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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF IMINOSULFURANES

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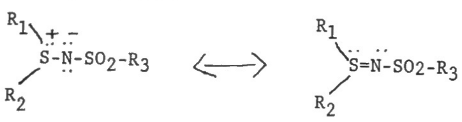
ABSTRACT

A new series of Thioxanthone and Diphenylenemethane iminosulfuranes have been prepared. [1] These compounds were tested against *Sarcina lutea* and *Bacillus subtilis* in the presence of an antibiotic medium I and IV. These compounds were shown to be inactive against *Plasmodium berghei* in mice.

INTRODUCTION

The formation of sulfur-nitrogen systems in iminosufurane is isoelectronic with the sulfonium ylid systems because in both ylids sulfur is hexavalent. For every sulfur ylid known, an isoelectronic sulfur-nitrogen compound could theoretically be prepared. (Johnson, 1966). Several compounds containing sulfur bonded to nitrogen have been prepared, but very little has been done in the way of exploring the scope of their reactions. Coincidental to the development of sulfur ylid chemistry has been the slower and less spectacular evolution of the sulfur-nitrogen system (containing quadrivalent sulfur) isoelectronic with sulfur ylid sysetems. The general N-sulfonyl sulfilimines may be formulated by either the ylid structure, the ylene structure or by the resonance hybrid of both.



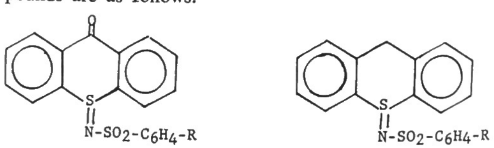
Ylide Ylene

There are five different types of iminosulfuranes known at the present time. They are classified as the diaryl iminosulfuranes, alkyl and aryl iminosulfuranes, dialkyl iminosulfuranes, free iminosulfuranes and cyclic iminosulfuranes. Diaryl, alkyl and aryl sulfides readily react with chloramines and form a corresponding iminosulfurane. Dialkyl sulfiides (Chattway, 1905; Nicolet and Willard 1921; Mann and Pope, 1922) do not readily react with chloramines and form a low percentage yield of the corresponding iminosulfuranes. In recent years and particularly through the efforts of Appel (1958, 1959) methods have been developed for the preparation of the free iminosulfuranes. O-alkyl or o-aryl mercapto benzene sulfonamides reacted with bromine and alkali or with tertiary amines to give in good yield, cyclic iminosulfuranes. (Wagner and Banholzer, 1959)

Recently Kremlen (1959) has also prepared the iminosulfuranes. The yields of the desired products were raised when instead of (N-cholorobenzene sulfonamide) sodium, the author used N-N-dichlorobenzene sulfonamide and conducted the reaction in a dry organic solvent. Iminosulfuranes and sulfonamides were also derived from N-chlorobenzimidates and sulfur nucleophiles. (Papa, 1970)

The author found the thioxanthone and diphenylene methane sulfide (thioxanthene) to react with chloramines-B, chloramine-T and a new reagent N-chloro-N-sodio-p-ethyl benzene sulfonamide (Shah, 1971, 1972) to obtain the corresponding iminosulfuranes.

All the iminosulfuranes were prepared from the corresponding sulfides and chloramines in the presence of ethyl alcohol at 50°C. The structure of these compounds are as follows:



Thioxanthone Iminosulfuranes   Thioxanthene Iminosulfuranes

Compound #1 and 4   R = -H
Compound #2 and 5   R = $-CH_3$
Compound #3 and 6   R = $-C_2H_5$

TABLE 1: *Physical Constant of Thioxanthone-Sulfilimines*

Compound No.	R	MP°C	%, Yield	Infrared cm^{-1}	Ultra Violet MeOH λ Max	Analysis
1	-H	167	25	1032, 1048 1210, 1135 932	25[illegible], 285.5 297	C,H,N,S[a]
2	$-CH_3$	169	29	1052, 1068 1230, 1158 952	255.5, 286 297	C,H,N,S[b]
3	$-C_2H_5$	[illegible]	[illegible]	[illegible] - 1050 [illegible] 1143 [illegible]	255.[illegible], 28[illegible] 296.5	C,H,N,S[c]

S[a] Calcd 17.44, Found 17.10; S[b], Calcd 16.80, Found 16.98; S[c], Calcd [illegible], Found [illegible]

[1] Presented at the Fourth Northeast Regional Meeting of the ACS, Hartford, Conn., 1972.

TABLE 2: *Physical Constants of Diphenylene Methane Sulfilimines*

Compound No.	R	MP°C	%, Yield	Infrared cm^{-1}	Ultra Violet MeOH λ Max	Analysis
4	-H	165	50	1025-1040, 1200,1135 922	253	C,H,N,S[d]
5	$-CH_3$	168	58	1055-1044 1137, 928	255.5	
6	$-C_2H_5$	182	60	1040,1200 1134, 925	250.0	

Calcd 18.13, Found 18.00

NOTE:
Melting points (capillary tube) are uncorrected. Infrared spectra were recorded on a Beckman Spectrophotometer 620® and ultraviolet spectra recorded on a Beckman Spectrophotometer Acta III.® Elemental analyses were determined at M-H-W Laboratories, Garden, City, Michigan 48135.

GENERAL METHOD FOR PREPARATION OF IMINOSULFURANES

The mixed solution of 0.02 mole of sulfide (thioxanthone and thioxanthene) and of 0.03 mole of chloramine (in 50 ml of 50% ethyl alcohol-water solution) were heated in a hot (60-70°C) water bath for 30 minutes. It was then covered and allowed to stand overnight at room temperature. The product formed upon standing, was filtered, washed thoroughly with water, dried and recrystallized from ethyl alcohol or methyl alcohol.

The thioxanthone itself was partly soluble in alcohol, but more soluble in chloroform. The recrystallized product from the alcohol reaction was dissolved in chloroform. The mixed solutions were heated in (60-70°C) waterbath for 10 minutes When product formed, it was filtered, dried and recrystalized from chloroform. More yield can be obtained in the chloroform reaction than the alcohol-water reaction. (McCall, Tarbell and Havill, 1951).

(1) *Thioxanthone-benzene-sulfonylimine:*
The recrystallized product as obtained by the general procedure outlined above; yield 25%, mp 167°C, ir ($CHCl_3$): (Asym SO_2): 1032, 1048, 1210 cm^{-1}, (SymSO_2): 1135 cm^{-1}, (S=N): 932 cm^{-1}. Anal. calcd. for $C_{19}H_{13}NS_2O$: C, 62.12; H, 3.54; N, 3.81; S, 17.44. Found C, 62.00; H, 3.60, N, 3.91; S, 17.10.

(2) *Thioxanthone-p-toluene-sulfonylimine:*
The recrystallized product as obtained by the general procedure outlined above; yield 29%, mp 169°C, ir ($CHCl_3$): (Asym SO_2): 1052, 1068, 1230 cm^{-1}; (Sym SO_2): 1158 cm^{-1}, (S=N) 952 cm^{-1}. *Anal.* calcd for $C_{20}H_{15}NS_2O_3$: C, 62.99; H, 3.94; N, 3.67; S, 16.80. Found C, 62.88; H, 4.03; N, 3.60; S, 16.98.

(3) *Thioxanthone-p-ethyl benzene sulfonylimine:*
The recrytallized product as obtained by the general procedure outlined above; yield 22%, mp 173°C. ir ($CHCl_3$): (Asym SO_2): 1040-1050, 1212 cm^{-1}; (Sym SO_2): 1143, (S=N): 935 cm^{-1}. *Anal.* calcd for $C_{21}H_{17}NS_2O_3$: C, 63.80; H, 4.30; N, 3.54; S, 16.20. Found C, 63.92; H, 4.44; N, 3.62; S, 16.38.

(4) *Diphenylenemethane-benzene-sulfonylimine:*
The recrystallized product as obtained by the general procedure outlined above; yield 50%, mp 165°C. ir ($CHCl_3$): (Asym SO_2): 1025-1040, 1200 cm^{-1}; (Sym SO_2): 1135 cm^{-1}, (S=N): 922 cm^{-1}. *Anal.* calcd for $C_{19}H_{15}NS_2O_2$: C, 64.59; H, 4.25; N, 3.96; S, 18.13; Found C, 64.66; H, 4.33; N, 4.02; S, 18.00.

(5) *Diphenylenemethane-p-toluene-sulfonylimine:*
The recrystallized product as obtained by the general procedure outlined above; yield 58%, mp 168°C. ir ($CHCl_3$): (Asym SO_2): 1035-1044 cm^{-1}, (Sym SO_2): 1137 cm^{-1}; (S=N): 928 cm^{-1}. Mol. Formula $C_{20}H_{17}NS_2O_2$.

(6) *Diphenylenemethane-p-ethyl-benzene sulfonylimine:*
The recrystallized product as obtained by the general procedure outlined above; yield 60%, mp 182°, ir ($CHCl_3$): (Asym SO_2): 1040, 1200 cm^{-1}, (Sym SO_2): 1134 cm^{-1}. (S=N) 925 cm^{-1}. Mol. formula $C_{21}H_{19}NS_2O_2$.

TEST METHODS

Accurately weigh 10 mg of each iminosulfurane derivative in separate 100 ml volumetric flask and dissolve in 10 ml HC1 and enough phosphate buffer (pH 6) to give an exact concentration of 100 μg/ml (solution a). Dilute approximate aliquots of solution (a) with enough pH 6 buffer to obtain concentrations of 70, 60, 50, 40 and 30 μg/ml. Add 10 ml melted Bacto-antibiotic medium I to sterile petri dishes, distribute evenly and let harden on perfectly level surface. For actual assay approximate amounts of organism-suspensions are added to (1 ml) Bacto-antibiotic medium IV previously melted and cooled to 48°C. Mix thoroughly and add 4.0 ml to each plate containing base layer and Bacto-antibiotic medium I. Distribute media evenly by tilting plates from side to side with circular motion and let harden.

Place three cylinders on each plate at approximately 60° intervals on a 2.8 cm radius. Fill all 3 cylinders with the test solution. Incubate plates overnight at 30-31°C and measure the diameters of zones of inhibition by means of mm ruler. Three plates were used for each assay solution and three plates for the standard solution. Determine the corrected value of the sample and standard. Plotting values of x^2 (square of the zone size) against. In mo (logarithm of the concentration in the reservoir) gives a straight line intercepting the concentration axis at In m' (critical concentration). (Horwitz, 1970)

BIOLOGICAL ACTIVITY

The compounds were tested for their antimalarial activtiy against *Plasmodium berghei* in mice according to a procedure already published. (Osdene, Russell and Rane, 1967). The test results are given in Table 3.

RESULTS AND DISCUSSION

Most of the workers have prepared iminosulfuranes from the reaction of the sulfides with chloramine-T and chloramine-B. Recently we have prepared a new chloramine (N-chloro-N-sodio-p-ethyl benzene sulfonamide). No one has tried to prepare iminosulfuranes from the reaction of sulfide with new chloramine. Also no one has reported the spectroscopic data of this type of iminosulfuranes. There are many different methods of preparation of iminosulfuranes, but there is very little known about their chemistry. There has been no attempt to explore the variety of reactions that may undergo by these iminosulfuranes nor has there been any serious attempts to study their physical properties because formation of a low percentage yield of iminosulfuranes was observed by most methods.

Analytical data are not adequate proof for the iminosulfuranes prepared but the spectral data (infrared, ultraviolet) verify the preparation of these new compounds in this work. Such verification has been successfully utilized by K-Tsujihara (1970) with iminosulfuranes. Figures 1 and 2 show that the inhibition of *Sarcina lutea* and *Bacillus subtilis* on thioxanthone iminosulfuranes.

The Penicillin G Potassium readily inhibits *Sarcina lutea* at a very low concentration (0.025 μg/ml) but at a high concentration (0.25 μg/ml) inhibits *Bacillus subtilis.* Thioxanthone iminosulfuranes inhibits *Sarcina lutea* at a low concentration (30 μg/ml) but at a high concentration (50 μg/ml) inhibits *Bacillus subtilis,* while diphenylenemethane iminosulfurane inhibits *Sarcina lutea* at a low concentration (1 μg/ml) but at a high concentration (3 μg/ml inhhibits *Bacillus subtilis.* Thioxanthone iminosufuranes are (1200:1) and diphenylenementhane iminosulfuranes are (40:1) less active than the Penicillin G Potassium in *Sarcina lutea,* while thiox-

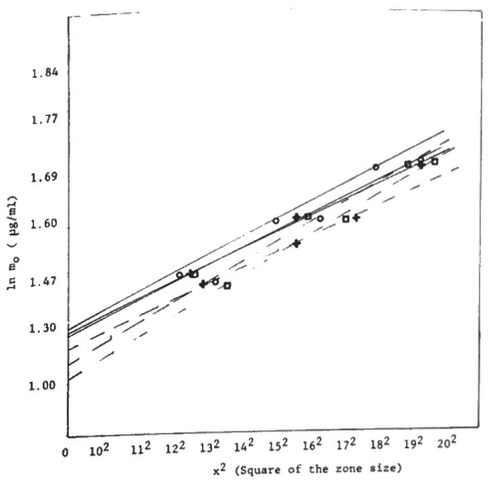
TABLE 3: *Microbiological Data of Sulfilimines*

Compound No.	Concentration m_o (μg/ml)	Sarcina lutea Diameter of Zones x(mm)	Critical Concentration m' (μg/ml)	Concentration m_o (μg/ml)	Bacillus subtilis Diameter of Zones x(mm)	Critical Concentration m' (μg/ml)
1	50 40 30	17.70 14.80 12.00	21.0	70 60 50	18.40 16.00 13.50	31.0
2	50 40 30	18.53 15.73 12.40	19.7	70 60 50	16.70 15.00 13.40	25.4
3	50 40 30	18.95 15.86 12.50	19.8	70 60 50	16.40 14.00 11.90	37.9
4	3 2 1	24.2 17.30 10.0	0.78	5 4 3	25.13 19.00 12.0	2.5
5	3 2 1	22.93 16.20 9.80	0.80	5 4 3	24.6 17.00 8.30	2.8
6	3 2 1	23.53 17.10 10.80	0.60	5 4 3	24.3 18.90 14.00	1.8

TABLE 4: *Antimalarial Report on Sulfilimines*[2]

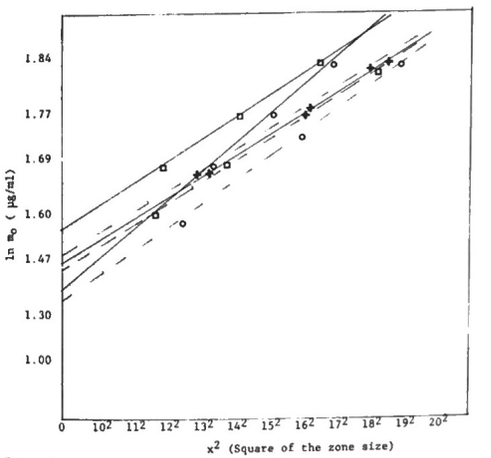
COMPOUND	ANIMAL	DOSE	CURES	MSTT*	MSTC*	T-C*	TOX.	MSTX
1	Mice	40	-	6.2	6.1	0.1	-	-
		160	-	6.4	6.1	0.3	-	-
		640	-	6.4	6.1	0.3	-	-
2	Mice	40	-	6.2	6.1	0.1	-	-
		160	-	6.4	6.1	0.3	-	-
		640	-	6.4	6.1	0.3	-	-
3	Mice	40	-	6.4	6.1	0.3	-	-
		160	-	6.6	6.1	0.5	-	-
		640	-	6.6	6.1	0.5	-	-
4	Mice	40	-	6.2	6.1	0.1	-	-
		160	-	6.2	6.1	0.1	-	-
		640	-	6.6	6.1	0.5	-	-
5	Mice	40	-	6.2	6.1	0.1	-	-
		160	-	6.4	6.1	0.3	-	-
		640	-	6.6	6.1	0.5	-	-
6	Mice	40	-	6.2	6.1	0.1	-	-
		160	-	6.4	6.1	0.3	-	-
		640	-	6.4	6.1	0.3	-	-

*MSTT - Means Survival Time of Treated Animals
*MSTC - Means Survival Time of Controls
* T-C - Changes in Survival Time (MSTT - MSTC)
[2] Conducted at the Walter Reed Army Institute, Washington, D.C.



Legend
0—0 Cmpd. #1 Alcohol
□—□ Cmpd. #2 Alcohol
+—+ Cmpd. #3 Alcohol
□--□ Cmpd. #1 Chloroform
+--+ Cmpd. #2 Chloroform
0--0 Cmpd. #3 Chloroform

FIG. 1: *Inhibition of* Sarcina lutea *on Thioxanthone-sulfilimines*



Legend
+—+ Cmpd. #1
0—0 Cmpd. #2 (Alcohol)
□—□ Cmpd. #3
□--□ Cmpd. #1
0--0 Cmpd. #2 (Chloroform)
+--+ Cmpd. #3

FIG. 2: *Inhibition* of Bacillus subtilis *on Thioxanthone-sulfilimines*

anthone iminosulfuranes are (200:1) times and diphenylenemethane iminosulfuranes are (12:1) times less active than the Penicillin G Potassium in *Bacillus subtilis*.

These results suggest that these iminosulfurane derivatives have some antibacterial properties. Tables 3 and 4 show the microbiological and antimalarial data of these iminosulfurane derivatives.

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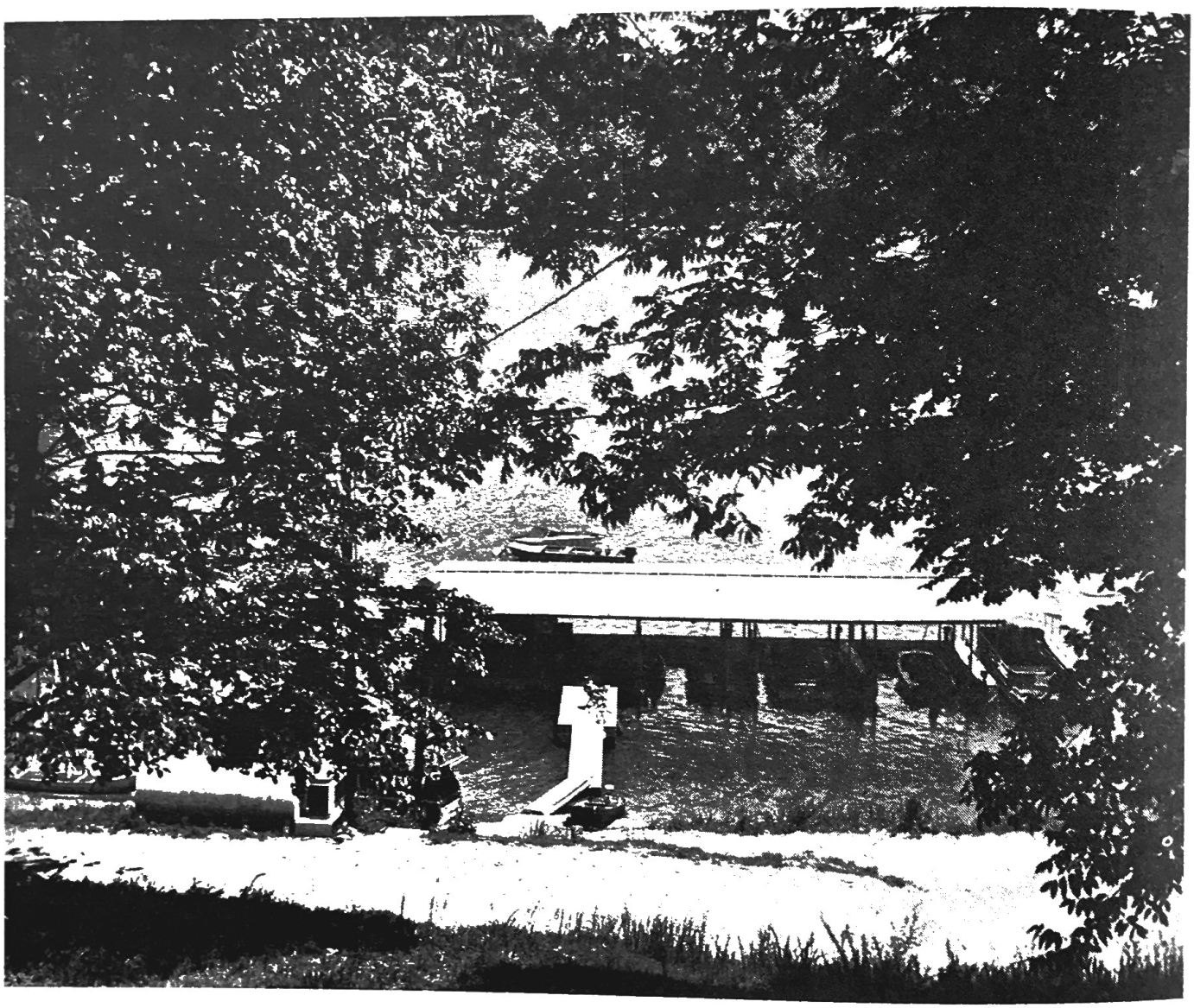

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