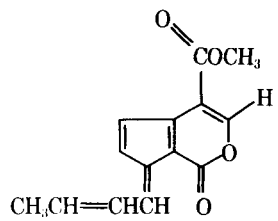


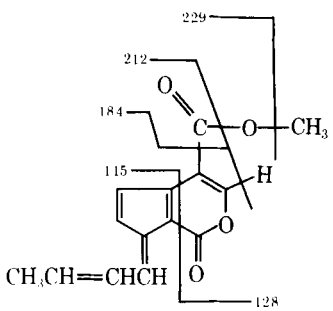
I

tionation of the stem bark was undertaken to isolate the active agent(s).

## EXPERIMENTAL[4]

The coarsely ground stem bark (2 kg) of *H. sucuuba* was extracted continuously for 24 hr using a soxhlet apparatus with *n*-hexane. The *n*-hexane extract was concentrated *in vacuo* and refrigerated. Two additional *n*-hexane extracts were similarly prepared from the marc. The combined extracts were concentrated *in vacuo* and refrigerated.

A yellow-orange compound (500 mg), which separated out on standing, was removed by filtration and dried. This compound was dissolved in hot *n*-hexane, and the undissolved portion was dissolved in chloroform and reduced *in vacuo*. Orange crystals (150 mg) formed and were recrystallized from hot ethanol. They proved to be the known compound fulvoplumierin (I), mp 149–150° [lit. (1–3) mp 151–152°].



II

Further evidence for the assigned structure of I was derived from mass spectrometric analysis. The parent ion (*m/e* 224) was also the base peak in the mass spectrum. The remaining major ions were accounted for by commonly encountered fragmentation pathways and rearrangements to II (Table I).

*Anal.*—Calc. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.64; H, 4.98.

An IR spectrum was superimposable with that of an authentic reference sample of fulvoplumierin[5].

**Table I—Fragmentation Ions of Fulvoplumierin**

| *m/e* | Relative Intensity, % | Postulated Fragmentation Pattern |
|---|---|---|
| 244 | 100 | $M^+$ |
| 243 | 60 | M − 1 |
| 229 | 20 | M − $CH_3$ |
| 212 | 70 | M − $CH_3OH$ |
| 184 | 40 | *m/e* 212 − CO |
| 156 | 50 | *m/e* 184 − CO |
| 128 | 75 | — |
| 115 | 25 | Loss of pyrone ring |

## DISCUSSION

Fulvoplumierin, a lactone previously isolated from the root bark of *Plumeria acutifolia* L. (1, 2) and the stem bark of *P. rubra* L., was isolated from *H. sucuuba*. It was devoid of pharmacological activities. The present investigation establishes the first occurrence of this compound in this genus.

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[4] Elemental analysis was performed by Geller Laboratories, Saddle River, N.J. Melting points were taken on a Mel-Temp apparatus and are uncorrected. IR and mass spectra were determined using a Beckman IR-8 and an LKB-9000 mass spectrophotometer, respectively.

[5] Supplied by Prof. Dr. H. Schmid, Universitat Zurich, and E. Venkata Rao, Andhra University, Waltair, India.

# Synthesis and Antimicrobial Properties of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxides


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Received October 21, 1977, from the *Monsanto Company, St. Louis, MO 63166.* Accepted for publication December 28, 1977.



**Abstract** □ Twenty aromatic alcohols and thiols were derivatized by reaction with 3-chloro-1,2-benzisothiazole 1,1-dioxide. The resulting 3-substituted 1,2-benzisothiazole 1,1-dioxides were tested against *Staphylococcus aureus, Salmonella typhosa,* and *Aspergillus niger,* and their activities were compared with the activities of the precursors.



**Keyphrases** □ 1,2-Benzisothiazole 1,1-dioxides, 3-substituted—synthesized, evaluated for antibacterial and antifungal activity □ Antibacterial activity—various 3-substituted 1,2-benzisothiazole 1,1-dioxides evaluated □ Antifungal activity—various 3-substituted 1,2-benzisothiazole 1,1-dioxides evaluated □ Structure–activity relationships—various 3-substituted 1,2-benzisothiazole 1,1-dioxides evaluated for antibacterial and antifungal activity


The herbicidal and fungicidal activities of some 3-substituted 1,2-benzisothiazole 1,1-dioxides were reported previously (1, 2). This paper is concerned with the preparation and antimicrobial activity of a series of these


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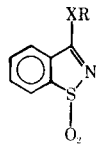


**Table I—3-Substituted 1,2-Benzisothiazole 1,1-Dioxides [a]**

| Compound | R | X | Melting Point | Yield, % | Formula | Analysis, % | Calc. | Found |
|---|---|---|---|---|---|---|---|---|
| I | $C_6H_5$ | O | 181–183° [b] | 89.7 | $C_{13}H_9NO_3S$ | S | 12.40 | 12.40 |
| II | 2-$ClC_6H_4$ | O | 196–197° [c] | 70.9 | $C_{13}H_8ClNO_3S$ | Cl | 12.07 | 12.10 |
| | | | | | | N | 4.77 | 4.79 |
| III | 4-$ClC_6H_4$ | O | 174–175° | 80.5 | $C_{13}H_8ClNO_3S$ | Cl | 12.07 | 12.10 |
| | | | | | | N | 4.77 | 4.88 |
| IV | 3-$CF_3C_6H_4$ | O | 126–127° | 58.7 | $C_{14}H_8F_3NO_3S$ | C | 51.54 | 51.14 |
| | | | | | | H | 2.16 | 2.29 |
| | | | | | | N | 4.29 | 4.27 |
| V | 2,4-$Cl_2C_6H_3$ | O | 205–206° | 76.7 | $C_{13}H_7Cl_2NO_3S$ | C | 47.57 | 47.63 |
| | | | | | | H | 2.15 | 2.31 |
| | | | | | | Cl | 21.61 | 21.60 |
| VI | 2,4,6-$Cl_3C_6H_2$ | O | 278–279° | 33.2 | $C_{13}H_6Cl_3NO_3S$ | C | 43.06 | 43.02 |
| | | | | | | H | 1.67 | 1.64 |
| | | | | | | N | 3.86 | 3.56 |
| VII | 2,4,5-$Cl_3C_6H_2$ | O | 192–197° | 24.0 | $C_{13}H_6Cl_3NO_3S$ | Cl | 29.33 | 29.30 |
| | | | | | | N | 3.86 | 4.01 |
| | | | | | | S | 8.84 | 8.91 |
| VIII | 2,3,4,5,6-$Br_5C_6$ | O | 261–270° | 31.9 | $C_{13}H_4Br_5NO_3S$ | C | 23.88 | 23.88 |
| | | | | | | H | 0.62 | 0.69 |
| | | | | | | Br | 61.11 | 61.00 |
| IX | 2,3,4,5,6-$Cl_5C_6$ | O | 272–273° | 56.0 | $C_{13}H_4Cl_5NO_3S$ | Cl | 41.08 | 40.90 |
| | | | | | | N | 3.28 | 3.38 |
| | | | | | | S | 7.43 | 7.30 |
| X | 2-Cyclopentyl-4-$ClC_6H_3$ | O | 201–202° | 33.2 | $C_{18}H_{16}ClNO_3S$ | C | 59.74 | 60.14 |
| | | | | | | H | 4.46 | 4.59 |
| | | | | | | N | 3.87 | 3.85 |
| XI | 2-Cyclohexyl-4-$ClC_6H_3$ | O | 202–204° | 32.0 | $C_{19}H_{18}ClNO_3S$ | N | 3.73 | 4.00 |
| | | | | | | S | 8.53 | 8.65 |
| XII | 2-Biphenyl | O | 206–208° | 56.0 | $C_{19}H_{13}NO_3S$ | N | 4.19 | 4.34 |
| | | | | | | S | 9.56 | 9.26 |
| XIII | 2-Benzyl-4-$ClC_6H_3$ | O | 173–174° | 78.5 | $C_{20}H_{14}ClNO_3S$ | C | 62.58 | 62.66 |
| | | | | | | H | 3.68 | 3.74 |
| | | | | | | Cl | 9.24 | 9.30 |
| XIV | 2-*sec*-Butyl-4,6-$NO_2C_6H_2$ | O | 134–135° | 74.0 | $C_{17}H_{15}N_3O_7S$ | C | 50.36 | 50.53 |
| | | | | | | H | 3.73 | 3.61 |
| | | | | | | N | 10.37 | 10.51 |
| XV | $C_6H_5$ | S | 224–225° [d] | 87.0 | $C_{13}H_9NO_2S_2$ | C | 56.71 | 56.61 |
| | | | | | | H | 3.29 | 3.06 |
| | | | | | | N | 5.09 | 5.04 |
| XVI | 4-$ClC_6H_4$ | S | 205–207° | 77.4 | $C_{13}H_8ClNO_2S_2$ | C | 50.40 | 50.53 |
| | | | | | | H | 2.60 | 2.71 |
| | | | | | | Cl | 11.44 | 11.50 |
| XVII | 2,3,4,5,6-$Cl_5C_6$ | S | 290–291° | 50.0 | $C_{13}H_4Cl_5NO_2S$ | C | 34.88 | 34.66 |
| | | | | | | H | 0.90 | 0.85 |
| | | | | | | N | 3.13 | 3.18 |
| XVIII | 2-Pyridyl | S | 194–196° | 78.2 | $C_{12}H_8N_2O_2S_2$ | C | 52.15 | 52.38 |
| | | | | | | H | 2.92 | 3.08 |
| | | | | | | S | 23.20 | 23.54 |
| XIX | 2-Pyridyl *N*-oxide | S | 184° (dec.) | 65.7 | $C_{12}H_8N_2O_3S_2$ | C | 49.30 | 49.11 |
| | | | | | | H | 2.76 | 2.50 |
| | | | | | | N | 9.58 | 9.63 |
| XX | 8-Quinonyl | O | 242–246° | 95.0 | $C_{16}H_{10}N_2O_3S$ | N | 9.03 | 8.83 |
| | | | | | | S | 10.33 | 9.94 |

[a] All compounds were recrystallized from toluene, except IX which was recrystallized from xylene, XIV from ether, XIX from acetic acid, and XX from tetrahydrofuran. [b] Lit. (4) mp 182°. [c] Lit. (2) mp 196–197°. [d] Lit. (5) mp 219.0–219.5°.

pseudosaccharin ethers and thioethers.

## RESULTS AND DISCUSSION

It is sometimes possible to derivatize a biologically active compound and thereby obtain a compound with more desirable physical properties while maintaining or improving the activity of the parent. If such chemically modified compounds are transformed to the parent compound before they elicit a pharmacological response, they are often referred to as prodrugs (3). On this premise, 20 pseudosaccharin derivatives (Table I) were prepared and tested against *Staphylococcus aureus*, *Salmonella typhosa*, and *Aspergillus niger*. These results were compared with those of the parent compounds, which were evaluated under identical conditions (Table II).

Derivatives XV and XVI had significantly greater activity (equivalent response at one-hundredth the concentration) against *S. aureus* and *A. niger* than their thiophenol precursors. Conversely, significantly lower activity (100-fold higher concentration required for equivalent response) was found with XI and XVII against *S. aureus*, with XIII and XIV against *S. typhosa*, and with IX, XI, and XIII against *A. niger*. The other pseudosaccharin derivatives were active at concentrations within a factor of ±10 of the precursors.

## EXPERIMENTAL[1]

**General Synthetic Procedure**—A mixture of 5 g (0.025 mole) of pseudosaccharin chloride (5), 2.6 g (0.025 mole) of triethylamine, 0.025

[1] Melting points were taken on a Fisher-Johns melting-point apparatus and are corrected. IR spectra were recorded on a Beckman IR-5 spectrophotometer.

**Table II—Antimicrobial Activity** [a]

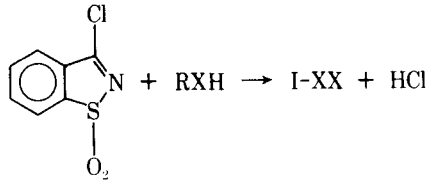
| Compound | *S. aureus* | *S. typhosa* | *A. niger* |
|---|---|---|---|
| I | T | T | T |
| II | T | T | T |
| III | T | T | T |
| IV | T | T | T |
| V | T | T | T |
| VI | 100T | T | 100T |
| VII | 100T | 10T | 100T |
| VIII | M | T | T |
| IX | M | 10 | T[b] |
| X | 100T | T | 10T |
| XI | +[b] | + | +[b] |
| XII | + | + | T |
| XIII | 100T | +[b] | +[b] |
| XIV | M | T[b] | 10T |
| XV | 10T[c] | + | 10T[c] |
| XVI | 100T[c] | + | 10T[c] |
| XVII | T[b] | T | T |
| XVIII | 10T | T | T |
| XIX | M | M | M |
| XX | M | 10T | 100T |

[a] The + represents growth at a dilution of $1 \times 10^3$; T, 10T, 100T, and M represent no growth at dilutions of $1 \times 10^3$, $1 \times 10^4$, $1 \times 10^5$, and $1 \times 10^6$, respectively. [b] The alcohol or thiol precursor showed equivalent response at one-hundredth the concentration. [c] The thiol precursur showed equivalent response at a 100-fold higher concentration.

mole of an alcohol or thiol, and 100 ml of toluene was stirred at reflux for 1–2 hr (Scheme I). The mixture was filtered free of by-product triethylamine hydrochloride, and the solvent was evaporated from the filtrate. The residue was recrystallized from the solvent indicated in Table I. The absence of carbonyl absorptions in the IR spectra confirmed that the compounds were not the *N*-substituted saccharin derivatives (6).

**Antimicrobial Test Procedure**—The derivatives were screened against *S. aureus* (ATCC 6538), *S. typhosa* (ATCC 6539), and *A. niger* (SN 111).

Stock solutions were prepared by dissolving 100 mg of the test compound in 10 ml of acetone, alcohol, or other solvent. The stock solutions




*Scheme I*

were diluted serially by pipetting 2 ml of the stock solutions into 18 ml of sterile agar to obtain a $1 \times 10^3$ dilution and continuing in the same manner for dilutions up to $1 \times 10^6$.

The agar was poured into petri dishes, allowed to harden, and spot inoculated with 1 drop of a cell suspension of the appropriate organism, prepared by suspending the growth from an agar slant culture in 10 ml of distilled water. The bacteria were incubated for 48 hr, and the *A. niger* was incubated for 5 days before examination for growth. The results reported are the minimum concentrations of the test compound that completely inhibited organism growth.

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## ACKNOWLEDGMENTS

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# Constituents of *Spartina cynosuroides:* Isolation and $^{13}$C-NMR Analysis of Tricin

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Received October 25, 1977, from the *Department of Chemistry, Mississippi State University, Mississippi State, MS 39762.* Accepted for publication January 4, 1978.

**Abstract** □ Tricin was isolated from the aerial parts of the marsh plant *Spartina cynosuroides*, which yielded a fraction enriched in antileukemic activity. The $^{13}$C-NMR spectrum of tricin is discussed.

**Keyphrases** □ Tricin—isolated from *Spartina cynosuroides* aerial parts, $^{13}$C-NMR spectral analysis □ *Spartina cynosuroides*—tricin isolated from aerial parts, $^{13}$C-NMR spectral analysis

The giant cordgrass, *Spartina cynosuroides*[1] (Graminae), is the second most abundant plant in the salt marshes of Southern and Southeastern United States. A preliminary study (1) involved the primary production and decomposition of *S. cynosuroides* and the food value of this plant to marsh and estuarine organisms. The analysis of the volatile constituents of this plant was reported (2). Apart from a superficial study (3), no report of a detailed chemical investigation of the organic constituents of *S. cynosuroides* has appeared.

## DISCUSSION

The 95% ethanolic extract of the aerial parts of *S. cynosuroides* showed high activity[2] against P-388 lymphocytic leukemia in $BDF_1$ mice. The activity[3] was considerably enriched in the chloroform extract at pH 4 of the acid-soluble part of the crude ethanolic extract. Column chromatography of the active extract yielded a yellow compound ($M^+$ 330), mp 288–290° dec., which gave a triacetate derivative, mp 254–256°, and was

[1] The plant material was identified by Dr. Sidney McDaniel, Department of Botany, Mississippi State University, Mississippi State, Miss. A voucher (preserved) specimen (SM-181) is available for inspection at the Herbarium of the Department of Botany, Mississippi State University.

[2] Percent T/C 146 at a dose level of 400 mg/kg against the National Cancer Institute murine P-388 lymphocytic leukemia system.

[3] Percent T/C 172 at a dose level of 400 mg/kg.

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