

## Synthesis of 2-Pyridyl- $\alpha$ -toluenesulfonates as Antimalarials

M. HAMER<sup>\*</sup>, O. F. BATZER, M. J. MOATS, C. C. WU, and  
E. P. LIRA

**Abstract** □ A series of substituted 2-pyridyl- $\alpha$ -toluenesulfonates was synthesized for antimalarial testing. They were prepared by treating various 2-pyridinols with  $\alpha$ -toluenesulfonyl chlorides in the presence of an alkali. In tests against *Plasmodium berghei* in mice at 640 mg/kg, only 3,5-dichloro-2-pyridyl- $\alpha$ -toluenesulfonate was considered active, *i.e.*, doubled the mean survival time.

**Keyphrases** □ 2-Pyridyl- $\alpha$ -toluenesulfonates—synthesis, screened for antimalarial activity □ Antimalarials, potential—synthesis and screening of 2-pyridyl- $\alpha$ -toluenesulfonates

Some time ago, a series of alkanesulfonate esters of variously substituted 2-pyridinols was prepared in these laboratories (1). In connection with this earlier study, some  $\alpha$ -toluenesulfonates also were prepared. One of these, 3,5-dichloro-2-pyridyl- $\alpha$ -toluenesulfonate (I), was found to be active against *Plasmodium berghei* in mice. The mean survival time (MST) for mice treated with I at 640 mg/kg was 15.8 days; for controls, it was 6.1 days. Consequently, a series of substituted 2-pyridyl- $\alpha$ -toluenesulfonates was prepared for antimalarial testing<sup>1</sup>.

### DISCUSSION

These compounds were prepared mainly by treatment of a 2-pyridinol<sup>2</sup> with an  $\alpha$ -toluenesulfonyl chloride in toluene at 25° in the presence of a small excess of triethylamine (Scheme I). The yields were generally in the range of 30–90%. In two instances, the insolubility of the pyridinol in the toluene and triethylamine mixture necessitated the use of 1% KOH or 1% NaOH in the Schotten-Baumann procedure (Table I, XXV and XXIX).

Sulfonylation of the 2-pyridinols occurred at the oxygen in all but one case. The single exception was the product from the reaction of 5-carbethoxy-3-chloro-2-pyridinol with  $\alpha$ -toluenesulfonyl chloride. The insolubility of this pyridinol also required the use of 1% KOH. In this case, only the *N*-substituted product was isolated, as evidenced by its IR and UV spectra (see *Experimental*).

Previous work from these laboratories showed that the products from the reaction of various 2-pyridinols with alkanesulfonyl chlorides gave exclusively sulfonate esters (1). When various arenesulfonyl chlorides were used with a specific 2-pyridinol, 3,5-dichloro-2-pyridinol, both *O*- and *N*-sulfonated products resulted (2) in each case.

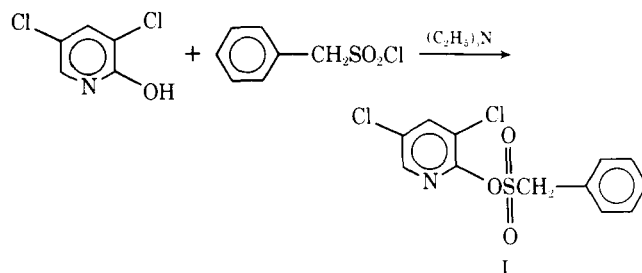
Four of the 2-pyridinols employed have not previously been reported (Table II). The product resulting from the chlorination of 3-methoxy-2-pyridinol at 25° in 10% hydrochloric acid (Table II, XXXII) proved to be the 6-chloro isomer, as evidenced by its

NMR spectrum. Chlorination of 4-methyl-2-pyridinol [from diazotization and hydrolysis (3) of 2-amino-4-picoline] gave the previously unreported 3,5-dichloro-4-methyl-2-pyridinol (Table II, XXXIII). The intermediate 5-carbethoxy-3-chloro-2-pyridinol (Table II, XXXIV) was synthesized *via* chlorination of the reported (4) 5-carbethoxy-2-pyridinol. Attempts at chlorinating the acid (6-hydroxynicotinic acid) prior to esterification were unsuccessful.

The reported 5-chloro-3-methyl-2-pyridinol (5) was obtained by chlorination of 3-methyl-2-pyridinol. However, when 5-methyl-2-pyridinol was chlorinated under the same conditions in an attempt to prepare the 3-chloro derivative, a semisolid was obtained which could not be purified by distillation or recrystallization without decomposition. This material gave a positive test for an active halogen with alcoholic silver nitrate, and treatment with dilute sodium hydroxide at 25° gave an intensely dark-violet solution within 5 min.

The known 3,5-dichloro-6-methyl-2-pyridinol (5) was prepared from 3-methyl-2-pyridinol. Chlorination (5) or bromination (6) of 2-pyridinol at room temperature in dilute mineral acid gave the 3,5-dihalo product in good yield; the 3,5-dinitro intermediate was obtained on treatment of 2-pyridinol with fuming nitric and sulfuric acids at 80° (7). Similarly prepared were the 3,5- and 5,3-chloronitro-2-pyridinols (8).

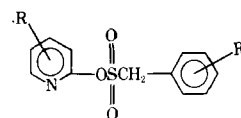
The  $\alpha$ -toluenesulfonyl chlorides were prepared by treatment of the appropriate chloromethylbenzene with sodium sulfite in refluxing 50% aqueous ethanol, and the sodium  $\alpha$ -toluenesulfonates thus obtained were treated with refluxing phosphorus oxychloride (Table III). This method worked fairly well with those chloromethylbenzenes that contained electronegative halogen groups. However, in the two cases where electron-donating methyl groups were present (Table III, XLI and XLII), the sodium salts were converted back to the original benzyl chlorides, instead of the expected sulfonyl chlorides, on treatment with refluxing phosphorus oxychloride. Presumably the sulfonyl chlorides formed and, activated by the 3- or 4-methyl, were displaced by a chloride ion. When the reactions were carried out with phosphorus oxychloride at a reduced temperature (60°), the desired 3- and 4-methyl- $\alpha$ -toluenesulfonyl chlorides were obtained. The unreported  $\alpha$ -toluenesulfonyl chlorides prepared are listed in Table III. The known  $\alpha$ -toluenesulfonyl chlorides utilized include: 2- and 4-chloro (9); 2,4- and 3,4-dichloro (9); 2-bromo, 3-chloro, and 2- and 3-fluoro (10); and 2,4,5-trichloro (11).



Scheme I

<sup>1</sup> Contract with the Walter Reed Army Institute of Research.

<sup>2</sup> Although the conventional name "2-pyridinol" is used throughout, spectroscopic evidence substantiates that the materials exist as the 2-pyridone (E. Spinner and J. C. B. White, *J. Chem. Soc. B*, 1966, 991).

Table I—2-Pyridyl- $\alpha$ -toluenesulfonates

Compound	R	R <sub>1</sub>	Melting Point	Re-crystallization Solvent <sup>a</sup>	Yield, %	Molecular Formula	Analysis, %	
							Calc.	Found
I	3,5-Cl <sub>2</sub> <sup>b</sup>	H	118–119°	A	61	C <sub>12</sub> H <sub>9</sub> Cl <sub>2</sub> NO <sub>3</sub> S	C 45.30 H 2.85 N 4.40	45.28 3.05 4.31
II	3,5-Cl <sub>2</sub>	2-Cl	86.5–88°	B	32	C <sub>12</sub> H <sub>8</sub> Cl <sub>3</sub> NO <sub>3</sub> S	C 40.87 H 2.29 N 3.97	40.65 2.32 3.80
III	3,5-Cl <sub>2</sub>	3-Cl	111.5–113.5°	B	68	C <sub>12</sub> H <sub>8</sub> Cl <sub>3</sub> NO <sub>3</sub> S	C 40.87 H 2.29 N 3.97	40.65 2.28 3.80
IV	3,5-Cl <sub>2</sub>	4-Cl	69.5–71°	C	51	C <sub>12</sub> H <sub>8</sub> Cl <sub>3</sub> NO <sub>3</sub> S	C 40.87 H 2.29 N 3.97	40.55 2.39 3.85
V	3,5-Cl <sub>2</sub>	2-Br	103–104.5°	B	71	C <sub>12</sub> H <sub>8</sub> BrCl <sub>2</sub> NO <sub>3</sub> S	C 36.30 H 2.03 N 3.53	36.43 2.15 3.33
VI	3,5-Cl <sub>2</sub>	3-Br	106.5–107.5°	B	92	C <sub>12</sub> H <sub>8</sub> BrCl <sub>2</sub> NO <sub>3</sub> S	C 36.30 H 2.03 N 3.53	36.03 2.19 3.30
VII	3,5-Cl <sub>2</sub>	4-Br	83.5–84.5°	B	24	C <sub>12</sub> H <sub>8</sub> BrCl <sub>2</sub> NO <sub>3</sub> S	C 36.30 H 2.03 N 3.53	36.07 1.87 3.36
VIII	3,5-Cl <sub>2</sub>	2-F	82–83.5°	A	56	C <sub>12</sub> H <sub>8</sub> Cl <sub>2</sub> FNO <sub>3</sub> S	C 42.87 H 2.40 N 4.17	43.03 2.69 4.12
IX	3,5-Cl <sub>2</sub>	3-F	120.5–121°	B	56	C <sub>12</sub> H <sub>8</sub> Cl <sub>2</sub> FNO <sub>3</sub> S	C 42.87 H 2.40 N 4.17	42.90 2.61 4.01
X	3,5-Cl <sub>2</sub>	4-F	80–88° <sup>c</sup>	A	15	C <sub>12</sub> H <sub>8</sub> Cl <sub>2</sub> FNO <sub>3</sub> S	C 42.87 H 2.40 N 4.17	42.70 2.47 4.14
XI	3,5-Cl <sub>2</sub>	2-CF <sub>3</sub>	65–66.5°	A	52	C <sub>13</sub> H <sub>8</sub> Cl <sub>2</sub> F <sub>3</sub> NO <sub>3</sub> S	C 40.43 H 2.09 N 3.63	40.19 2.36 3.47
XII	3,5-Cl <sub>2</sub>	3-CF <sub>3</sub>	84–86°	B	62	C <sub>13</sub> H <sub>8</sub> Cl <sub>2</sub> F <sub>3</sub> NO <sub>3</sub> S	C 40.43 H 2.09 N 3.63	40.61 2.06 3.61
XIII	3,5-Cl <sub>2</sub>	4-CF <sub>3</sub>	97–105° <sup>c</sup>	A	60	C <sub>13</sub> H <sub>8</sub> Cl <sub>2</sub> F <sub>3</sub> NO <sub>3</sub> S	C 40.43 H 2.09 N 3.63	40.27 2.08 3.58
XIV	3,5-Cl <sub>2</sub>	2,4-Cl <sub>2</sub>	102–103°	B	57	C <sub>12</sub> H <sub>7</sub> Cl <sub>4</sub> NO <sub>3</sub> S	C 37.24 H 1.82 N 3.62	37.09 1.87 3.56
XV	3,5-Cl <sub>2</sub>	2,6-Cl <sub>2</sub>	126–127°	B	36	C <sub>12</sub> H <sub>7</sub> Cl <sub>4</sub> NO <sub>3</sub> S	C 37.24 H 1.82 N 3.62	37.08 1.82 3.50
XVI	3,5-Cl <sub>2</sub>	3,4-Cl <sub>2</sub>	137–138°	B	61	C <sub>12</sub> H <sub>7</sub> Cl <sub>4</sub> NO <sub>3</sub> S	C 37.24 H 1.82 N 3.62	37.14 1.82 3.53
XVII	3,5-Cl <sub>2</sub>	2,4,5-Cl <sub>3</sub>	129.5–131°	A	38	C <sub>12</sub> H <sub>6</sub> Cl <sub>5</sub> NO <sub>3</sub> S	C 34.19 H 1.44 N 3.32	34.30 1.67 3.35
XVIII	3,5-Cl <sub>2</sub>	2,3,4,5,6-F <sub>5</sub>	117–118°	B	66	C <sub>12</sub> H <sub>4</sub> Cl <sub>2</sub> F <sub>5</sub> NO <sub>3</sub> S	C 35.30 H 0.99 N 3.43	35.16 1.23 3.49
XIX	3,5-Cl <sub>2</sub>	3-CH <sub>3</sub>	69–71°	A	62	C <sub>13</sub> H <sub>11</sub> Cl <sub>2</sub> NO <sub>3</sub> S	C 47.00 H 3.34 N 4.22	47.10 3.35 4.11
XX	3,5-Cl <sub>2</sub>	4-CH <sub>3</sub>	80–80.5°	A	45	C <sub>13</sub> H <sub>11</sub> Cl <sub>2</sub> NO <sub>3</sub> S	C 47.00 H 3.34 N 4.22	47.10 3.38 4.19
XXI	3-Br, 5-Cl	H	117–118°	B	48	C <sub>12</sub> H <sub>9</sub> BrClNO <sub>3</sub> S	C 39.75 H 2.50 N 3.86	39.91 2.48 3.84
XXII	5-Br, 3-Cl <sup>d</sup>	H	121–122°	A	66	C <sub>12</sub> H <sub>9</sub> BrClNO <sub>3</sub> S	C 39.75 H 2.50 N 3.86	39.70 2.55 3.67
XXIII	3,5-Br <sub>2</sub>	H	126–126.5°	A	34	C <sub>12</sub> H <sub>9</sub> Br <sub>2</sub> NO <sub>3</sub> S	C 35.40 H 2.23 N 3.44	35.53 2.36 3.35
XXIV	5-Cl, 3-CH <sub>3</sub>	H	135.5–136°	D	72	C <sub>13</sub> H <sub>12</sub> ClNO <sub>3</sub> S	C 52.44 H 4.06 N 4.70	52.53 3.96 4.71

Table I—Continued

Compound	R	R <sub>1</sub>	Melting Point	Re-crystallization Solvent <sup>a</sup>	Yield, %	Molecular Formula	Analysis, %	
							Calc.	Found
XXV	6-Cl, 3-OCH <sub>3</sub> <sup>e</sup>	H	131.5–132.5°	D	17	C <sub>13</sub> H <sub>12</sub> ClNO <sub>4</sub> S	C 49.77 H 3.86 N 4.47	49.69 3.95 4.58
XXVI	3-Cl, 5-NO <sub>2</sub>	H	102.5–103°	A	24	C <sub>12</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>5</sub> S	C 43.85 H 2.76 N 8.52	43.96 2.89 8.59
XXVII	5-Cl, 3-NO <sub>2</sub>	H	103–104°	A	71	C <sub>12</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>5</sub> S	C 43.85 H 2.76 N 8.52	43.90 2.88 8.46
XXVIII	3,5-Cl <sub>2</sub> , 4-CH <sub>3</sub> <sup>f</sup>	H	134–135°	A	61	C <sub>13</sub> H <sub>11</sub> Cl <sub>2</sub> NO <sub>3</sub> S	C 47.00 H 3.34 N 4.22	47.34 3.28 4.31
XXIX	3,5-Cl <sub>2</sub> , 6-CH <sub>3</sub> <sup>g</sup>	H	110.5–111.5°	— <sup>h</sup>	17	C <sub>13</sub> H <sub>11</sub> Cl <sub>2</sub> NO <sub>3</sub> S	C 47.00 H 3.34 N 4.22	46.92 3.43 4.11
XXX	3,5,6-Cl <sub>3</sub>	H	123–124°	A	76	C <sub>12</sub> H <sub>8</sub> Cl <sub>3</sub> NO <sub>3</sub> S	C 40.87 H 2.29 N 3.97	41.20 2.32 3.77

<sup>a</sup> A = isopropanol, B = cyclohexene, C = cyclohexane, and D = ethyl acetate. <sup>b</sup> NMR (CDCl<sub>3</sub>): δ 4.93 (s, 2H, CH<sub>2</sub>), 7.47 (m, 5H, phenyl), 7.85 (d, 1H, pyridyl, *J*<sub>AB</sub> = 2.5 Hz), and 8.52 (d, 1H, pyridyl, *J*<sub>AB</sub> = 2.5 Hz) ppm. <sup>c</sup> Single spot on TLC (silica gel, hexane). <sup>d</sup> NMR (CDCl<sub>3</sub>): δ 4.91 (s, 2H, CH<sub>2</sub>), 7.43 (m, 5H, phenyl), 7.95 (d, 1H, pyridyl, *J*<sub>AB</sub> = 2.5 Hz), and 8.52 (d, 1H, pyridyl, *J*<sub>AB</sub> = 2.5 Hz) ppm. <sup>e</sup> Prepared using 1% NaOH as the base: NMR (CDCl<sub>3</sub> + CD<sub>3</sub>SOCD<sub>3</sub>): δ 3.86 (s, 3H, OCH<sub>3</sub>), 4.90 (s, 2H, CH<sub>2</sub>), 7.45 (m, 5H phenyl), 7.45 (d, 1H, pyridyl, *J*<sub>AB</sub> = 2.5 Hz), and 7.90 (d, 1H, pyridyl, *J*<sub>AB</sub> = 2.5 Hz) ppm. <sup>f</sup> NMR (CDCl<sub>3</sub>): δ 2.51 (s, 3H, CH<sub>3</sub>), 4.91 (s, 2H, CH<sub>2</sub>), 7.47 (m, 5H, phenyl), and 8.24 (s, 1H, pyridyl) ppm. <sup>g</sup> Prepared using 1% KOH as the base; NMR (CDCl<sub>3</sub>): δ 2.62 (s, 3H, CH<sub>3</sub>), 4.93 (s, 2H, CH<sub>2</sub>), 7.44 (m, 5H, phenyl), and 7.80 (s, 1H, pyridyl). <sup>h</sup> Purified on silica gel column, eluting with benzene–hexane (1:1).

Table II—Unreported 2-Pyridinols

Compound	R	Melting Point	Re-crystallization Solvent <sup>a</sup>	Yield, %	Molecular Formula	Analysis, %	
						Calc.	Found
XXXI	5-Br, 3-Cl	199–201°	A	73	C <sub>7</sub> H <sub>5</sub> BrClNO	C 28.81 H 1.45 N 6.72	28.81 1.62 6.69
XXXII	6-Cl, 3-OCH <sub>3</sub> <sup>b</sup>	196–197°	B	48	C <sub>6</sub> H <sub>6</sub> ClNO <sub>2</sub>	C 45.16 H 3.79 N 8.78	44.97 3.76 8.83
XXXIII	3,5-Cl <sub>2</sub> , 4-CH <sub>3</sub> <sup>c</sup>	192–193.5°	B <sup>d</sup>	53	C <sub>6</sub> H <sub>5</sub> Cl <sub>2</sub> NO	C 40.48 H 2.83 N 7.87	40.70 2.66 7.91
XXXIV	5-CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> , 3-Cl <sup>e</sup>	178–178.5°	C	39	C <sub>8</sub> H <sub>8</sub> ClNO <sub>3</sub>	C 47.66 H 4.00 N 6.95	47.89 4.15 6.92

<sup>a</sup> A = isopropanol, B = ethanol, and C = butanone. <sup>b</sup> NMR (CDCl<sub>3</sub> + CD<sub>3</sub>SOCD<sub>3</sub>): δ 3.8 (s, 3H, CH<sub>3</sub>), 6.7 (d, 1H, pyridyl), 7.0 (d, 1H, pyridyl), and 13.2 (diffuse, 0.6H, N—H) ppm. <sup>c</sup> NMR (CDCl<sub>3</sub>): δ 2.48 (s, 3H, CH<sub>3</sub>), 7.47 (s, 1H, pyridyl), and ~12.5 (diffuse, 1H, N—H) ppm. <sup>d</sup> Analytical sample was recrystallized from 95% ethanol; previously from ethyl acetate. <sup>e</sup> NMR (CDCl<sub>3</sub>): δ 1.37 (t, 3H, CH<sub>3</sub>), 4.32 (q, 2H, CH<sub>2</sub>), 8.11 (d, 1H, pyridyl), and 8.15 (d, 1H, pyridyl) ppm.

## EXPERIMENTAL

**Activity**—This series of compounds was tested<sup>3</sup> for blood schizonticidal antimalarial activity according to a literature method (12).

Only one compound, 3,5-dichloro-2-pyridyl- $\alpha$ -toluenesulfonate (I), was considered active, *i.e.*, gave an increase in mean survival time of at least 100% (+6.1 days) in mice infected with *P. berghei*. It gave an increase in mean survival time of 9.7 days at 640 mg/kg. Two other compounds, 3,5-dichloro-2-pyridyl-4-chloro- $\alpha$ -toluenesulfonate (Table I, IV) and 3,5-dichloro-4-methyl-2-pyridyl- $\alpha$ -toluenesulfonate (Table I, XXVIII), caused significant prolongation of life with infected mice, but the increases were not sufficient for them to be considered active. They increased the mean survival

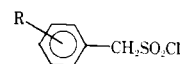
time by 5.6 (92%) and 4.9 (80%) days, respectively, at 640 mg/kg.

**Chemistry**—A single detailed example is given for the preparation of each of the two types of intermediates and also of an  $\alpha$ -toluenesulfonate ester and an *N*-sulfonated product. In cases where the experimental procedure differed markedly from the examples given, the details are given in the table footnotes.

**3-Bromo- $\alpha$ -toluenesulfonyl Chloride**—To a boiling solution of 3-bromobenzyl bromide<sup>4</sup> (20.0 g, 0.08 mole) in 50 ml of 95% ethanol was added a solution of sodium sulfite, 10.1 g (0.08 mole), in 50 ml of water, dropwise with stirring over about 0.5 hr. The mixture was heated at reflux for 64 hr and cooled. The crystals were removed by filtration, washed with benzene, and dried under vacuum over phosphorus pentoxide, giving 13.7 g (63%) of dried sodium salt. All of this material (0.05 mole) was treated with 40 ml of

<sup>3</sup> Rane Laboratory, University of Miami.

<sup>4</sup> In most of the cases, the benzyl chloride was used.

Table III—Unreported  $\alpha$ -Toluenesulfonyl Chlorides

Compound	R	Melting Point	Recrystallization Solvent <sup>a</sup>	Yield, %	Molecular Formula	Analysis, %	
						Calc.	Found
XXXV	3-Br	88.5–89.5°	A	62	C <sub>7</sub> H <sub>6</sub> BrClO <sub>2</sub> S	C 31.20 H 2.24	31.38 2.28
XXXVI	4-Br	108–109°	A	49	C <sub>7</sub> H <sub>6</sub> BrClO <sub>2</sub> S	C 31.20 H 2.24	31.11 2.58
XXXVII	4-F	25–30° <sup>b</sup>	—	14	C <sub>7</sub> H <sub>6</sub> ClFO <sub>2</sub> S	C 40.29 H 2.90	39.89 2.83
XXXVIII	2-CF <sub>3</sub>	37–39°	A	43	C <sub>8</sub> H <sub>6</sub> ClF <sub>3</sub> O <sub>2</sub> S	C 37.14 H 2.34	36.75 2.15
XXXIX	3-CF <sub>3</sub>	98–100°	—	62	C <sub>8</sub> H <sub>6</sub> ClF <sub>3</sub> O <sub>2</sub> S	C 37.14 H 2.34	36.79 2.37
XL	4-CF <sub>3</sub>	57–58°	A	59	C <sub>8</sub> H <sub>6</sub> ClF <sub>3</sub> O <sub>2</sub> S	C 37.14 H 2.34	36.83 2.44
XLI	3-CH <sub>3</sub>	50°	B	70 <sup>c</sup>	C <sub>8</sub> H <sub>9</sub> ClO <sub>2</sub> S	C 46.91 H 4.43	46.90 4.50
XLII	4-CH <sub>3</sub>	33°	B	33 <sup>c</sup>	C <sub>8</sub> H <sub>9</sub> ClO <sub>2</sub> S	C 46.91 H 4.43	46.93 4.44
XLIII	2,6-Cl <sub>2</sub>	47–50°	A	43	C <sub>7</sub> H <sub>5</sub> Cl <sub>2</sub> O <sub>2</sub> S	C 32.40 H 1.94	32.49 1.90
XLIV	2,3,4,5,6-F <sub>5</sub>	103° (3.5) <sup>d</sup>	—	16	C <sub>7</sub> H <sub>2</sub> ClF <sub>5</sub> O <sub>2</sub> S	C 29.96 H 0.72	30.09 0.63

<sup>a</sup>A = isopropanol, and B = cyclohexane. <sup>b</sup>Distilled at 120° (2.5 mm). <sup>c</sup>Treatment of the sodium  $\alpha$ -toluene sulfonate with phosphorus oxychloride was carried out at 60° instead of the usual 105°. <sup>d</sup>Boiling point (mm).

phosphorus oxychloride by heating at reflux for 18 hr.

The excess phosphorus oxychloride was removed under vacuum, and the residue was treated with ice and then extracted with ether. The ether extract was washed with water and then with sodium bicarbonate solution and dried over magnesium sulfate. The ether was removed by evaporation, and the residue was recrystallized from 2-propanol, giving 8.5 g (62%) of white solids, mp 88.5–89.5°.

*5-Bromo-3-chloro-2-pyridinol*—Into a solution of 5-bromo-2-pyridinol (20.8 g, 0.12 mole) in 70 ml of 12% hydrochloric acid was bubbled chlorine (8.5 g, 0.12 mole) over 30 min. Water was added to keep the mixture stirrable as solids precipitated. After the addition, the mixture was stirred another hour, and the solids were filtered, washed with water, and dried *in vacuo* to give 18.2 g (73%) of white solids, mp 195–200°.

Two recrystallizations from isopropanol raised the melting point to 199–201.5°.

*3,5-Dichloro-2-pyridyl- $\alpha$ -toluenesulfonyl chloride* (31.5 g, 0.165 mole) in 200 ml of toluene was added to a solution of 3,5-dichloro-2-pyridinol (27.0 g, 0.165 mole) in 100 ml of toluene and triethylamine (20.0 g, 0.20 mole) at 25° with cooling in 15 min. The mixture was stirred at 25° for 1 hr and filtered to remove triethylamine hydrochloride, which was washed with fresh toluene (150 ml). The washings were collected with the filtrate.

Excess triethylamine was removed by distilling about 375 ml, and this volume of fresh toluene was added back before washing, first with 4% sodium hydroxide and then with 1% acetic acid. The toluene was removed under vacuum, and the residue was stirred with 100 ml of cyclohexane after crystallization commenced. The mixture was filtered, and the solids were dried and purified by recrystallization from ethanol, giving 32.2 g (61%) of white crystals, mp 117–118°. The analytical sample was purified by another recrystallization from ethanol, mp 118–118.5°.

*5-Carboxy-3-chloro-1-( $\alpha$ -toluenesulfonyl)-2-pyridone*— $\alpha$ -Toluenesulfonyl chloride (3.4 g, 0.02 mole) in 80 ml of toluene was added to a solution of 5-carboxy-3-chloro-2-pyridinol (3.6 g, 0.02 mole) in 1% potassium hydroxide solution over 10 min at 22°. The mixture was then stirred for an additional 0.5 hr, while sufficient 5% potassium hydroxide solution was added to maintain the pH at 9–10. The reaction mixture was then filtered to remove unreacted 2-pyridinol (0.5 g, 14%). The aqueous layer was separated and acidified, yielding an additional 1.0 g (28%) of starting material.

The toluene layer was washed once with dilute sodium hydroxide and then with cold water until neutral and evaporated under vacuum. The crude solids left on evaporation were purified on a silica gel column by eluting first with hexane–benzene (3:1) to remove unreacted  $\alpha$ -toluenesulfonyl chloride, then with mixtures of

these solvents progressively richer in benzene, and finally with benzene alone to yield 0.7 g (11%) of white solids, mp 130–131°; NMR (deuteriochloroform):  $\delta$  1.32 (t, 3H, CH<sub>3</sub>), 4.29 (q, 2H, CH<sub>2</sub>), 5.13 (s, 2H, CH<sub>2</sub>), 7.35 (s, 5H, phenyl), 8.04 (d, 1H, pyridone,  $J_{AB}$  = 2.5 Hz), and 8.27 (d, 1H, pyridone,  $J_{AB}$  = 2.5 Hz,  $J_{AX}$  = 14 Hz) ppm; IR (potassium bromide):  $\lambda_{\max}$  5.8, 5.9, 7.1, 7.35, 7.85, 8.6, 11.2, and 13.2  $\mu$ m; UV (methanol):  $\lambda$  265 ( $\epsilon$  12.3  $\times$  10<sup>3</sup>) and 300 ( $\epsilon$  5.9  $\times$  10<sup>3</sup>) nm.

*Anal.*—Calc. for C<sub>15</sub>H<sub>14</sub>ClNO<sub>5</sub>S: C, 50.64; H, 3.97; N, 3.94. Found: C, 51.07; H, 4.09; N, 3.88.

## REFERENCES

- (1) M. Hamer, C. W. Huffman, and S. S. Ristich, *J. Agr. Food Chem.*, **18**, 57(1970).
- (2) M. Hamer and E. P. Lira, *J. Heterocycl. Chem.*, **9**, 215(1972).
- (3) O. Seide, *Chem. Ber.*, **57**, 791(1924).
- (4) C. Rath and F. Schiffman, *Ann.*, **487**, 127(1931).
- (5) M. P. Cava and N. K. Bhattacharya, *J. Org. Chem.*, **23**, 1614(1958).
- (6) A. E. Tschitschibabin and V. S. Tyashelowa, *J. Russ. Phys. Chem. Soc.*, **50**, 483(1920).
- (7) A. Signor, E. Schoffone, L. Biondi, and S. Bezzi, *Gazz. Chim. Ital.*, **93**, 65(1963).
- (8) T. Batkowski, *Rocz. Chem.*, **42**, 2079(1968).
- (9) C. Ziegler and J. M. Sprague, *J. Org. Chem.*, **16**, 621(1951).
- (10) B. A. Ekstrom and B. O. H. Sjöberg, U.S. pat. 3,471,474 (1969).
- (11) W. V. Farrar, *J. Chem. Soc.*, **1960**, 3063.
- (12) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431(1967).

## ACKNOWLEDGMENTS AND ADDRESSES

Received November 1, 1974, from *International Minerals & Chemical Corporation, IMC Plaza, Libertyville, IL 60048*

Accepted for publication March 25, 1975.

Supported by the U.S. Army Medical Research and Development Command under Contract DADA-17-73-C3117; it is contribution 1295 to the Army Research Program on Malaria.

The authors express their appreciation to Dr. Edgar E. Steck of the Walter Reed Army Institute of Research and to Dr. Raymond P. Mariella of Loyola University for their many helpful suggestions.

\* To whom inquiries should be directed.