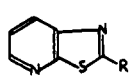
Studies in the Heterocyclic Series II. 3,6-Diazaphenothiazine Sulfoxides and Other Potential Antiparasitic and Pesticidal Agents[1]

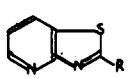
CHARLES OKOLO OKAFOR
Department of Chemistry, University of Nigeria, Nsukka, Nigeria

New derivatives of thiazolo(5,4-*b*)pyridine and 3,6-diazaphenothiazine are described. The yields of products spotlight a definite trend in the role of substituents in the conversion of pyridine derivatives to thiazolo(5,4-*b*)pyridines. Some derivatives of these compounds were hydrolyzed and converted to nitrothienyl pyridyl sulfides of antibacterial and pesticidal interests by reacting with 2-bromo-3,5-dinitrothiophene. The latter similarly reacts with aminopyridines to yield thienyl aminopyridines. In an attempt to convert 7-methoxy- and 7-chloro-1-nitro-3,6-diazaphenothiazines to their dinitro-3,6-diazaphenothiazine derivatives, only 7-methoxy- and 7-chloro-1-nitro-3,6-diazaphenothiazine sulfoxides, identified by their strong sulfoxide band in the 1035- to 1045-cm^{-1} region, were obtained. These new compounds were characterized.

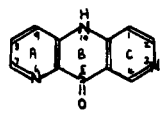
Because of increasing interest in thiazolopyridine (*1, 2*), nitrodiaryl sulfides (*3, 4*), and phenothiazine sulfoxide (*5, 6, 7*), as antiparasitic and pesticidal agents, a program aimed at extending their chemistry was initiated in these laboratories. In an earlier communication (*8*), a preliminary report on some thiazolo(4,5-*b*)pyridine derivatives (*9*) was made and in a subsequent paper (*10*) a novel 3,6-diazaphenothiazine system was reported. The substrate, 3,6-diazaphenothiazine, is the fourth reported phenothiazine analog bearing heteroatoms in all the three rings, A, B, and C, the first being 1,6-diazaphenothiazine (*11*).



2-Thiazolo(5,4-*b*)-pyridine derivative



2-Thiazolo(4,5-*b*)-pyridine derivative



3,6-Diazapheno-thiazine sulfoxide

In continuation of this work, the synthesis and properties of the isomeric thiazolo(5,4-*b*)pyridine system, nitrothienyl pyridyl sulfides and 3,6-diazaphenothiazine sulfoxides, are described.

DISCUSSION

Thiazolo(5,4-*b*)pyridines were obtained by treating 3-aminopyridines with potassium thiocyanate and bromine in acid medium at low temperatures. Results obtained from these laboratories suggest that the reaction is highly influenced by the substituent *para* to the 3-amino group. The yields show that electron-withdrawing groups *para* to the amino group retard the conversion to thiazolo(5,4-*b*)pyridine, while electron-releasing groups enhance the formation of the product. This conclusion was substantiated by the results obtained with 2-substituted-5-aminopyridines. It therefore spotlights a definite trend in the role of substituents in the conversion of aminopyridine derivatives to thiazolo(5,4-*b*)pyridines. This result is thus contrary to the previous report on 6-substituted-2-aminopyridine in which electron-withdrawing groups accelerate the reaction, leading to increased yields. Although a few of these compounds were reported previously (*12*), their yields and proper rationalization of substituent effects have not been reported. The compounds were converted to 2-acetamidothiazolo(5,4-*b*)pyridine derivatives by reaction with acetyl chloride in the presence of pyridine. Table I summarizes these results.

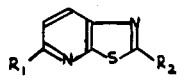
Hydrolysis of these compounds gave the corresponding 3-amino-2-mercaptopyridines. The latter compounds as well as the related aminopyridines were allowed to react with 2-bromo-3,5-dinitrothiophene, giving varying yields of (3,5-dinitro-2-thienyl)-2-pyridyl sulfides and amines similar structurally to their benzene analogs (*3, 4*), which have germicidal activity. The properties of these new compounds are outlined in Table II.

Despite the general success of these hydrolysis reactions, attempts to hydrolyze 5-*n*-butoxy-2-aminothiazolo(5,4-*b*)-pyridine even in 50% aqueous sodium hydroxide and for several hours were unsuccessful. In all cases, the starting materials were recovered in good yields. The failure of this reaction has been attributed to steric inhibition because the replacement of the methyl group (compound V) by the bulkier butyl group (compound IX) does not affect the inductive and conjugative effects of the saturated alkoxy groups to any appreciable extent. Like other compounds in that series, it was converted to the acetamido derivative by reaction with acetyl chloride.

In a previous report, some aminomercaptopyridines mentioned above were converted to 1-nitro-3,6-diazaphenothiazine derivatives (*10*). As an extension of this work and in an attempt to prepare the dinitro derivative, these compounds were allowed to react with mixed nitric and sulfuric acids. It was anticipated that since the 3- and 7-positions

[1] Part I was published in *J. Org. Chem.*, **32**, 2006 (1967).

Table I. Thiazolo(5,4-*b*)pyridine Derivatives[a]



Compound	R_1	R_2	Mp, °C	Yield, %	Recrystallization Solvent
I	H	NH_2	236–37	10	Ethanol
II	Cl	NH_2	247	91	Methanol
III	Cl	NHCOMe	263[b,c]	98	Ethanol-acetone
IV	OH	NH_2	251[b]	5	Ethanol
V	OMe	NH_2	201–02[b]	88	Chloroform
VI	OMe	NHCOMe	230[b]	99	Methanol
VII	OEt	NH_2	204[b,c]	92	Methanol
VIII	OEt	NHCOMe	230–31[b,c]	97	Methanol
IX	OBu	NH_2	140[c]	93	Methanol
X	OBu	NHCOMe	168–69[c]	95	Ethanol

[a] Elemental analyses for C, H, N, and S for the new compounds have been submitted for review and are in agreement with the theoretical values. [b] White needles. [c] Melts with decomposition.

were blocked, nitration would occur in the 9-position. Although a similar reaction with phenothiazine (*5*) and 1-nitro-3-azaphenothiazine (*13*) gave the 3,7-dinitro- and 1,7-dinitrosulfoxides, respectively, no nitration occurred in the case of 7-methoxy-1-nitro-3,6-diazaphenothiazine. In this case, only the sulfoxide, 7-methoxy-1-nitro-3,6-diazaphenothiazine sulfoxide, was obtained. Structural assignments were made by analysis and infrared spectra, which showed strong absorption at 1042 cm^{-1} corresponding to the S=O group. A similar result was obtained with 7-chloro-1-nitro-3,6-diazaphenothiazine.

EXPERIMENTAL

All melting points were determined in capillary tubes on an electrothermal Gallenkamp apparatus and were uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 237 spectrophotometer.

7-Methoxy-1-nitro-3,6-diazaphenothiazine Sulfoxide. To a stirred solution of 2.76 grams (0.01 mole) of 7-methoxy-1-nitro-3,6-diazaphenothiazine in 25 ml of concentrated sulfuric acid placed in an ice bath was added 10 ml of concentrated nitric acid drop by drop to ensure that the temperature of the solution never rose beyond 0° C. After all the nitric acid had been added, the mixture was stirred for 1 hour at 0° C and for an additional hour at room temperature. It was then poured onto a few cubes of ice and neutralized with concentrated ammonia solution which was added to a slight excess and later restored to yellow color by addition of a little dilute acetic acid. The yellow product which separated was collected by filtration and crystallized twice from ethanol after treatment with Norite to yield 2.05 grams (70%) of yellow crystals of 7-methoxy-1-nitro-3,6-diazaphenothiazine sulfoxide (mp 237–38° C).

Anal. Calcd. for $C_{11}H_8N_4SO_4$: C, 45.20; H, 2.76; N, 19.17; S. 10.97.

Found: C, 45.26; H, 2.71; N, 19.19; S, 11.04.

7-Chloro-1-nitro-3,6-diazaphenothiazine Sulfoxide. This compound was obtained by a procedure similar to that described above.

From 2.8 grams (0.01 mole) of 7-chloro-1-nitro-3,6-diazaphenothiazine, 1.54 grams (52%) of 7-chloro-1-nitro-3,6-diazaphenothiazine sulfoxide was obtained as yellow needles (mp 233–34° C).

Anal. Calcd. for $C_{10}H_5ClN_4SO_3$: C, 40.47; H, 1.70; N, 18.88; S. 10.81; Cl, 11.95.

Found: C, 40.55; H, 1.68; N, 19.00; S, 10.76; Cl, 12.02.

2-Aminothiazolo(5,4-*b*)pyridine, I. 3-Aminopyridine [14.6 grams, 0.15 mole (mp 65–66° C] was gradually added to a stirred mixture of potassium thiocyanate (67.1 grams, 0.9 mole) in 400 ml of glacial acetic acid previously cooled to −10° C. Bromine (15 ml) in 50 ml of glacial acetic acid was added drop by drop over a period of 1 hour while the temperature was maintained between −10° and −5° C. The mixture was stirred for an additional 5 hours at this temperature, and then at room temperature overnight. The orange residue was collected by filtration and the filtrate neutralized to pH 5 with solid sodium carbonate, with cooling. The use of a strong base such as potassium hydroxide was avoided, since thiazolo(5,4-*b*)pyridine hydrolyzes readily in strong basic conditions. The precipitated product was collected by filtration. The orange residue was boiled in water for 30 minutes, filtered, and neutralized to pH 5. This gave a combined yield of 2.27 grams (10%) of 2-aminothiazolo(5,4-*b*)pyridine, I (mp 236–37° C).

Anal. Calcd. for $C_6H_5N_3S$: C, 47.66; H, 3.33; N, 27.79; S, 21.21.

Found: C, 47.79; H, 3.38; N, 27.70; S. 21.10.

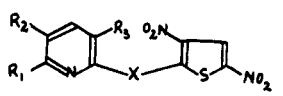
2-Acetamido-5-*n*-butoxythiazolo(5,4-*b*)pyridine, X. 2-Amino-5-*n*-butoxythiazolo(5,4-*b*)pyridine (2.23 grams, 0.01 mole) was mixed with 30 ml of acetyl chloride and 5 ml of pyridine. The mixture was refluxed with vigorous stirring at 140° for 3 hours. The brown solution was poured onto a few ice cubes, stirred, and cooled. The product was collected by filtration and recrystallized from methanol after treatment with Norite to give pure white glistening needles of 2-acetamido-5-*n*-butoxythiazolo(5,4-*b*)pyridine (2.5 grams, 94%) (mp 168–69° C).

Anal. Calcd. for $C_{12}H_{15}N_3O_2S$: C, 54.33; H, 5.70; N, 15.84; S, 12.09.

Found: C, 54.34; H, 5.68; N. 15.93; S, 12.16.

Other acylamido thiazolo(5,4-*b*)pyridines were prepared by a similar procedure.

Table II. (3,5-Dinitro-2-thienyl)-2-pyridyl Sulfides and Amines



Compound	R_1	R_2	R_3	X	Mp, °C.[a]	Yield, %	Formula	Reaction Time, Hr
XI	OMe	H	NH_2	S	240–241[b]	98	$C_{10}H_8N_4O_5S_2$	1
XII	Cl	H	NH_2	S	141–142[c]	67	$C_9H_5N_4O_4S_2Cl$	72
XIII	H	H	H	NH	250–251[c]	85	$C_9H_6N_4O_4S$	15
XIV	CH_3	H	H	NH	264–265[d]	88	$C_{10}H_8N_4O_4S$	45 min
XV	OH	H	H	NH	above 280[e]	94	$C_9H_6N_4O_5S$	1
XVIr	Ho	Cl	H	NH	248–249[d]	84	$C_9H_5N_4O_4SCl$	24

[a] Melt with decomposition. [b] Orange needles from acetone. [c] Pink microneedles from methanol. [d] Yellow microneedles from acetone. [e] Red crystals from ethanol.

Hydrolysis of 2-Aminothiazolo(5,4-*b*)pyridines. These compounds were hydrolyzed as described by Takahashi and Yoshii (*14*) and later modified by Okafor (*10*).

Attempted Hydrolysis of 2-Amino-5-*n*-butoxythiazolo(5,4-*b*)pyridine, IX. The procedure adopted here is similar to that described for the hydrolysis of 2-amino-5-methoxythiazolo(5,4-*b*)pyridine. The following concentrations were tried:—10, 20, 30, 40, and 50% sodium hydroxide solution and saturated barium hydroxide. Even after the reflux time was increased to 24 hours, no hydrolysis took place and in all cases the starting material was recovered in yields better than 80%.

(3,5-Dinitro-2-thienyl)-3-amino-6-methoxy-2-pyridyl Sulfide, XI. 6-Methoxy-3-amino-2-mercaptopyridine (1.56 grams, 0.01 mole) was dissolved in 40 ml of boiling methanol and added to a methanolic solution of 2-bromo-3,5-dinitrothiophene (*15*) (3.04 grams, 0.012 mole). The mixture was stirred in an ice bath for 2 hours. The yellow precipitate formed was collected by filtration and recrystallized from acetone after treatment with decolorizing carbon. Yellow plates of (3,5-dinitro-2-thienyl)-3-amino-6-methoxy-2-pyridyl sulfide separated (3.15 grams; 96%) (mp 240–41° C).

Anal. Calcd. for $C_{10}H_8N_4O_5S_2$: C, 36.58; H, 2.46; N, 17.06; S, 19.54.

Found: C, 36.39; H, 2.50; N, 17.05; S, 19.59.

Compound XII was prepared in a similar manner (mp 141–42° C).

3,5-Dinitro-2-thienyl-2-aminopyridines. These compounds, XIII to XVI, were prepared from 2-aminopyridine, 6-amino-2-picoline, 6-amino-2-pyridinol (*16*), and 2-amino-5-chloropyridine, respectively, by procedures similar to that reported for (3,5-dinitro-2-thienyl)-3-amino-6-methoxy-2-pyridyl sulfide, except that the reaction time varied as indicated in Table II.

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Organodichlorosilanes and Cyclotrisiloxanes Containing Polar Groups

TSE C. WU

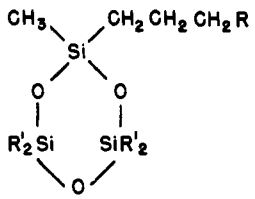
Silicone Products Department, General Electric Co., Waterford, N. Y. 12188

The preparation and properties of 28 new organodichlorosilanes and cyclotrisiloxanes containing polar groups are described.

A convenient way to introduce an organofunctional group into a polysiloxane is to synthesize a cyclotrisiloxane and to rearrange it into a polymer in the presence of a basic catalyst. To study the effects of some polar groups on the polysiloxane properties, some organocyclotrisiloxanes were prepared by condensing a tetrasubstituted disiloxane diol with a dichlorosilane. The dichloromethyl-(γ-substituted-propyl)silanes were prepared by adding dichloromethylsilane to an olefinic compound in the presence of a platinum catalyst. The reactions involved are shown below.

$$CH_3SiHCl_2 + CH_2{=}CHCH_2R \xrightarrow{Pt} RCH_2CH_2CH_2SiCH_3Cl_2 \quad (1)$$

$$RCH_2CH_2CH_2SiCH_3Cl_2 + HOSiO(SiR'_2O)_2SiOH \xrightarrow{\text{pyridine}}$$



(2)

The properties of 10 dichlorosilanes thus prepared are summarized in Tables I and II. The relatively low yields