibits a very strong, broad absorption band at 1240 cm^{-1}, well within the region which is typical for aromatic N → O stretching (11a, 12a). Unfortunately, the IR spectrum of II is somewhat ambiguous inasmuch as it also shows a very sharp band of medium intensity at 1040 cm^{-1}, *i.e.*, in the region for S=O stretching (11b). However, this latter band does not have the typically strong, broad characteristics of a sulfoxide absorption, such as are displayed at 1035 cm^{-1} in the spectrum of dibenzothiophene 5-oxide (13) run under identical conditions. Third, efforts to convert I to *bona fide* thieno[2,3-*b*]pyridine 1-oxide by other methods commonly used to obtain sulfoxides from sulfides failed. Partial success was attained by means of chlorine and water (13) or iodobenzene dichloride and water (14) which formed 2,3-dichloro-2,3-dihydrothieno[2,3-*b*]pyridine 1-oxide (XVII) in low yield.

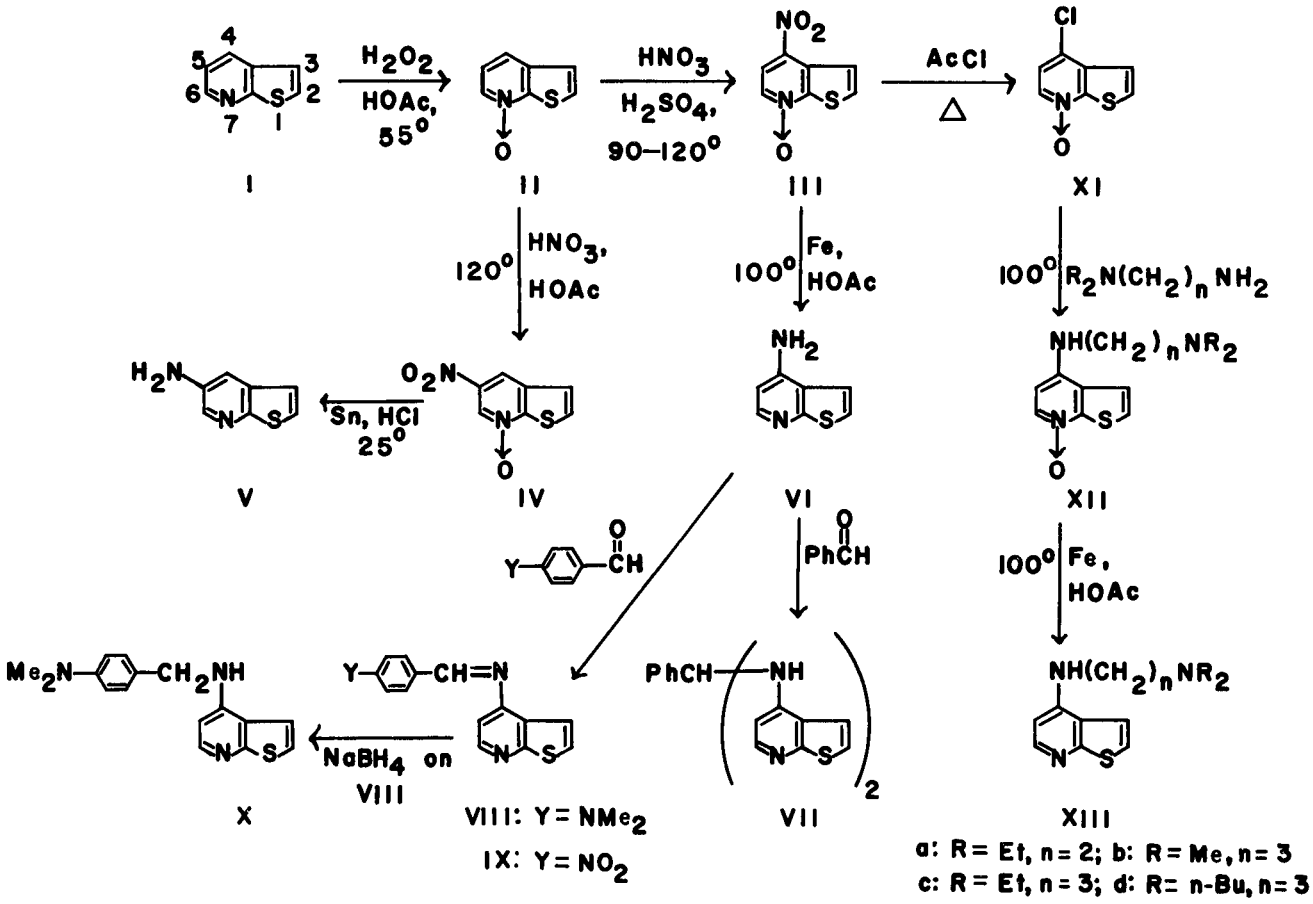


XVII

Fourth, the chemical properties (failure to undergo oxidation to a sulfone under the reaction conditions; behavior in nitration reactions -- *vide infra*) of II seem more consistent with its formulation as an *N*-oxide rather than as a sulfoxide (15).

Nitration of II with nitric-sulfuric acids at 90-120° gave a 50% yield of the 4-nitro derivative III, in close analogy with results on pyridine 1-oxide and quinoline 1-oxide (6,7). On the other hand, use of nitric-acetic acids at approximately the same reaction temperature converted II into the 5-nitro derivative IV in 54% yield. Reasonably, formation of III involves an electrophilic attack at C-4 of a nitronium ion onto non-protonated II, in the manner proposed for nitration of pyridine 1-oxide (16). The concentration of nitronium ions in nitric-acetic acid would be very small, but the anions nitrate and acetate (OG^-), and

SCHEME I

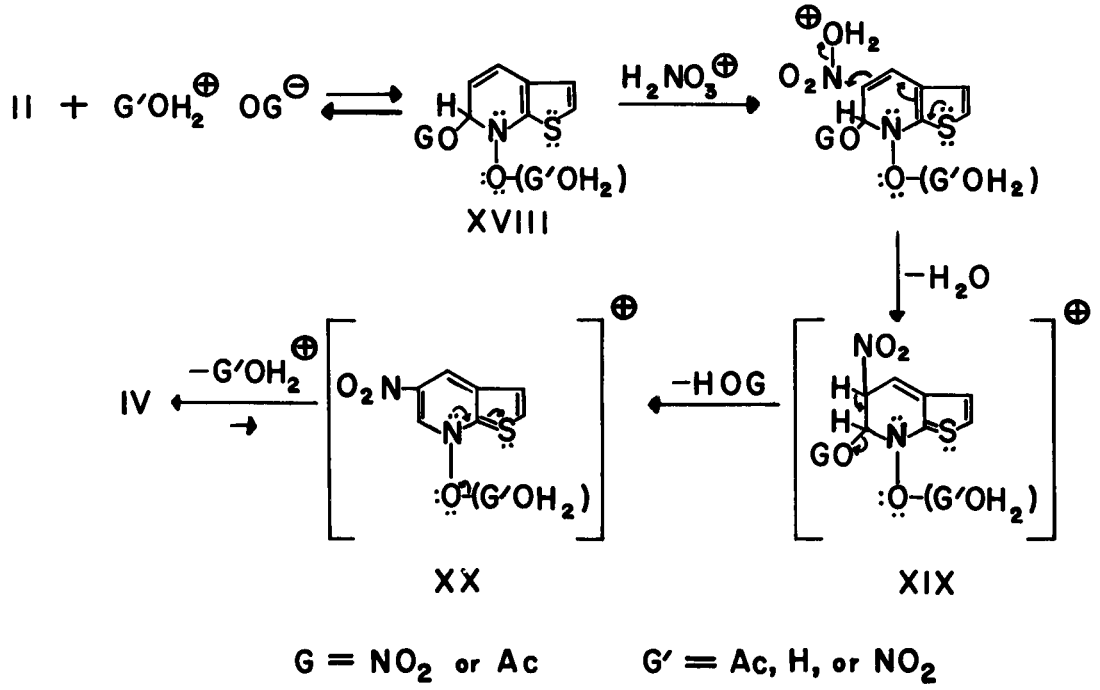


the cations resulting from protonation of water, nitric acid, and acetic acid ($G'OH_2^+$) should be present. We suggest that a plausible mechanism for the formation of IV is indicated in Scheme 2, which is an adaptation of the mechanism proposed by Ochiai and Kaneko (12b, 17, 18a) for reaction of acetyl nitrate with quinoline 1-oxide to form 3-nitroquinoline 1-oxide. It is proposed that 1,3-dipolar addition (with or without loss of water) occurs to the C = N→O moiety of II to form XVIII (or its dehydrated form). Electromeric shift of a non-bonding pair from sulfur (as shown) or of a pair from nitrogen should foster electrophilic attack by protonated nitric acid at C-5, with concomitant loss of water to give cation XIX. Subsequent 1,2-elimination of nitric acid or acetic acid HOG (to form XX) plus loss of $G'OH_2^+$ (or G'^+) would result in IV.

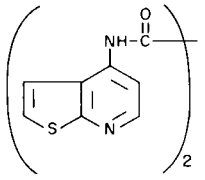
Reduction of IV with tin and hydrochloric acid at 25° produced 5-aminothieno[2,3-*b*]pyridine (V) in 41% yield (5% overall yield for the five-step synthesis from 2-nitrothiophene, the precursor of I). The alternative five-step synthetic pathway from 2-nitrothiophene to V *via* the intermediate 5-acetylthieno[2,3-*b*]pyridine (21% overall yield) which was described previously (4,5) is, however, preferred. Reduction of III by means of iron and acetic acid at 100° gave 4-aminothieno[2,3-*b*]pyridine (VI) in 67% yield (8% overall yield for 5 steps from 2-nitrothiophene). In this case, the alternative route to VI from 2-nitrothiophene *via* the 5-acetyl and 5-bromo derivitaves is both inferior in yield and longer (5).

In earlier studies (5) we noted that amine V condenses with benzaldehyde and *p*-dimethylaminobenzaldehyde in refluxing benzene (with mechanical trapping of evolved liquid water) to give Schiff's bases. However, neither *p*-dimethylaminobenzaldehyde nor *p*-nitrobenzaldehyde (expected to be more reactive) condensed with amine VI under these same conditions (or in refluxing xylene, in refluxing glacial acetic acid, or without solvent at 110°). Success was achieved, nonetheless, by use of molecular sieves in refluxing xylene containing a few drops of glacial acetic acid. Under the latter conditions, Schiff's bases VIII and IX were obtained in 42% and 47% yields, respectively. Benzaldehyde likewise reacted at these conditions but to give an 18-22% yield of the 2:1 condensate VII.

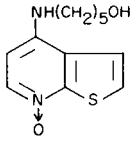
SCHEME 2



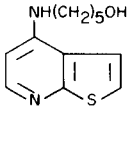
N-Methylpyrrole-2-carboxaldehyde, on the other hand, did not react. Imine VIII was readily reduced to the amine X (83%) by means of sodium borohydride in refluxing ethanol. Amine VI also reacted with oxalyl chloride to form *N*,*N*'-bis(4-thieno[2,3-*b*]pyridine)oxamide (XIV).



XIV



XV

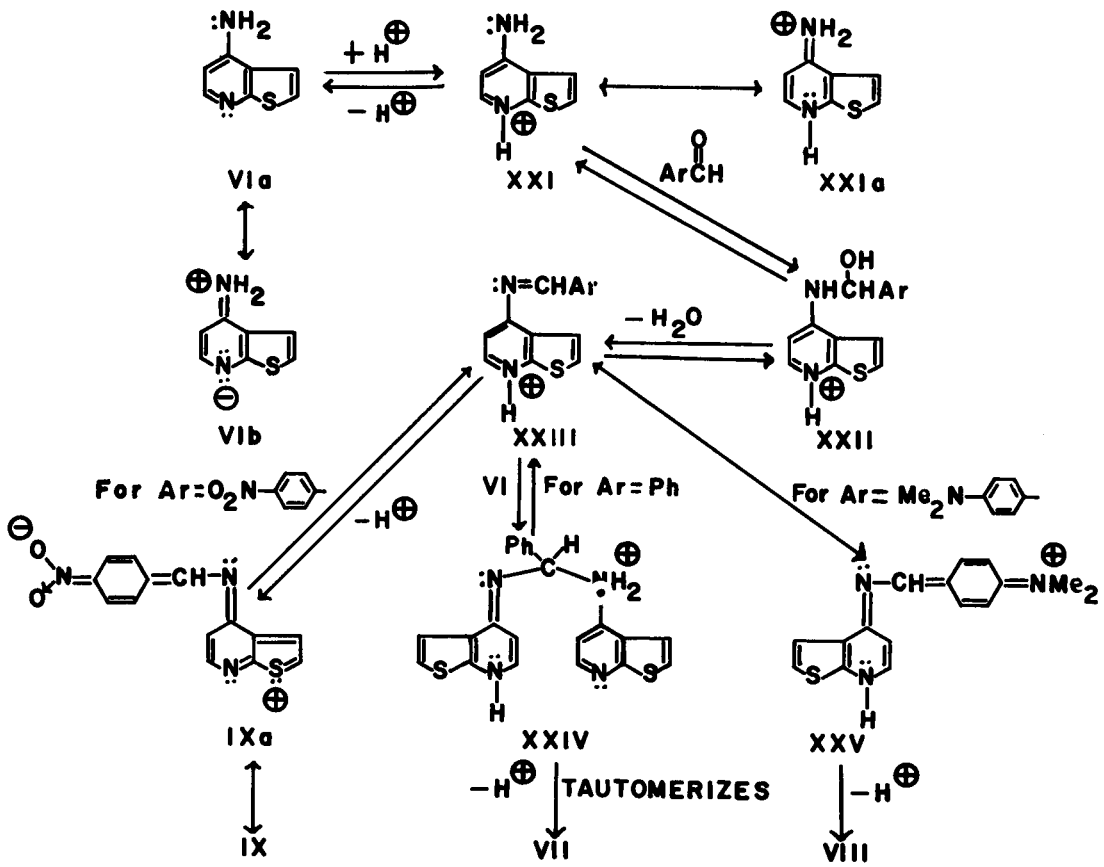


XVI

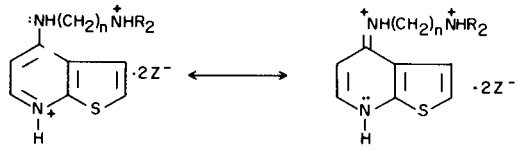
In Scheme 3 is presented a rationalization of the reactivity of amine VI toward aromatic aldehydes. Structure VIb probably contributes significantly to resonance stabilization of VI while structure VIa (with its non-bonding electron pair on the primary amino nitrogen atom) should be the main contributing form toward reaction with the aldehydes. For amine V a dipolar contributing structure analogous to VIb (*i.e.*, with a negative charge on the ring nitrogen atom) cannot be written and a structure analogous to VIa should be the principal resonance contributor (19). In the presence of acetic acid, protonation of VI should occur on the heterocyclic nitrogen atom to give the resonance-stabilized XXI (and XXIa) (19). In the equilibrated system involving VI, XXI, XXII, and XXIII the high stability of XXI may well keep the concentrations of XXII and XXIII from becoming sufficiently large that a separate phase of water forms. Thus, it becomes necessary to remove water *in situ* (e.g. by molecular sieves) rather than by a remote mechanical trap in order to force the reaction toward formation of XXIII. For Ar equals phenyl little resonance stabilization by contributors which involve distribution of the positive charge into the benzene ring of XXIII is likely. Hence, nucleophilic attack of a second molecule of VI onto the aldimino carbon of XXIII may occur to produce XXIV and VII. For Ar equals *p*-dimethylaminophenyl, however, reactivity of XXIII toward further condensation should be small due to resonance stabilization by structure XXV. For Ar equals *p*-nitrophenyl, on the other hand, the electron-attracting nitro group should foster deprotonation of XXIII to the stabilized product IX (and IXa) and likewise preclude further reaction with VI.

Refluxing III with acetyl chloride effected replacement of the 4-nitro group with chlorine to produce XI (81%) (20). The chlorine atom was in turn replaceable by alkylamino side chains of the type $R_2N(CH_2)_nNH$- to form XII or by $HO(CH_2)_5NH$- to form XV (23-60% yields). Deoxygenation of these *N*-oxides occurred with iron and acetic acid at 100° to give XIII and XVI, respectively. Compound XVI (44%) was obtained as a crystalline free amine, while the dialkylaminoalkylamino derivatives XIIIa-

SCHEME 3



XIIIc formed various crystalline salts (47-63% overall from XIIa-XIIc, respectively) containing two moles of acidic moiety (picric acid, sulfuric acid, or orthophosphoric acid) per mole of amine XIII. These salts are formulated as resonance-stabilized structures XXVI,



XXVI

where Z^- is the corresponding monovalent anion (19).

In Table I are presented chemical shifts and coupling constants for many of the 4-substituted thieno[2,3-*b*]-pyridines and thieno[2,3-*b*]pyridines 7-oxides which are reported in this paper. In general, it will be noted that the four thienopyridine protons produce a series of four nmr doublets ($J_{2,3} \simeq 6$Hz, $J_{5,6}$ = 5-7 Hz) which occur in the order $\delta_6 > \delta_2 \geqslant \delta_3 > \delta_5$. A clear exception to this order is found for III, wherein the 4-nitro group shifts the signals for H-3 and H-5 downfield by *ca.* 1 ppm each. It is noteworthy that the 4-NH- group, on the other hand, causes a large upfield shift of the H-5 signal, but far less change in the position of the H-3 signal.

Pharmacologically, compounds XIII are of special interest since they are isosteres of the 4-dialkylamino-alkylaminoquinoline antimalarial drugs (21). Biological tests under auspices of the U. S. Army antimalarial screening project showed high activity of XIIIb (as its bis-hydro-orthophosphate monohydrate salt) *versus Plasmodium gallinaceum* in the form of sporozoites in the salivary glands and oocysts in the midgut of the mosquito *Aedes aegypti.* However, similar activity of XIIIb has not been found in higher animals as hosts to these parasites (22). A summary of test results on XIIIb and other substituted thieno[2,3-*b*]pyridines is presented in Table II (Experimental Section).

EXPERIMENTAL (23)

Thieno[2,3-*b*]pyridine 7-Oxide (II).

A mixture of 27 g. (0.2 mole) of freshly distilled thieno[2,3-*b*]-pyridine (I) (4), 68 ml. (0.67 mole) of 30% hydrogen peroxide,

TABLE I

Nuclear Magnetic Resonance Data for 4-Substituted Thieno[2,3-*b*]pyridines and Their 7-Oxides

Compound No.	Substituents Present at C-4	at N	Solvent (a)	Chemical Shift, in δ H-2	H-3	H-5	H-6	$J_{2,3}$ in Hz	$J_{5,6}$ in Hz	Other Signals
II	H	O	A	7.59	7.34	7.31	8.33	5.8	6	7.76 (d of doublets; $J_{4,5}$ = 8, $J_{4,6}$ = 1; H-4)
III	NO_2	O	B	8.02	8.29	8.37	8.62	6	7	
VI (b)	NH_2	-	A	7.26	7.10	6.41	8.16	6	5.5	*ca.* 4.6 (broad s, NH_2)
VII	NHCH(Ph)NH(4′-TP) (c)	-	AB	7.86	7.42	6.52	8.09	6	5.5	3.38 (s, PhC*H*), *ca.* 6.3 (broad, NH) (d)
VIII		-	A	7.42	7.36 (e)	6.71	8.47	5-6	5	3.00 (s, 6H, CH_3), 6.68 (d, $J_{2',3'}$ = 9, H-3′ and H-5′) (f)
X		-	A	7.19	7.13 (g)	6.42	8.21	(h)	5.5	2.93 (s, 6H, CH_3), 4.34 (d, J_{CH_2NH} = 5, 2H, CH_2) (i)
XI	Cl	O	A	7.64	7.40	7.30	8.24	6	6.6	
XIIa	$NHCH_2CH_2NEt_2$	O	A	7.64	7.35	6.37	8.11	5.8	7	1.02 (t, J_{Et} = 7, 6H, CH_3), 2.3-2.9 [m, 6H, -CH_2N(CH_2CH_3)$_2$] (j)
XIIb	$NHCH_2CH_2CH_2NMe_2$	O	A	7.42	7.38 (g)	6.33	8.11	6	7	1.6-2.7 (m, 10H total, 4H for $NHCH_2CH_2CH_2N$) (k)
XIIc	$NHCH_2CH_2CH_2NEt_2$	O	A	7.63	7.42	6.38	8.18	6	7	1.04 (t, 6H, CH_3), 1.4-2.1 (m, 2H, $NHCH_2CH_2CH_2N$) (ℓ)
XIId	$NHCH_2CH_2CH_2N(n\text{-}Bu)_2$	O	A	7.50	7.38	6.33	8.10	5.8	7	0.5-2.1 [complex m, 16H, $N(CH_2CH_2CH_2CH_3)_2$ and $NHCH_2CH_2CH_2N$] (m)
XIIIa	$NHCH_2CH_2\overset{+}{N}HEt_2\ HSO_4^-$	$H^+\ HSO_4^-$	C	7.72	7.62 (e)	6.93	8.36	6	7	1.47 (broadened t, J_{Et} = 7, 6H, CH_3) (n)
XIIIc	$NHCH_2CH_2CH_2\overset{+}{N}HEt_2\ HSO_4^-$	$H^+\ HSO_4^-$	C	7.67	7.48	6.80	8.22	6	7	1.47 (t, J_{Et} = 7.5, 6H, CH_3), (o)
XV	$NH(CH_2)_5OH$	O	AB	7.83	7.60	6.47	8.06	6	7	1.2-2.0 (m, 6H, $NHCH_2CH_2CH_2CH_2CH_2OH$) (p)
XVI	$NH(CH_2)_5OH$	-	AB	7.65	7.37	6.38	8.09	6	5.5	1.1-2.0 (m, 6H, $NHCH_2CH_2CH_2CH_2CH_2OH$) (q)

(a) A is deuteriochloroform; B, DMSO-d_6; AB, a mixture of A and B; and C, deuterium oxide with sodium γ-trimethylsilylpropanesulfonate as internal standard. (b) See ref. 5. (c) 4′-TP is 4-thieno[2,3-*b*]pyridyl. (d) Also *ca.* 7.5 (broad, C_6H_5). (e) Assignments for H-2 and H-3 may be reversed. (f) Also 7.80 (d, 2H, H-2′ and H-6′), 8.32 (s, 1H, –N=CH-). (g) H-2 and H-3 signals occur as a pseudotriplet. Assignments may be reversed. (h) Signals for H-2 and H-3 are obscured by those for H-2′ and H-6′. (i) Also *ca.* 5.1 (broad, 1H, NH), 6.70 (d, $J_{2',3'}$ = 8.5, 2H, H-3′ and H-5′), 7.23 (d, H-2′ and H-6′). (j) Also 3.1-3.5 (m, 2H, $NHCH_2$), 6.89 (broad t, 1H, NH). (k) Plus 6-H singlet at 2.31 for CH_3), 3.1-3.6 (m, 2H, $NHCH_2$). (ℓ) Also 2.3-2.9 [complex m, 6H, $CH_2N(CH_2CH_3)_2$], 3.1-3.6 (m, 2H, $NHCH_2$), *ca.* 7.2 (broad, overlapping the H-6 signal, NH). (m) Also 2.1-2.8 [m, 6H, -$CH_2N(CH_2CH_3)_2$], 3.1-3.5 (m, $NHCH_2$), *ca.* 6.9 (broad, 1H, NH). (n) Also 3.2-4.3 (complex m, 8H, CH_2 groups). (o) Also 2.1-2.6 (broad, 2H, $NHCH_2CH_2CH_2N$), 3.1-3.9 [m, 8H, $NHCH_2CH_2CH_2N(CH_2CH_3)_2$]. (p) Also 3.0-3.7 (m, 4H, $NHCH_2$ and CH_2OH), *ca.* 4.1 (broad, 1H, OH), *ca.* 7.3 (broad t, 1H, NH). (q) Also 3.0-3.7 (overlapping multiplets, 4H, $NHCH_2$ and CH_2OH), 4.25 (s, 1H, OH), 6.93 (broad t, J_{CH_2NH} = 5.5, NH).

and 60 ml. of glacial acetic acid was heated at 55° for 24 hours and then poured into 400 ml. of water. This mixture was cooled, neutralized with solid sodium bicarbonate, treated with solid sodium bisulfite until a test with starch-iodide paper was no longer positive, and extracted repeatedly with chloroform. Evaporation of the dried extracts and crystallization of the residue from acetane-cyclohexane gave 16.1 g. (53%) of white solid, m.p. 87-89°. Recrystallizations from chloroform-carbon tetrachloride followed by evaporative distillation at 120° (0.4 mm.) gave colorless prisms, m.p. 93-94°; ir (chloroform) 1250 cm^{-1} (N → O).

Anal. Calcd. for C_7H_5NOS: C, 55.61; H, 3.33; N, 9.26; S, 21.21. Found: C, 55.59; H, 3.18; N, 9.12; S, 21.00.

When the preceding anhydrous product was allowed to equilibrate with the laboratory atmosphere it absorbed moisture equivalent to the formation of II dihydrate. This product crystallized from ether-acetonitrile as colorless needles, m.p. 54.5-55.5°; ir (chloroform) 1260 cm^{-1} (N → O); positive Katritsky test (10). Drying the dihydrate *in vacuo* at room temperature for 20 hours regenerated the anhydrous form (which was used in all subsequent reactions).

4-Nitrothieno[2,3-*b*]pyridine 7-Oxide (III).

To a stirred mixture of 13.9 ml. (0.25 mole) of 96% sulfuric acid and 15.9 ml. (0.25 mole) of 70% nitric acid at 0° were added, in small quantities, 15.1 g. (0.1 mole) of anhydrous II. The resulting mixture was heated rapidly to 90° and then slowly (over a period of 75 minutes) to 120°, where it was maintained for 45 minutes longer. The mixture was allowed to cool and then poured into a stirred mixture (*ca.* 400 g.) of ice and water. The yellow precipitate was collected by filtration, washed with water, dried at 100°, and recrystallized either (a) by extraction with boiling chloroform, concentration of the extract, and cooling (yield 9.8 g., 50%, m.p. 190-194°) or (b) directly from 95% ethanol-dimethylformamide. An analytical sample was obtained as deep orange prisms by repeated crystallization from chloroform-ligroin, m.p. 195-196° (sintering at 187°); ir (chloroform) 1525 (NO_2 asym. stretching), 1335 (NO_2 sym. stretching), 1280 cm^{-1} (N → O).

Anal. Calcd. for $C_7H_4N_2O_3S$: C, 42.85; H, 2.06; N, 14.28; S, 16.34. Found: C, 42.78; H, 2.40; N, 14.36; S, 16.48.

5-Nitrothieno[2,3-*b*]pyridine 7-Oxide (IV).

A mixture of 10 g. (0.066 mole) of II, 90 ml. of glacial acetic acid, and 4 ml. of 70% nitric acid (0.063 mole) was heated at 120° for 2 hours and then refluxed 7 hours longer. Excess solvent was removed by distillation, the *p*H of the residue was adjusted to 5, and the solution was extracted with chloroform. Charcoal treatment plus cooling of the extract gave 7 g. (54%, based on II) of crude IV, obtained as bright yellow platelets, m.p. 220-221°, on repeated crystallization from the same solvent; ir (chloroform) 1540 (NO_2 asym. stretching), 1350 (NO_2 sym. stretching), 1270 cm^{-1} (N → O); nmr (hexadeuterio-DMSO) δ_6 9.12 (d, $J_{4,6}$ = 1.5 Hz), δ_4 8.82 (d), δ_2 8.08 (d, $J_{2,3}$ = 5.5 Hz), δ_3 7.72 ppm (d).

Anal. Calcd. for $C_7H_4N_2O_3S$: C, 42.85; H, 2.06; N, 14.28; S, 16.34. Found: C, 42.66; H, 2.18; N, 14.20; S, 16.07.

4-Aminothieno[2,3-*b*]pyridine (VI).

A mixture of 1.96 g. (0.01 mole) of III, 2.8 g. (0.05 mole) of iron powder, and 50 ml. of glacial acetic acid was stirred at 100° for one hour. It was cooled, poured into water, basified with sodium hydroxide, and extracted first with ether and then with chloroform. Evaporation of the extracts gave a yellow solid which was crystallized (charcoal) from benzene to form 1.01 g. (67%) of white leaves of VI, m.p. 144.5-145.5°, identical in melting point and nmr spectrum with a sample of 4-aminothieno[2,3-*b*]pyridine prepared by treatment of 5-bromo[2,3-*b*]pyridine with potassium amide in liquid ammonia (5).

5-Aminothieno[2,3-*b*]pyridine (V).

A stirred mixture of 98 mg. of IV, 4 ml. of concentrated hydrochloric acid, and 356 mg. of granular tin was maintained at 25° (by cooling) for 12 hours. Basification of the mixture and extraction with chloroform gave (on evaporation of the extract) 31 mg. (41%) of long needles of V, m.p. 110-111°, identical in nmr spectrum with a sample of 5-aminothieno[2,3-*b*]pyridine obtained by hydrolysis of 5-acetylamino[2,3-*b*]pyridine (5).

4-(*p*-Nitrobenzylideneimino)thieno[2,3-*b*]pyridine (IX).

A mixture of 1.5 g. (0.01 mole) of amine VI, 1.51 g. (0.01 mole) of *p*-nitrobenzaldehyde, 50 ml. of xylene, 10 drops of glacial acetic acid, and 50 spheroids of activated molecular sieves (Linde, type 4A) was refluxed for 24 hours and filtered hot. The crude imine which precipitated from the chilled filtrate was collected by filtration, washed with ether, and dried *in vacuo*. Dilution of the mother liquor with hexane gave additional product. Crystallization from acetonitrile produced yellow needles, yield 1.32 g. (47%), m.p. 183.5-185° (sintering at 180°). Recrystallization from acetonitrile raised the melting point to 187-188° (sintering at 185°); ir (chloroform) 1630 (imino C=N), 1525 (NO_2 asym. stretching), 1345 cm^{-1} (NO_2 sym. stretching).

Anal. Calcd. for $C_{14}H_9N_3O_2S$: C, 59.35; H, 3.20; N, 14.84; S, 11.32. Found: C, 59.48; H, 3.22; N, 14.84; S, 11.44.

4-(*p*-Dimethylaminobenzylideneimino)thieno[2,3-*b*]pyridine (VIII).

In the foregoing manner, amine VI was condensed with *p*-dimethylaminobenzaldehyde. One crystallization of the crude product gave bright yellow prisms of VIII, 1.17 g. (42%), m.p. 140.5-141.5°, raised to 141.5-142.5° on recrystallization; ir (chloroform) 1630 cm^{-1} (imino C=N).

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.94; S, 11.40. Found: C, 68.63; H, 5.54; N, 14.84; S, 11.47.

4-(*p*-Dimethylaminobenzylamino)thieno[2,3-*b*]pyridine (X).

A mixture of 843 mg. (3 mmoles) of imine VIII, 114 mg. (3 mmoles) of sodium borohydride, and 30 ml. of absolute ethanol was refluxed for 2 hours, while the yellow color gradually faded. The mixture was poured into water, buffered to *p*H 7 by addition of glacial acetic acid and solid sodium bicarbonate, and extracted with chloroform. Evaporation of the organic extract and crystallization of the residue from acetonitrile gave 708 mg. (83%) of cream-colored plates, m.p. 171.5-172.5°; ir (chloroform) 3490 cm^{-1} (NH).

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.81; H, 6.05; N, 14.83; S, 11.32. Found: C, 67.86; H, 6.11; N, 14.65; S, 11.25.

α,α-Bis(4-thieno[2,3-*b*]pyridylamino)toluene (VII).

In the manner used to prepare IX, 500 mg. (3.3 mmoles) of amine VI was reacted with 385 mg. (3.6 mmoles) of benzaldehyde. The hot filtrate was evaporated to dryness to give an orange tarry product which was triturated with hexane-ether to leave a cream-colored powder. Repetitive evaporation-trituration of the triturate gave additional powder (total yield 488 mg.). Crystallization of the powder from acetonitrile formed 118 mg. (18%) of faintly cream-colored needles of VII, m.p. 133.5-134.5°, raised to 140-141° on recrystallization; ir (nujol-hexachlorobutadiene) 3250 cm^{-1} (NH).

Anal. Calcd. for $C_{21}H_{16}N_4S_2$: C, 64.91; H, 4.15; N, 14.42;

TABLE II

Antimalarial Screening Data for Some Thieno[2,3-*b*]pyridine Derivatives (a)

Compound No. (b)	Concentration (d)	For the Mosquito Test (c) (s) Toxic Deaths (%)	% Abnormal Oocysts Formed	% Suppression of Oocysts	% Suppression of Sporozoites	Other Test Results (e)(t)
II	0.01	26 (f)	0	0	0	R (g)
IV	0.1	6	0	0	100 (h)	RI, BI
X	0.1	20 (i)	0	50	0	RI
XIIb	0.1	37	0	25	0	
XIId	0.1	49	0	0	0	RI
XIIIa (j)	0.1	86	0	50	0	
XIIIb (k)	0.1	3	0	100	100	RI, BI
	0.01	6, 9	0	100	75, 100	
	0.001	6, 11	0, 100	100, 0	100	
	10^{-4}	3, 29	50, 25	25	75, 100	
	10^{-5}	23	0	0	0	
XIIIc (j)	0.1 (ℓ)	17, 43	0	25, 0	75	RI
XV	0.1	14	0	25	0	
XVI	0.1	80	50	0	0	
XVII	0.1	71	0	0	0	R (m)
2 (n)	0.1	14	0	25	0	RI
7 (o)	0.1	57	0	25	0	RI
12 (p)	0.1	100	--	--	--	RI
21 (q)	0.1	17	0	50	0	RI

(a) Conducted in the U. S. Army antimalarial screening project. (b) Arabic numbers refer to compounds reported in ref. 5. See also footnote *r*. (c) The test is performed on a standard strain of *Aedes aegypti* infected with *Plasmodium gallinaceum* (*cf.* report MEDEC-ZMB, Walter Reed Army Medical Center, Division of Medicinal Chemistry, Washington, D. C. 20012). (d) In % by wt. of sucrose solution used as food supply. (e) R = rodent test conducted at the University of Miami on mice infected with *Plasmodium berghei*. B = bird test conducted at the University of Miami on chicks infected with *Plasmodium gallinaceum*, I = inactive. (f) 100% at 0.1% concentration. (g) 100% toxic at 640 mg/kg. dosage. (h) Inactive at 0.01% concentration. (i) 34% in control group. (j) As bis-hydrosulfate salt. (k) As bis-hydroorthophosphate monohydrate salt. (ℓ) Inactive, non-toxic at 0.01%. (m) Toxic at $\geqslant$ 40 mg./kg. dosage; inactive, non-toxic at 10 mg./kg. (n) 5-Br derivative. (o) 5-Ac derivative. (p) 5-α-Acetothiomorpholide derivative. (q) 5-(2-Furylmethylamino) derivative. (r) Other data: Inactive, non-toxic at 0.1% concentration in the mosquito test--III (RI), V, VI (RI), XIIa (RI), XIIc. Inactive, non-toxic in the rodent test: V, **3** (5-chloro), **4** (5-hydroxy), **13** (5-acetylamino). (s) See ref. 26. (t) See ref. 27.

S, 16.51. Found: C, 65.17; H, 4.50; N, 14.20; S, 16.18.

Repetition of the reaction with a molar ratio of VI:benzaldehyde = 2:1 gave 22% yield (after crystallization) of VII and 43% of recovered VI.

N,N'-Bis(4-thieno[2,3-*b*]pyridine)oxamide (XIV).

To a stoppered flask containing a stirred solution of 750 mg. (5 mmoles) of amine VI in 40 ml. of chloroform was added all at once (by means of a syringe) 0.43 ml. (5 mmoles) of oxalyl chloride. After 30 minutes 1.5 ml. of diethylamine was added slowly and the mixture was stirred 1.5 hours longer. The mixture was washed with water and evaporated to furnish a tarry product which was triturated with ether. The resultant powder was crystallized from ethanol-dimethylformamide to form cream-colored needles, yield 63 mg. (7%), m.p. 266.5-268.5° (dec.); ir (nujol) 3280 (NH), 1685 cm^{-1} (carbonyl).

Anal. Calcd. for $C_{16}H_{10}N_4O_2S_2$: C, 54.23; H, 2.84; N, 15.81; S, 18.09. Found: C, 54.41; H, 3.21; N, 15.88; S, 18.12.

4-Chlorothieno[2,3-*b*]pyridine 7-Oxide (XI).

A suspension of 9.8 g. of 4-nitro compound III in 75 ml. of acetyl chloride was refluxed for 4 hours, during which time nitrogen oxides were evolved and an orange solution resulted. The cool solution was poured slowly into vigorously stirred ice and water. The filtered solution was brought to *p*H 8 and extracted with chloroform. Evaporation of the extract afforded 7.5 g. (81%) of yellow crystals, m.p. 189-193°. Recrystallizations from chloroform-petrol gave an analytical sample of white prisms, m.p. 197-198°; ir (chloroform) 1250 cm^{-1} (N $\rightarrow$ O).

Anal. Calcd. for C_7H_4ClNOS: C, 45.29; H, 2.17; Cl, 19.10; N, 7.55; S, 17.27. Found: C, 45.28; H, 2.29; Cl, 18.93; N, 7.62; S, 17.07.

4-(ω-Dialkylaminoalkylamino)thieno[2,3-*b*]pyridine 7-Oxides (XII).

A mixture of 0.93 g. (5 mmoles) of chloro compound XI and

15 mmoles of anhydrous ω-dialkylaminoalkylamine (24) was heated at 100° for 15 hours. The cooled, dark brown mixture was stirred with 10-20 ml. of 5% aqueous sodium hydroxide solution and washed with 25-120 ml. of cyclohexane to remove unreacted amine. The aqueous layer was then extracted with 50-175 ml. of chloroform. This extract was evaporated nearly to dryness, treated with 40-200 ml. of cyclohexane, and refrigerated. The precipitated solid was separated and crystallized once from acetonitrile, yields 23-60% (melting range 1°). One recrystallization from the same solvent gave an analytical sample.

4-(β-Diethylaminoethylamino)thieno[2,3-*b*]pyridine 7-oxide (XIIa) formed long yellow needles, m.p. 175.5-176° (sintering at 170°); ir (chloroform) 3390 (NH), 1220 cm^{-1} (broad, N → O).

Anal. Calcd. for $C_{13}H_{19}N_3OS$: C, 58.84; H, 7.22; N, 15.83; S, 12.08. Found: C, 58.74; H, 7.15; N, 15.95; S, 12.15.

4-(γ-Dimethylaminopropylamino)thieno[2,3-*b*]pyridine 7-oxide (XIIb) formed yellow needles, m.p. 171.5-172°; ir (chloroform) 3255 (NH), 1250 cm^{-1} (N → O).

Anal. Calcd. for $C_{12}H_{17}N_3OS$: C, 57.34; H, 6.82; N, 16.71; S, 12.75. Found: C, 57.53; H, 6.91; N, 16.94; S, 12.70.

4-(γ-Diethylaminopropylamino)thieno[2,3-*b*]pyridine 7-oxide (XIIc) formed lustrous, cream-colored plates, m.p. 140-141°; ir (chloroform) 3220 (NH), 1245 cm^{-1} (N → O).

Anal. Calcd. for $C_{14}H_{21}N_3OS$: C, 60.19; H, 7.58; N, 15.04; S, 11.48. Found: C, 60.39; H, 7.52; N, 15.16; S, 11.33.

4-(γ-Di-*n*-butylaminopropylamino)thieno[2,3-*b*]pyridine 7-oxide (XIId) was more difficult to purify than were XIIa-XIIc due to the presence of acetonitrile-soluble tars. Each crystallization step involved charcoal treatment, fractional precipitation of tar plus XIId, decantation, and refrigeration of the decantate to give a crop of purified XIId. Repetitive dissolution-precipitation of the tarry residue gave additional quantities of purified XIId in the decantate. The analytical sample consisted of white leaflets, m.p. 83.5-84.5° (sintering at 80°); ir (chloroform) 3225 (NH), 1245 cm^{-1} (N → O).

Anal. Calcd. for $C_{18}H_{29}N_3OS$: N, 12.53; S, 9.56. Found: N, 12.28; S, 9.31.

4-(ε-Hydroxypentylamino)thieno[2,3-*b*]pyridine 7-Oxide (XV).

As in the preparation of XII, chlorocompound XI was heated with 5-amino-1-pentanol (Aldrich). Stirring the cooled, tarry mixture with aqueous sodium hydroxide solution caused separation of a cream-colored solid which was collected by filtration. The solid was washed with chloroform and then with ether, dried, and crystallized from methanol-ether to furnish yellow plates, dried *in vacuo* at 80° to remove methanol of crystallization, m.p. 183-184° (50%); ir (nujol-hexachlorobutadiene) 3300 (broad, OH and NH), 1235 cm^{-1} (N → O).

Anal. Calcd. for $C_{12}H_{16}N_2O_2S$: C, 57.14; H, 6.39; N, 11.11; S, 12.71. Found: C, 57.32; H, 6.52; N, 10.75; S, 12.80.

4-(ω-Dialkylaminoalkylamino)thieno[2,3-*b*]pyridines (XIII).

A stirred mixture of 2.5 mmoles of preceding 4-(ω-dialkylaminoalkylamino)thieno[2,3-*b*]pyridine 7-oxide (XIIa, XIIb, or XIIc), 560 mg. (10 mmoles) of iron powder, and 20-25 ml. of glacial acetic acid was heated at 100° for 2 hours. The cooled, dark brown mixture was poured into 100 ml. of water, basified with solid potassium hydroxide, and shaken with 200 ml. of ether. The emulsion-suspension was filtered through a pad of calcium carbonate to remove suspended iron compounds. Combined organic solutions (from separation of the ether layer, extraction of the aqueous layer with chloroform, and washings of the filter pad with 100 ml. each of ether and chloroform) were dried with anhydrous magnesium sulfate and evaporated to leave a brown liquid; ir (neat) *ca.* 3300 cm^{-1} (NH). Crystalline derivatives of these crude products are described in the following paragraphs.

4-(β-Diethylaminoethylamino)thieno[2,3-*b*]pyridine (XIIIa).

Some preceding, crude XIIIa was treated with excess picric acid in aqueous ethanol. The dried precipitate was recrystallized from acetonitrile-95% ethanol to give XIIIa dipicrate, obtained as clusters of yellow prisms, m.p. 210-211° (47% yield based on XIIa); ir (nujol-hexachlorobutadiene) 3400 (NH), 1520 (NO_2 asym. stretching), 1300 cm^{-1} (NO_2 sym. stretching).

Anal. Calcd. for $C_{25}H_{25}N_9O_{14}S$: C, 42.43; H, 3.56; N, 17.82; S, 4.53. Found: C, 42.67; H, 3.69; N, 17.71; S, 4.90.

A stirred solution of other crude XIIIa in anhydrous ether was treated dropwise with excess 96% sulfuric acid. The gum which precipitated immediately was transformed into a white solid on further stirring. This solid was collected by filtration, washed with ether, dried *in vacuo*, and crystallized from methanol-ether as white needles of XIIIa bis-hydrosulfate (63% from XIIa), m.p. 223-224.5° (sintering at 220°); ir (nujol-hexachlorobutadiene) 3250 (NH), 1160, 1010, and 880 cm^{-1} (broad, HSO_4^-).

Anal. Calcd. for $C_{13}H_{23}N_3O_8S_3$: C, 35.03; H, 5.20; N, 9.43; S, 21.59. Found: C, 34.95; H, 5.18; N, 9.32; S, 21.69.

4-(γ-Dimethylaminopropylamino)thieno[2,3-*b*]pyridine (XIIIb).

To a stirred solution of the foregoing crude XIIIb in 40 ml. of anhydrous ether was added dropwise excess 86% orthophosphoric acid. Since the precipitated gum did not crystallize on extended stirring alone, the mixture was treated with 5 ml. of ethanol and 2-3 ml. of water and stirred 16 hours longer. The resultant white solid was collected by filtration, washed with methanol-ether, and crystallized from aqueous dimethylformamide to give clusters of white needles of XIIIb bis-hydroorthophosphate monohydrate (50% from XIIb), m.p. 214.5-215.5°; ir (nujol) 3340 (NH or H_2O), 1100 cm^{-1} (broad, $H_2PO_4^-$).

Anal. Calcd. for $C_{12}H_{25}N_3O_9P_2S$: C, 32.07; H, 5.61; N, 9.35; P, 13.79; S, 7.13. Found: C, 32.21; H, 5.62; N, 9.10; P, 13.66; S, 7.17.

4-(γ-Diethylaminopropylamino)thieno[2,3-*b*]pyridine (XIIIc).

A stirred ether solution of foregoing crude XIIIc was treated with sulfuric acid (as for XIIIa) to give a gum, which crystallized on addition of a small amount of methanol. The solid was crystallized from methanol-ether to give cream-colored needles (61% from XIIc) of XIIIc bishydrosulfate, m.p. 184.5-185.5°; ir (nujol-hexachlorobutadiene) 3320 (NH), 1150, 1010, and 890 cm^{-1} (broad, HSO_4^-).

Anal. Calcd. for $C_{14}H_{25}N_3O_8S_3$: C, 36.59; H, 5.48; N, 9.14; S, 20.92. Found: C, 36.42; H, 5.60; N, 9.07; S, 20.63.

4-(ε-Hydroxypentylamino)thieno[2,3-*b*]pyridine (XVI).

As in the conversion of XII to XIII, amino-*N*-oxide XV was reduced with iron and acetic acid, but at 100° for 4 hours. Extraction with ether alone, concentration of the dried extract to a small volume, and stirring gave a powder (44% yield), which formed faintly tan prisms on crystallization from acetonitrile, m.p. 96-97°; ir (nujol-hexachlorobutadiene) 3330 (OH), 3200 and 1580 (NH), 1360 and 1050 cm^{-1} (OH).

Anal. Calcd. for $C_{12}H_{16}N_2OS$: C, 60.98; H, 6.83; N, 11.85; S, 13.57. Found: C, 61.07; H, 6.93; N, 11.73; S, 13.22.

2,3-Dichloro-2,3-dihydrothieno[2,3-*b*]pyridine 1-Oxide (XVII).

Chlorine gas was passed into a refluxing mixture of 18 g. of I, 150 ml. of chloroform, and 10 ml. of water for 3 hours. Most of the solvent was removed *in vacuo*. The residue was basified with

saturated aqueous sodium bicarbonate solution and extracted with more chloroform. Evaporation of this extract gave 6.9 g. of brown crystals, m.p. 143-147° (25). Evaporative distillation at 150° (0.3 mm) and repetitive crystallizations from benzene-cyclohexane and benzene alone gave white prisms, m.p. 163-164° (sintering at 150°); ir (chloroform) 1060 cm^{-1} (S=O); nmr (hexadeuterio-DMSO-deuteriochloroform) δ_6 8.96 (d of doublets, $J_{4,6}$ = 2 Hz, $J_{5,6}$ = 5 Hz), δ_4 8.26 (d of doublets, $J_{4,5}$ = 8 Hz), δ_5 7.82 (d of doublets), δ_2 5.88 (d, $J_{2,3}$ = 5.5 Hz), δ_3 5.57 ppm (d).

Anal. Calcd. for $C_7H_5Cl_2NOS$: C, 37.85; H, 2.27; Cl, 31.93; N, 6.31; S, 14.44. Found: C, 37.87; H, 2.68; Cl, 31.80; N, 6.35; S, 14.33.

This compound was a skin irritant to one of the authors.

Antimalarial Screening Tests.

Data obtained in antimalarial screening tests are presented in Table II.

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