222–225°, *ca.* 1:1 diastereomeric mixture at the anisaldehyde residue) by treatments with methanolic hydrogen chloride at 50° and then anisaldehyde in methylene chloride containing a trace of boron trifluoride etherate at room temperature.[4] The overall yield from **2** to **4** was 45%. Compound **4** was converted to the 1:1 diastereomeric mixture of the chlorides **5a**[7,8] (mp 212–213°) and **5b**[7,9] [mp 119–120° (from benzene)] by the following four steps in 41% overall yield: (1) sodium hydroxide in aqueous dioxane at room temperature, (2) *N,N'*-carbonyldiimidazole in THF at room temperature, (3) lithium borohydride at 0°,[10] and (4) carbon tetrachloride and tri-*n*-octylphosphine at room temperature.

Treatment of the diastereomeric mixture (*ca.* 1:1) of the chlorides **5a** and **5b** in THF at −110° with butyllithium (1.1 equiv), followed by acetic acid work-up, gave the cyclized compound **6a**[7] [38%, mp 223–224°; $\delta_{ppm}^{CDCl_3}$ 3.15 (3 H, s), 3.75 (3 H, s), and 3.98 (3 H, s)] and recovered chloride **5b** (35%). This result can be explained, as the position of the carbanion formation is determined by the stereochemistry of the anisaldehyde residue and, therefore, only the diastereomeric chloride **5a** can be used for the cyclization.[4] Alkylation of **6a** with chloromethyl methyl ether (1.0 equiv of BuLi in THF at −78°) afforded the methoxymethyl derivative **7a**[7] [mp 172–173°; $\delta_{ppm}^{CDCl_3}$ 3.23 (3 H, s), 3.46 (3 H, s), 3.76 (3 H, s), and 4.01 (3 H, s)] in 61% yield.[11]

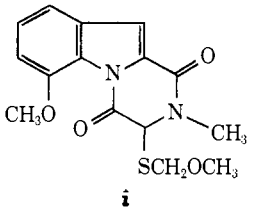
The chloride **5b**, recovered from the cyclization with butyllithium, can be utilized for the synthesis in two ways. One is to epimerize **5b** under acidic conditions to an equilibrium mixture with respect to the asymmetric center associated with the anisaldehyde residue; namely, treatment of **5b** with boron trifluoride etherate in boiling methylene chloride for 15 hr formed an equilibrium mixture of **5a** (3 parts) and **5b** (2 parts), which can be used for the cyclization with butyllithium. Thus, an overall yield from a mixture of **5a** and **5b** to **6a** went up 55% after two cycles of the equilibration. The second way is to use the monocarbanion of **5b** for alkylation with chloromethyl methyl ether first. Namely, the chloride **5b** was converted to the compound **8**[7] (mp 141–142°) in 49% yield under the standard conditions.[4] Addition of butyllithium (1.1 equiv) to **8** in THF at −78° generated the carbanion at the desired position, to yield the cyclized compound **7b**[7] [mp 228–229°; $\delta_{ppm}^{CDCl_3}$ 3.39 (3 H, s), 3.48 (3 H, s), 3.77 (3 H, s), and 3.94 (3 H, s)] in 80% yield. The cyclized compound **7b** is epimeric to **7a** at the anisaldehyde residue.

(8) About the assignment of the stereochemistry of **5a** and **5b**, see ref 4. Pure **5a** was isolated by crystallization of the about 3:2 diastereomeric mixture of **5a** and **5b** from hot ethyl acetate.

(9) Pure **5b** was obtained from the material recovered in the cyclization with butyllithium on the mixture of **5a** and **5b**.

(10) The intermediate at this stage (R = CH_2OH in the structure **4**) could be prepared directly from **4** by lithium aluminum hydride reduction in THF at 0°, but the yield by a one-step procedure was lower.

(11) One of the by-products was **i**.



i

Finally, the compounds **7a** and **7b** were converted to *d,l*-dehydrogliotoxin (**1**) by treatment with *m*-chloroperbenzoic acid in methylene chloride and then boron trichloride in methylene chloride at 0°. *d,l*-Dehydrogliotoxin (**1**)[7] (mp 177–178°; M^+ (found) 324.0251, (cald) 324.0238) was isolated by preparative tlc (silica gel) in 20% yield and identified as authentic dehydrogliotoxin (**1**)[3,12] by comparison with nmr,[13] ir, uv, and mass[13] spectra and tlc behavior.

Acknowledgment. Support of our work by the National Science Foundation (GP-12692X) and Hoffmann-La Roche Co. is gratefully acknowledged.

(12) We are indebted to Dr. Safe, National Research Council of Canada, Halifax, and Drs. Nagarajan and Neuss, Eli Lilly and Co., for their generous gifts of natural gliotoxin.

(13) We thank Drs. Dudek and Balaram, Harvard University, for the measurement of the exact mass spectrum and the FT-nmr spectrum.

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Received June 23, 1973

A Total Synthesis of Sporidesmin A

Sir:

Sporidesmins are toxic metabolites of *Pithomyces chartarum*, which cause the serious disease in sheep known as "facial eczema" in New Zealand. Successful isolation and structure determination of seven different sporidesmins, A through G, were carried out by Taylor and his coworkers.[1] In this communication we report a formal stereospecific total synthesis of sporidesmin A (**1**), the major metabolite of *Pithomyces*.

The diketopiperazine moiety of the sporidesmins was synthesized in the following way. Treatment of 1,6-dimethylpiperazine-2,5-dione[2] with chloromethyl methyl ether in *tert*-butyl alcohol containing potassium *tert*-butoxide (1.2 equiv) at room temperature gave 1,6-dimethyl-4-methoxymethylpiperazine-2,5-dione **2**[3a] (mp 46–48°) in 70% yield. Bromination of **2** by NBS benzoyl peroxide in carbon tetrachloride, followed by potassium thioacetate work-up in methylene chloride at room temperature, afforded the thioacetate **3**[3a] (mp 83–84°) in 74% yield. The thioacetate **3** was converted into the thioacetal **4**[3a] (mp 132–142°, *ca.* 1:2 syn and anti mixture with respect to the anisaldehyde and methoxymethyl residues) by treatment with hydrogen chloride in methanol at 50° and then the trithiane derivative[4] of anisaldehyde in boiling methylene chloride containing boron trifluoride etherate. The reaction with the trithiane probably involves a carbonium ion

(1) Sporidesmins. Parts I to XIII. The latest report: S. Safe and A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 472 (1972).

(2) L. Birkofer, A. Ritter, and P. Neuhausen, *Justus Liebigs Ann. Chem.*, **659**, 190 (1962).

(3) (a) Satisfactory analytical and spectroscopic data were obtained on this compound. (b) Satisfactory spectroscopic data were obtained on this compound.

(4) E. Baumann and E. Fromm, *Chem. Ber.*, **24**, 1441 (1891).

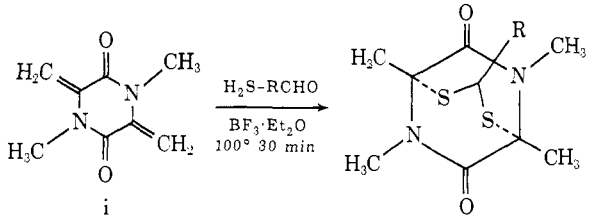
such as **5**, where X is a thiol or hemithioacetal group.[5] The overall yield from **3** to **4** was 80%.

The indole part of the sporidesmins was synthesized as follows. Chlorination of 6,7-dimethoxyoxindole[6] with chlorine in aqueous methanol at room temperature yielded 5-chloro-6,7-dimethoxyoxindole **6**[3a] (mp 205–207°) in a quantitative yield. The position of the chlorine atom in **6** was confirmed by a transformation of **6** into the known 1-methyl-5-chloro-6,7-dimethoxyisatin[7] by oxidation with selenium dioxide and N-methylation with dimethyl sulfate. N-Methylation of **6** with methyl iodide in boiling xylene in the presence of sodium hydride and reduction with diisobutylaluminum hydride in ether at −78°[8] gave 1-methyl-5-chloro-6,7-dimethoxyindole **7**[3a] (mp 44–45°) in 71% overall yield from 6,7-dimethoxyoxindole. Oxalyl chloride and **7** in ether afforded the oxamic acid chloride **8**[3b] (decomposes around 140°), which was then subjected to pyrolysis in tetrachloroethane at 120°, to give the acid chloride **9**[3b] (mp 220–225° dec). The overall yield from **7** to **9** was 72%.

The carbanion[9] from **4** (1.1 equiv of BuLi) was treated with the acid chloride **9** in THF at −110° to yield the condensed compound **10**[3a] as a syn and anti mixture (pure syn **10b** mp 237–238°, pure anti **10a** mp 209–211°) in 61% yield. Concentrated hydrochloric acid on **10** in TFA at 70° for 40 min,[10] followed by sodium hydroxide work-up, afforded a diastereomeric mixture of **11a** (50%; mp 230–231°) and **11b** (12%; mp 172–174°) which was easily separable by preparative tlc on silica gel.

The ketone **11a** was stereospecifically reduced to the alcohol **12a**[3a] (mp 222–223°) by diisobutylaluminum hydride in THF at −78° in 86% yield.[11] The configuration of the alcoholic group is expected to be the desired one for the following reasons. Namely (1), since compound **10** is inert to reducing reagents such as $LAlH_4$, diisobutylaluminum hydride, or sodium borohydride, the first process of the reduction may involve a complex formation between the amide N–H group and the reducing reagent and the second process is an intramolecular hydride transfer and (2) the crucial intramolecular hydride transfer process may occur from the desired direction because the α side of the diketopiper-

(5) The same type of reaction was possible on compound i, but it is not suitable for the synthetic purposes because of the low yield (30%).



i

ii (R = p-CH3OC6H4)

(6) J. M. Gulland, R. Robinson, J. Scott, and S. Thornley, *J. Chem. Soc.*, 2924 (1929).

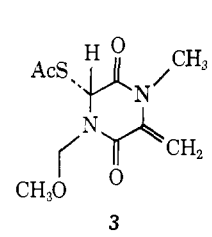
(7) R. Hodges, J. W. Ronaldson, A. Taylor, and E. P. White, *J. Chem. Soc.*, 5332 (1963).

(8) A small amount of the over-reduced product, an indoline derivative, was produced when the reduction was carried out at room temperature or with $LAlH_4$ at 0°.

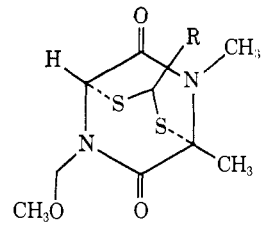
(9) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, **95**, 6492 (1973).

(10) The product at this stage is the hydroxymethyl derivative (X = CH_2OH in **10**).

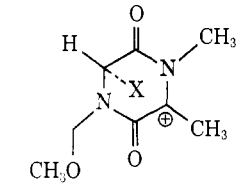
(11) The exactly parallel experiments could be carried out in the diastereomeric series (**11b** → **12b** → **13b** → **14b**).



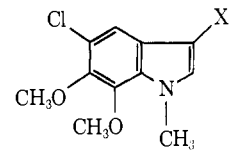
3



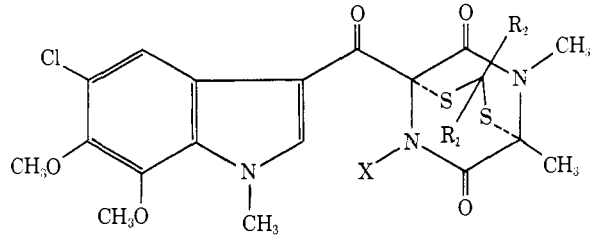
4, R = p-CH3OC6H4



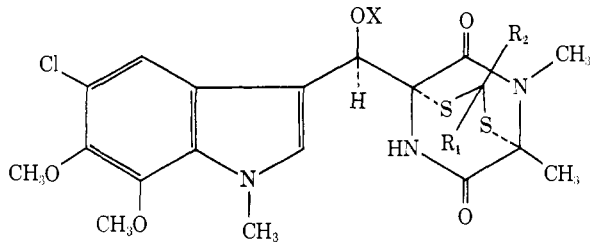
5, X = SH or SCH(SH)-p-C6H4OCH3



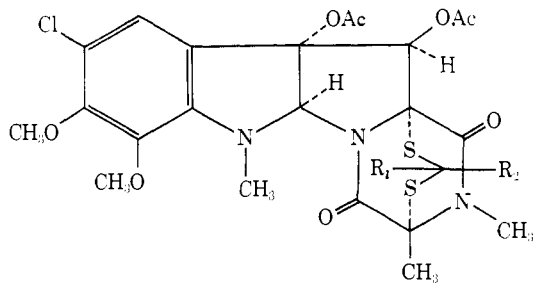
7, X = H
8, X = COCOCl
9, X = COCl



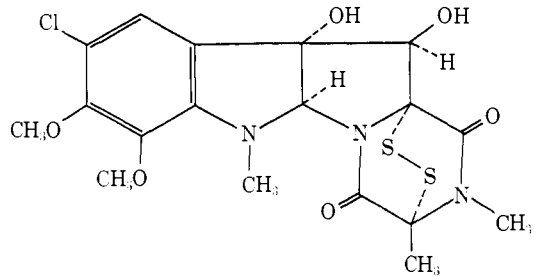
10, X = CH_2OCH_3; R_1 or R_2 = p-$CH_3OC_6H_4$ or H (syn and anti mixture)
11a, X = H; R_1 = H; R_2 = p-$CH_3OC_6H_4$
b, X = H; R_1 = p-$CH_3OC_6H_4$; R_2 = H



12a, X = H; R_1 = H; R_2 = p-$CH_3OC_6H_4$
b, X = H; R_1 = p-$CH_3OC_6H_4$; R_2 = H
13a, X = Ac; R_1 = H; R_2 = p-$CH_3OC_6H_4$
b, X = Ac; R_1 = p-$CH_3OC_6H_4$; R_2 = H



14a, R_1 = H; R_2 = p-$CH_3OC_6H_4$
b, R_1 = p-$CH_3OC_6H_4$; R_2 = H



1, sporidesmin A

azine ring is bulkier than the β side and, therefore, in a preferred conformation the α side of the diketopiperazine will stay as far as possible from the bulky indole part.

By the usual method, the alcohol **12a** was converted to the acetate **13a**[3a,11] [95% with acetic anhydride and pyridine; mp 176–178°; $\delta_{ppm}^{CDCl_3}$ 1.89 (3 H, s), 2.08 (3 H, s), 3.24 (3 H, s), 3.77 (3 H, s), 3.90 (3 H, s), 3.94 (3 H, s), and 4.00 (3 H, s)] which was oxidized with iodosobenzene diacetate in acetonitrile containing dimethyl sulfide, to afford the cyclized diacetate **14a**[3b,11] [amorphous solid; M^+ (found) 677.1288 and 679.1266, (cald) 677.1268 and 679.1239; $\delta_{ppm}^{CDCl_3}$ (1.2 mg in 0.3 ml) 1.63 (3 H, s), 1.95 (3 H, s), 2.01 (3 H, s), 3.02 (3 H, s), 3.51 (3 H, s), 3.80 (3 H, s), 3.86 (3 H, s), 3.87 (3 H, s)][12] in 30% yield.[11,13] The two new asymmetric centers introduced in this step are expected to be desired ones for the steric reasons.

The synthetic diacetate **14a** was identified by comparison of spectroscopic data (nmr, ir, uv, and mass spectral)[12] as well as tlc behavior with the authentic diacetate **14a**, which was prepared from natural sporidesmin A (**1**)[14] in three steps: sodium borohydride reduction in methanol, anisaldehyde treatment in methylene chloride containing boron trifluoride etherate, and acetylation with acetic anhydride and pyridine.[15]

The authentic diacetate **14a** was successfully converted back to sporidesmin A (**1**) in 25% overall yield in three steps: sodium hydroxide in aqueous methanol at room temperature, *m*-chloroperbenzoic acid in methylene chloride at room temperature, and boron trifluoride etherate in methylene chloride at room temperature. Therefore, the synthesis of the diacetate **14a** formally constitutes the completion of a total synthesis of sporidesmin A (**1**).

Acknowledgment. Support of our work by the National Science Foundation (GP-12692X) and Hoffmann-La Roche Co. is gratefully acknowledged.

(12) We thank Drs. Dudek and Balaram, Harvard University, for the measurement of the exact mass spectrum and the FT-nmr spectrum.

(13) The same type of reaction takes place with **12** and **13** by NBS-oxidation in methylene chloride to yield the cyclized compound bearing a bromine in place of the tertiary acetoxy group in **14**.

(14) We are indebted to Dr. Safe, National Research Council of Canada, Halifax, and Dr. E. P. White, Ruakura Animal Research Station, New Zealand, for their generous gifts of natural sporidesmin A.

(15) By preparative tlc (silica gel), the diastereomers **14a** (amorphous solid) and **14b** [amorphous solid: $\delta_{ppm}^{CDCl_3}$ (1 mg in 0.3 ml) 1.62 (3 H, s), 1.93 (3 H, s), 2.06 (3 H, s), 3.15 (3 H, s), 3.45 (3 H, s), 3.80 (3 H, s), and 3.85 (6 H, s)] were separated at this stage. The diastereomer **14b** corresponds to the (**11b** → **12b** → **13b** → **14b**) series (see ref 11).

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(17) Supported by the Exchange Program between the National Academy of Sciences of the U. S. A. and the Czechoslovakia Academy of Sciences.

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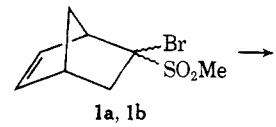
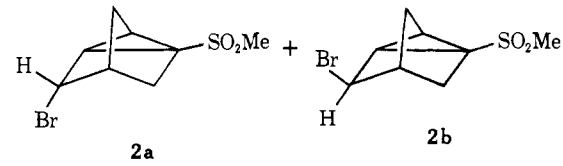
Free Radicals from α-Bromo Sulfones

Sir:

Recently we reported evidence for the unprecedented formation of free-radical intermediates in competition with the normal Ramberg–Bäcklund rearrangement of bromo sulfones **1a**, **1b**.[1] The formation of **2a** and **2b**[2]



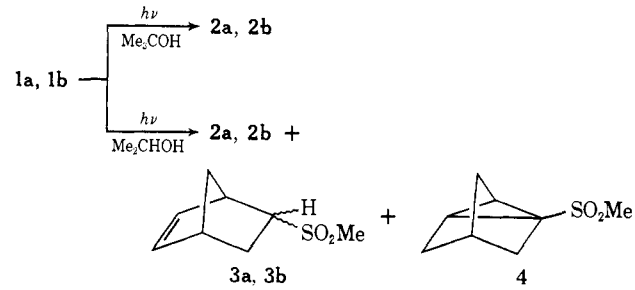
1a, 1b



2a **2b**

was observed in an aqueous sodium hydroxide medium, or more conveniently **1a** or **1b** could be rearranged to **2a**, **2b** by the action of free-radical initiators, *e.g.*, benzoyl peroxide or potassium persulfate in the absence of base.[1] In this communication we wish to describe the photochemistry of **1** and **2** and to comment on the mechanistic aspects and the generality of this free-radical chemistry.

Direct irradiation of **1a** or **1b** in *tert*-butyl alcohol with 2537-Å light for 3 hr afforded a **2a**, **2b** mixture of identical composition to that resulting from treatment of **1a**, **1b** with aqueous sodium hydroxide or with potassium persulfate in 50% aqueous *tert*-butyl alcohol or with benzoyl peroxide in benzene. In all of the above reactions the **2a**:**2b** ratio was 57:43. The same photochemical reaction in pure isopropyl alcohol, a hydrogen atom donor solvent, afforded **3a**, **3b**[3] and **4** in addition to **2a** and **2b**. These same three bromine-free sulfones were obtained in addition to **2a**, **2b** in the reactions induced by persulfate[1] and hydroxide ions in aqueous isopropyl alcohol. A careful tlc and nmr analysis of incomplete transformations revealed no interconversion of **1a** and **1b** in any of the above reactions.



3a, 3b **4**

The formation of nortricyclane sulfone **4** as a major product of the reaction in aqueous isopropyl alcohol prompted us to investigate the photochemistry of **2a** and **2b** with the intention, among other things, of producing a cleaner, synthetically useful preparation of **4**. Irradiation of either **2a** or **2b** in pure *tert*-butyl alcohol produced the same **2a**, **2b** mixture observed in previous reactions. While this photochemical epimerization demonstrates the lability of the carbon–bromine bond in **2a** and **2b**, the presence of norbornenyl bromo sulfones **1a** or **1b** could not be detected. Irradiation of **2a**, **2b** in 10% aqueous isopropyl alcohol containing 1 equiv of sodium carbonate afforded a 92% yield of

(1) J. C. Philips and M. Oku, *J. Amer. Chem. Soc.*, **94**, 1012 (1972).

(2) Independent syntheses confirming the gross structures and stereochemistry of **2a** and **2b** will be reported in the full paper.

(3) J. C. Philips and M. Oku, *J. Org. Chem.*, **37**, 4479 (1972).