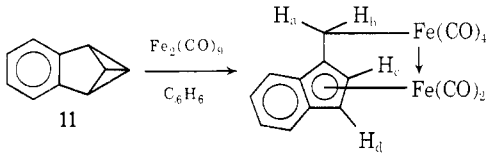
diene and $Fe(CO)_5$.[13] Cycloelimination of carbon is observed in the decomposition of the C_7 carbene of quadricyclane (or norbornadiene) to yield benzene.[14] The driving force in the present reaction **8** → **9** → **3** + **4** is formation of the very stable biscyclopentadienyl complex. We propose that **10** may act as a hydrogen acceptor from **9** and the reduction product dimerizes to yield **5**. Apparently only a very small amount of the π-methylcyclopentadienyldicarbonyliron reacts with π-cyclopentadienyldicarbonyliron to give the mixed bridged complex.

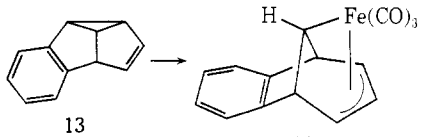
The reason for postulating a different route for the formation of **2**, **3** + **4**, and **5** is due to the fact that benzobenzvalene (**11**)[4] yields only the benzofulvene



11 12

complex **12**[15] upon treatment with diiron nonacarbonyl and no π-indenyl complex analogous to **3**, **4**, or **5**.

We interpret this behavior as being due to the fact that formation of a σ–π allyl intermediate analogous to **8** is impossible in the case of **11**. Also relevant to this point is the fact that benzosemibullvalene **13** yields only the σ–π allyl complex **14**.[1b]



13 14

Acknowledgment. Discussion of this work with Dr. R. Aumann, University of Münster, was valuable. The authors also wish to thank Dr. R. Minard of this Department for assistance with the mass spectral work.

(13) H. W. Sternberg and I. Wender, *Chem. Soc., Spec. Publ.*, **No. 13**, 35 (1959).

(14) P. B. Shevlin and A. P. Wolf, *Tetrahedron Lett.*, 3987 (1970); R. A. Moss, U.-H. Dolling, and J. R. Whittle, *ibid.*, 931 (1971).

(15) Compound **12**, mp 118° dec, has ir (C≡O) 1943, 1960–2000, 2060 cm^{-1}; the mass spectrum showed the parent molecular ion at *m/e* 408; other peaks occurred at *m/e* 380, 352, 324, 296, 268, and 240 corresponding to successive loss of CO; nmr showed aromatic absorption δ (relative to Me_4Si) at 7.20 ppm (four proton), H_d 5.66 ppm (d), H_c 3.80 ppm (d, J_{cd} = 2.8 Hz), H_a and H_b centered at 2.21 ppm (q, J_{ab} = 13.1 Hz). *Anal.* Calcd for $C_{16}H_8O_6Fe_2$: C, 47.06; H, 1.96. Found: C, 47.10; H, 2.03.

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Received June 1, 1973

A New Method for the Synthesis of Epidithiodiketopiperazines

Sir:

The epidithiodiketopiperazine structure is a common functionality in the natural products of the gliotoxin–sporidesmin class.[1] Although a few simple epidithiodiketopiperazine derivatives have been synthesized,[2] a general method is lacking. Here we report a method which is expected to be generally useful for the synthesis of this functionality, starting from 1,4-dimethylpiperazine-2,5-dione-(*cis* or *trans*)-3,6-dithiol **1a** or **1b**.[2a,b]

Anisaldehyde reacted smoothly with the cis dithiol **1a** in methylene chloride containing boron trifluoride etherate at room temperature, to yield the thioacetal **2**[3] (mp 267–268°) in 80% yield. As expected, the same thioacetal **2** could also be obtained from trans dithiol **1b** under the same conditions in similar yield. The thioacetal **2** is stable under acidic, basic, or reductive conditions.

The thioacetal **2** can be used as a protected precursor of the epidithiodiketopiperazine ring,[4] since **2** can be smoothly cleaved into the epidithiodiketopiperazine **3** and anisaldehyde in two steps: the oxidation of **2** to a sulfoxide with *m*-chloroperbenzoic acid in methylene chloride at 0°, followed by acidic treatment, *e.g.*, $BF_3 \cdot Et_2O$, BCl_3, H_2SO_4, or $HClO_4$. In the acidic cleavage reaction of the sulfoxide, a facile carbon–sulfur bond fission—note the resonance stabilization of the carbonium ion by the *p*-methoxybenzene ring—is obviously crucial, because the cleavage reaction does not take place in the thioacetals derived from formaldehyde, acetaldehyde, or benzaldehyde (R = H, CH_3, or C_6H_5 in **2**). Related to this point, a smooth and efficient formation of **3** was observed from the di(tetrahydropyranyl) cis dithiol **4**[3] (mp 164–165°) by iodine oxidation in methylene chloride.

One equivalent of butyllithium in THF at −78° generated the monocarbanion at the bridgehead position of **2**.[5] A large difference in the acidity of the two bridgehead hydrogens was observed. Namely, when the monocarbanion was quenched with DCl, only one bridgehead hydrogen was clearly replaced with deuterium (the chemical shifts of H_a and H_b in **2** are 4.88 and 5.03 ppm and only the signal at 4.88 ppm disappeared).

The monoanion was found to react smoothly with primary halides, acid halides, and aldehydes in THF at −78°, to give the monosubstituted thioacetals **5** and a small amount of the disubstituted thioacetals **10**. The monosubstituted thioacetal **5** was a single material, not a diastereomeric mixture, that is again attributed to the difference in the acidity between two bridgehead hydrogens.

In the following case, the identification of the more acidic hydrogen was possible by a chemical method. Namely, the diastereomeric chlorides **6a**[3,6] (mp 212–

(1) Gliotoxin, sporidesmins, aranotins, chaetocins, verticillin A, and chetomin belong to this class.

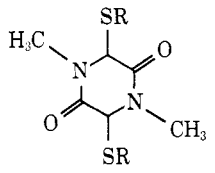
(2) (a) P. W. Trown, *Biochem. Biophys. Res. Commun.*, **33**, 402 (1968); (b) U. Schmidt, *et al.*, *Angew. Chem.*, **83**, 114 (1971); *Chem. Ber.*, **104**, 1714 (1971); **105**, 625, 635, 3658 (1972); **106**, 165, 396 (1973); (c) T. Hino and T. Sato, *Tetrahedron Lett.*, 3127 (1971); (d) S. G. Svokos and R. B. Angier, *Chem. Abstr.*, **74**, 53845 (1971).

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

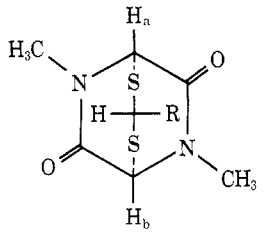
(4) The epidithiodiketopiperazines can be efficiently converted into the thioacetals by sodium borohydride reduction in methanol, followed by an anisaldehyde treatment under acidic conditions.

(5) The monocarbanion is stable at −78°, but decomposes slowly at 0°. The thioacetal **2** decomposed in THF even at −78°, when potassium *tert*-butoxide was used as a base. The dicarbanion, generated from 2 equiv of butyllithium in THF, decomposed into unidentified compounds at −78°.

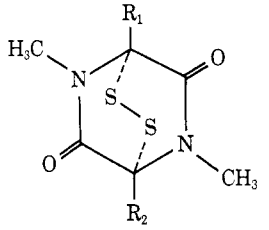
(6) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, **95**, 6492 (1973).



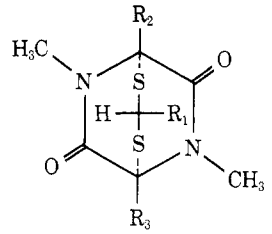
1a, R = H; cis
b, R = H; trans
4, R = THP; cis



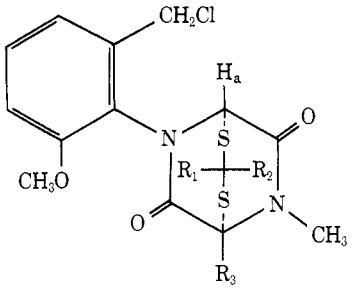
2, R = p-$CH_3OC_6H_4$



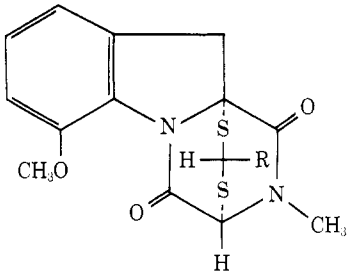
3, $R_1 = R_2 = H$
9, R_1 = substituted; $R_2 = H$
11, R_1, R_2 = substituted



5, R_1 = p-$CH_3OC_6H_4$; R_2 = substituted; $R_3 = H$
10, R_1 = p-$CH_3OC_6H_4$; R_2, R_3 = substituted



6a, R_1 = H*; R_2 = p-$CH_3OC_6H_4$; $R_3 = H_b$
b, R_1 = p-$CH_3OC_6H_4$; R_2 = H*; $R_3 = H_b$
8, R_1 = p-$CH_3OC_6H_4$; $R_2 = H$; $R_3 = CH_2OCH_3$



7, R = p-$CH_3OC_6H_4$

213°) and **6b**[3,6] (mp (from benzene) 119–120°) were isolated in a pure form, and the stereochemistry was assigned from the analysis of the nmr spectra. In one isomer the signal of the H* proton appears at 6.32 ppm and in the other isomer at 5.38 ppm, which is close to the chemical shift (5.14 ppm) of this proton in **2**. Since the large downfield shift, observed in only one isomer, is attributed to the ring current of the methoxybenzene ring, the structure **6a** is assigned to the isomer with the resonance at 6.32 ppm. One equivalent of butyllithium cleanly converts **6a** into **7**, but **6b** is recovered under the same conditions after an acidic work-up.[6] Moreover, the monocarbanion from **6b** reacted with chloromethyl methyl ether, to give **8** in good yield.[6] These results lead to the conclusion that the H_a hydrogen is more acidic in **6a** and the H_b hydrogen is more acidic in **6b**; clearly the relative acidity of these two bridgehead hydrogens is determined by the stereochemistry of the anisaldehyde residue. Because a conclusive structure determination including conformational profile is required for a consideration of the reasons[7] for these interesting phenomena, an X-ray structure determination on the monomethyl thioacetal **5** ($R_2 = CH_3$) is in progress.

The monosubstituted thioacetal **5** was converted to epidithiodiketopiperazine **9** in good yield (50–80%) by oxidation with *m*-chloroperbenzoic acid and acid treatment, as described earlier.

Carbanion formation from the monosubstituted thioacetals **5** with butyllithium in THF at −78° and the subsequent alkylation or acylation were found to be as clean as before and yielded the disubstituted thioacetals **10** in good yield. From the disubstituted thioacetals **10**, the disubstituted epidithiodiketopiperazines **11** were efficiently obtained.

The details of the new methods are illustrated by the following procedures for the synthesis of alanylglycine anhydride **9**[3] ($R_1 = CH_3$ and $R_2 = H$) and alanylserine anhydride **11**[3] ($R_1 = CH_2OH$ and $R_2 = CH_3$) with the disulfide bridge. By a similar or slightly modified procedure, the epidithiodiketopiperazines, composed of alanine, asparagine, glutamine, glycine, leucine, lysine, phenylalanine, serine, threonine, tryptophan, and tyrosine, can be synthesized.

In the preparation of 3,6-epidithio-1,3,4-trimethylpiperazine-2,5-dione (**9**) ($R_1 = CH_3$, $R_2 = H$) the thioacetal **2**, 200 mg, was dissolved in 25 ml of freshly distilled THF and cooled with a Dry Ice–acetone bath. With stirring, 400 μl of 1.69 *M* butyllithium was added. After 30 sec 400 μl of methyl iodide was added. After the reaction mixture had been kept at −78° for 5 min, the cooling bath was removed. When the temperature of the solution reached to 0°, 0.1 ml of acetic acid was added to the solution, which was then evaporated to dryness. The residue was worked up in the usual way, and the products were isolated by preparative tlc (silica gel), to give 120 mg of **5**[3] ($R_2 = CH_3$, $R_3 = H$) (mp (EtOAc) 205–206°, 58%) and 7 mg of **10**[3] ($R_2 = R_3 = CH_3$) (mp (EtOAc) 190–191°, 3%) and 35 mg of recovered starting material (18%).

The monomethyl thioacetal **5** ($R_2 = CH_3$ and $R_3 = H$), 150 mg, was dissolved in 30 ml of methylene chloride and cooled with an ice bath. *m*-Chloroperbenzoic acid, 95 mg, was added portion-wise (the reaction was monitored with tlc). After the reaction was over (about 10 min), the solution was washed with saturated sodium chloride solution containing sodium sulfite and sodium bicarbonate. The methylene chloride layers were dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was dis-

(7) One of the explanations could be that the efficiency of the overlap of 3d orbitals on sulfur with the sp^3 orbital at the bridgehead carbon is angle dependent.

solved in 40 ml of methylene chloride and treated with 2.1 ml of THF containing 63 mg of 70% $HClO_4$ solution at room temperature for 1.5 hr. The reaction mixture was washed with saturated sodium chloride solution. The methylene chloride layers were dried over Na_2SO_4 and evaporated to dryness. The products were isolated by silica gel column chromatography, to give 63 mg of **9**[3] (R_1 = CH_3, R_2 = H) (mp (EtOAc) 127–128°, 65%).

In the preparation of 3,6-epidithio-1,3,4-trimethyl-6-hydroxymethyl-2,5-dione (**11**) (R_1 = CH_2OH, R_2 = CH_3) the monomethoxymethyl thioacetal **5**[3] (R_2 = CH_2OCH_3, R_3 = H) was prepared in 60% yield by the same procedure as above. The second alkylation with methyl iodide was again carried out under the same conditions to yield the methoxymethyl methyl thioacetal **10**[3] (R_2 = CH_2OCH_3, R_3 = CH_3) (mp 200–201°) in 76% yield.

The methoxymethyl methyl thioacetal **10**, 50 mg, was dissolved in 5 ml of methylene chloride and cooled with an ice bath. *m*-Chloroperbenzoic acid, 28 mg, was added portion-wise. After the reaction mixture had been kept at 0° for 10 min, 5 ml of BCl_3 was added at 0°. After 10 min the reaction mixture was evaporated under reduced pressure. The residue was dissolved in 5 ml of methanol and taken to dryness. The products were isolated by preparative tlc (silica gel) to afford 18 mg of **11**[3] (R_1 = CH_2OH, R_2 = CH_3) (mp-(EtOAc) 122–125°, 56%).

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

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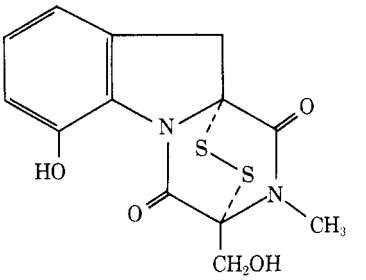
A Total Synthesis of Dehydrogliotoxin

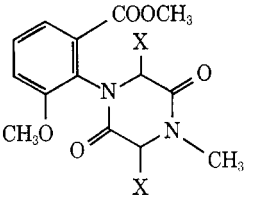
Sir:

Dehydrogliotoxin (**1**),[1] the dehydrogenation product of gliotoxin,[2] was found in surface cultures of an isolate of *Penicillium terlikowskii* and shown to inhibit the growth of *Bacillus subtilis* at concentrations similar to the inhibitory concentration of gliotoxin.[3] In this communication we report the first total synthesis of *d,l*-dehydrogliotoxin (**1**) based on the method described in the preceding paper.[4]

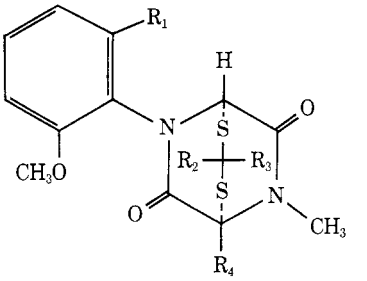
Heating 1-methylpiperazine-2,5-dione[5] with 2-iodo-3-methoxybenzoic acid[6] in nitrobenzene in the presence of cuprous iodide and potassium carbonate at 170° for 40 min, followed by esterification with diazomethane, afforded the diketopiperazine **2**[7] (mp 140–141°) in 50% yield. Oxidation of **2** with NBS benzoyl peroxide in carbon tetrachloride and work-up with potassium thioacetate in methylene chloride at room temperature gave



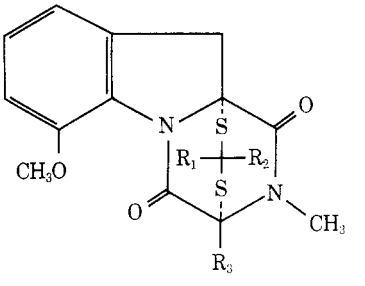
1, dehydrogliotoxin



2, X = H
3, X = SAc (1:1 cis and trans mixture)



4, R_1 = $COOCH_3$; R_4 = H;
R_2 or R_3 = H or *p*-$CH_3OC_6H_4$
(1 : 1 diastereomeric mixture)
5a, R_1 = CH_2Cl; R_2 = R_4 = H;
R_3 = *p*-$CH_3OC_6H_4$
b, R_1 = CH_2Cl; R_2 = *p*-$CH_3OC_6H_4$;
R_3 = R_4 = H
8, R_1 = CH_2Cl; R_2 = *p*-$CH_3OC_6H_4$;
R_3 = H; R_4 = CH_2OCH_3



6a, R_1 = R_3 = H; R_2 = *p*-$CH_3OC_6H_4$
7a, R_1 = H; R_2 = *p*-$CH_3OC_6H_4$;
R_3 = CH_2OCH_3
b, R_1 = *p*-$CH_3OC_6H_4$; R_2 = H;
R_3 = CH_2OCH_3

the dithioacetate **3**[7] (mp 168–175°, *ca.* 1:1 mixture of cis and trans isomers). This cis–trans mixture of **3** was transformed into the anisaldehyde adduct **4**[7] (mp

(1) H. Herrmann, R. Hodges, and A. Taylor, *J. Chem. Soc.*, 4315 (1964).
(2) M. R. Bell, J. R. Johnson, B. S. Wildi, and R. B. Woodward, *J. Amer. Chem. Soc.*, **80**, 1001 (1958).
(3) G. Lowe, A. Taylor, and L. C. Vining, *J. Chem. Soc.*, 1799 (1966).
(4) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, **95**, 6490 (1973).
(5) P. A. Levene, L. W. Bass, A. Rothen, and R. E. Steiger, *J. Biol. Chem.*, **81**, 697 (1929).
(6) W. M. Stanley, E. McMahon, and R. Adams, *J. Amer. Chem. Soc.*, **55**, 706 (1933).
(7) Satisfactory analytical and spectroscopic data were obtained on this compound.