employing a methylene chloride–ethyl acetate gradient to afford **5**.

5a: 40% yield; mp 147–148 °C (from chloroform–hexane); IR (CH_2Cl_2) 1800 (β-lactam), 1750 (ester), 1685 (amide), 1645 cm^{-1} (thiol lactone); ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H, CH_3), 4.6 (s, 2 H, CH_2O), 5.0 (s, 2 H, CH_2CCl_3), 5.8–6.1 (m, 2 H, H-6/H-7), 6.8–7.5 (m, 5 H, Ph), 7.7 (d, 1 H, J = 8 Hz, NH); $[\alpha]^{25}_D$ –91° (c 1, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 312 (ϵ 7400). Anal. Calcd for $C_{18}H_{15}Cl_3N_2O_6S$: C, 43.78; H, 3.06; N, 5.67. Found: C, 44.05; H, 3.25; N, 5.79.

5b: 38% yield; R_f 0.9 (9:1 $CHCl_3$–AcOEt); IR (CH_2Cl_2) 1800, 1740, 1680, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8 (s, 3 H), 4.6 (s, 2 H), 4.8 and 5.1 (AB q, 2 H, J = 12 Hz), 5.8–6.1 (m, 2 H, H-6/H-7), 6.8–7.9 (m, 12 H); $[\alpha]^{25}_D$ –110° (c 1, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 308 (ϵ 6000).

5c: 10% yield; R_f 0.8 (4:1 $CHCl_3$–AcOEt); IR (CH_2Cl_2) 1785, 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 3.0–4.0 (m, 2 H), 5.55 (dd, 1 H, J = 2, 5 Hz), 7.1 (s, 1 H), 7.0–7.6 (m, 10 H).

5d: 26% yield; R_f 0.9 (4:1 $CHCl_3$–AcOEt); IR (CH_2Cl_2) 1800, 1750, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9 H), 2.05 (s, 3 H), 3.2–4.05 (m, 2 H), 4.8 and 5.2 (AB q, 2 H, J = 12 Hz), 5.6 (dd, 1 H, J = 3, 6 Hz), 6.0 (s, 2 H).

2-Oxo-3-(acetoxymethyl)-7β-(phenoxyacetamido)ceph-3-em-4-carboxylic Acid (5e). To a solution of 98 mg (0.17 mmol) of **5b** in 15 mL of methylene chloride at 0 °C were added 90 mg (0.84 mmol) of anisole and 743 mg (6.52 mmol) of trifluoroacetic acid.[11] After 0.5 h at 0 °C the reaction was diluted with 50 mL of ice-cold toluene and evaporated to dryness. The residue was dissolved in methylene chloride, treated with 17 mg (0.17 mmol) of triethylamine, and again evaporated to dryness. Trituration with ether afforded 45 mg of **5e** as the amorphous triethylamine salt (54%): IR (CH_2Cl_2) 1780, 1650, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (s, 3 H), 4.5 (s, 2 H), 4.8 and 5.2 (AB q, 2 H, J = 12 Hz), 5.8–6.0 (m, 2 H), 6.8–7.6 (m, 6 H).

Acknowledgment. The authors wish to thank Professor E. J. Corey for helpful discussions.

Registry No. **1a**, 66614-35-5; **1b**, 71786-01-1; **1c**, 71786-02-2; **1d**, 71786-03-3; **5a**, 71786-04-4; **5b**, 71786-05-5; **5c**, 71786-06-6; **5d**, 71786-07-7; **5e**, 71786-08-8; 2,2,2-trichloroethyl 1β-oxo-3-methyl-7β-(phenoxyacetamido)ceph-3-em-4-carboxylate, 24689-52-9; diphenylmethyl 1β-oxo-3-(acetoxymethyl)-7β-(phenoxyacetamido)-ceph-3-em-4-carboxylate, 71786-09-9; diphenylmethyl 1β-oxo-3-methylceph-3-em-4-carboxylate, 71786-10-2; *tert*-butyl(carbonyloxy)methyl 1β-oxo-3-(acetoxymethyl)ceph-3-em-4-carboxylate, 71786-11-3.

Regiospecific Dimerization Leading to a 14-Membered Heterocyclic Ring. Synthesis and X-ray Structure

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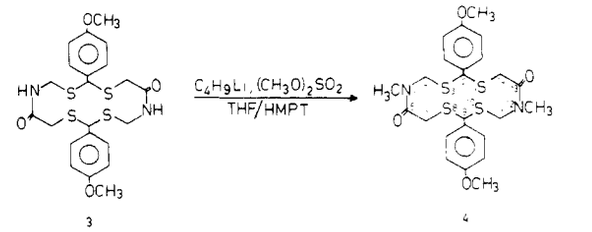
Received August 6, 1979

In connection with work related to natural products of the gliotoxin–sporidesmin class of compounds,[1] we became interested in studying simple 4-aza-1,2-dithian-5-ones.

An approach involving preparation of *N*-(thiomethyl)-thioglycolic acid amide (**2**), followed by protection of the thiol functions along the route used by Kishi et al.[2] seemed to be promising, but in our case the outcome, although not entirely unexpected, was not the desired one.

We prepared *N*-[(acetylthio)methyl](acetylthio)acetic acid amide **1** through the reaction of *N*-(chloromethyl)-chloroacetamide[3] with potassium thioacetate. From **1** the dithiol **2** was obtained by hydrolysis with 1.2 N methanolic hydrochloric acid. When **2** was reacted with anisaldehyde



and small amounts of boron trifluoride etherate in methylene chloride,[2] a compound **3** was obtained in 61% yield. This highly insoluble compound was converted to a more soluble derivative by treatment of a solution of **3** in HMPA/THF (hexamethylphosphorictriamide/tetrahydrofuran) cooled to –95 °C with butyllithium and then with dimethyl sulfate, which gave the N-methylated derivative **4** in good yield.

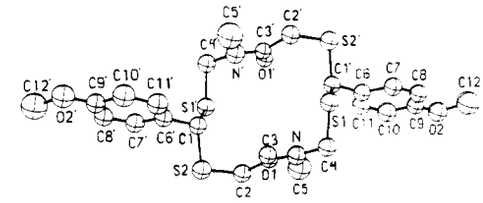


Figure 1. Computer-generated drawing of the X-ray model of **4**.

An X-ray crystal structure determination undertaken for **4** showed unequivocally that this compound is dimeric (see Figure 1), being 2,9-bis(*p*-methoxyphenyl)-5,12-dimethyl-5,12-diaza-1,3,8,10-tetrathiacyclotetradecane-6,13-dione, **3** thus being 2,9-bis(*p*-methoxyphenyl)-5,12-diaza-1,3,8,10-tetrathiacyclotetradecane-6,13-dione.

4 was recrystallized from chloroform. The very thin, nearly square crystals are orthorhombic with a = 9.171 (4), b = 29.049 (4), and c = 9.593 (13) Å. Systematic extinctions indicate space group *Pbca*, with Z = 4. The structure, determined from 1801 graphite-monochromatized Cu Kα reflections, measured at –125 °C (isotropic temperature factors, no H atoms), was solved by symbolic addition and refined by full-matrix least-squares methods to R = 0.12. Despite the low-temperature data many of the thermal parameters are quite high (B = 4–8 Å^2), but all geometric parameters are within normal ranges (see supplementary material).

Compound **3** gave correct analysis for the desired thioacetal, and a very weak peak at m/e 510 in its mass spectrum is also consistent with the dimeric structure. The mass spectrum of **4** also gave some evidence for a dimeric structure: m/e (11 eV) 538 (6.3%).

An interesting point is that, in accordance with the X-ray crystal structure determination, only one of two possible dimeric products was formed. The exclusive formation of **3** might be due to dimerization of intermediates of either type **5** or type **6** and indicates a large difference in the nucleophilicity of the SH groups of **2**.

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(1) P. W. Trown, *Biochem. Res.*, **33**, 402 (1968).
(2) Y. Kishi, T. Kukugama, and S. Nakatsuka, *J. Am. Chem. Soc.*, **95**, 6490 (1973).
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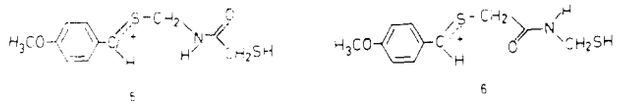
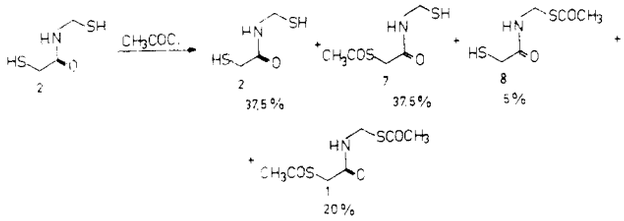
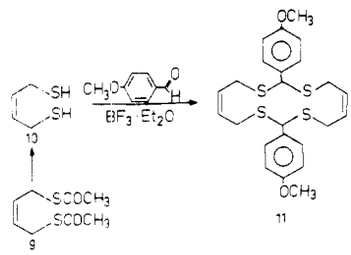


The intermediate 6 was in fact shown to be the more probable one, as in reaction of **2** with acetyl chloride in 1,2-dichloroethane at room temperature the thiol group in the α-position to the carbonyl was the most reactive one.



Using symmetrical α,ω-dithiols such as pentamethylene dimercaptan, Authenrieth et al. obtained a dimeric 16-membered ring with acetone but polymeric products with benzaldehyde, benzophenone, and acetaldehyde.[4] Also with *p*-xylyl dimercaptan and *m*-xylyl dimercaptan 18- and 16-membered mercaptols were reported.[5] More than 40 years later Marvel and co-workers found that a wide variety of carbonyl compounds gave polymers with hexamethylene dimercaptan.[6] However, decamethylene dimercaptan gave as the main product 26-membered dimercaptals together with minor yields of polymeric material upon reaction with aromatic aldehydes.[7] Heptamethylene dimercaptan gave a low molecular weight linear product with vanillin. However, both heptamethylene dimercaptan and nonamethylene dimercaptan gave good yields of the 18- and 22-membered rings.[8] The molecular weights of these compounds were demonstrated by ebullioscopic methods. In the light of these and our investigations, the monothioacetalization of derivatives of 2,5-diketopiperazine-3,6-dithiol[2] seems to be quite exceptional. In order to find out if this was due to cis arrangement in Kishi's dithiols, we reacted *cis*-1,4-dimercapto-2-butene (**10**),[8] obtained by hydrolysis of the diacetate **9**, with anisaldehyde in the presence of boron trifluoride etherate. Again a highly insoluble, crystalline product, **12**, was obtained, melting sharply at 244 °C and also giving mass spectral evidence for a dimeric structure, showing that the cis position of the thiol groups is not a sufficient condition for monothioacetalization. It is obvious that the formation of monomeric thioacetals, dimeric thioacetals, or polymers is highly dependent on the length of the α,ω-dithiol and the nature of the carbonyl compounds and that more systematic studies are necessary for a complete understanding.



Experimental Section

***N*-[(Acetylthio)methyl](acetylthio)acetic Acid Amide (1).** To 14.2 g (0.1 mol) of freshly prepared *N*-(chloromethyl)chloroacetamide[3] in 100 mL of methylene chloride was added 25 g of potassium thioacetate in one portion. The mixture was stirred overnight at room temperature, whereafter 100 mL of ethanol was added and the mixture stirred for an additional 2 h. After filtration and evaporation, the crude product dissolved in 100 mL of methylene chloride was washed (3 × 50 mL) with saturated NaCl solution, dried over $MgSO_4$, and recrystallized from ethanol, giving 16.7 g (71% yield) of **1**: mp 62.5–63.5 °C; NMR (Me_2SO-d_6) δ 2.37 (s, 3 H), 2.40 (s, 3 H), 3.60 (s, 2 H), 4.66 (d, 2 H, J = 6.1 Hz), 7.3–7.4 (br, 1 H, NH).

Anal. Calcd for $C_7H_{11}NO_3S_2$: C, 38.0; H, 5.01; N, 6.33; S, 28.9. Found: C, 38.0; H, 5.05; N, 6.38; S, 29.1.

***N*-(Thiomethyl)thioglycolic Acid Amide (2).** Compound **1** (22.1 g, 0.1 mol) was hydrolyzed during 24 h at room temperature in 300 mL of 1.2 N methanolic hydrochloric acid, whereafter the solvent was evaporated, the residue extracted with ether continuously for 24 h, and the solvent again evaporated. The oily residue (8.2 g, 75%) was characterized by the following: NMR ($CDCl_3$) δ 2.25 (t, 1 H, J = 6.3 Hz), 2.61 (t, 1 H, J = 8.7 Hz), 3.33 (d, 2 H, J = 6.3 Hz), 4.41 (dd, 2 H, J_{SH} = 8.7 Hz, J_{NH} = 6.2 Hz), 8.18 (br, 1 H, NH).

Anal. Calcd for $C_3H_7NOS_2$: C, 26.2; H, 5.14; N, 10.2. Found: C, 26.4; H, 5.12; N, 9.85.

2,9-Bis(*p*-methoxyphenyl)-5,12-diaza-1,3,8,10-tetrathiacyclotetradecane-6,13-dione (3). The freshly prepared dithiol **2** described above was dissolved in 300 mL of methylene chloride. To this mixture was added first in one portion 2.5 mL of boron trifluoride etherate, and then 13.8 g (0.1 mol) of anisaldehyde in 50 mL of methylene chloride was added dropwise with stirring. The reaction mixture was then stirred for 24 h and the product filtered and washed with ethanol. The dried product (16.6 g, 61%) melted at 214–217 °C dec; NMR (Me_2SO-d_6, 100 °C) δ 3.03 (d, 2 H, J = 16 Hz, H7, 14), 3.45 (d, 2 H, J = 16 Hz, H7, 14), 3.80 (s, 6 H), 3.97–4.64 (octet, 4 H, H4, 11), 5.20 (s, 2 H), 6.9 (d, 4 H, J = 8 Hz), 7.4 (d, 4 H, J = 8 Hz).

Anal. Calcd for $C_{11}H_{13}NO_2S_2$: C, 51.7; H, 5.13; N, 5.49; S, 25.1. Found: C, 51.7; H, 5.07; N, 5.60; S, 25.4.

2,9-Bis(*p*-methoxyphenyl)-5,12-dimethyl-5,12-diaza-1,3,8,10-tetrathiacyclotetradecane-6,13-dione (4). The dithioacetal **3** (7.30 g, 28.6 mmol) was dissolved under nitrogen in 100 g of dry, boiling HMPA and transferred into a round-bottomed, three-necked flask containing 1000 mL of dry THF. The solution was cooled to −95 °C, and 20.0 mL (30 mmol) of 1.50 N BuLi/hexane was added dropwise with stirring. The addition was completed within 15 min, and the mixture was stirred for an additional 15 min and treated with 4.0 mL of dimethyl sulfate. After 30 min, the mixture was allowed to warm to room temperature, the solvent was evaporated, and the residue was poured onto 500 mL of ice–water containing 2 mL of concentrated ammonia and left overnight. The product was filtered, washed with water, and dried under vacuum. After recrystallization from chloroform the product (7.5 g, 97% yield) melted at 206–208 °C; NMR (Me_2SO-d_7, 130 °C)[9] δ 2.96 (s, 3 H), 3.50 (s, 2 H, H7, 14), 3.53 (s, 2 H, H7, 14), 3.75 (s, 3 H), 4.68 (s, 2 H, H4, 11), 4.75 (s, 2 H, H4, 11), 5.31 (s, 2 H), 6.9 (d, 4 H, J = 8 Hz), 7.4 (d, 4 H, J = 8 Hz).

Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.5; H, 5.61; N, 5.20; S, 23.8. Found: C, 52.8; H, 5.52; N, 5.18; S, 22.7.

Acetylation of 2. To a stirred solution of 0.685 g (0.500 mmol) of **2** in 5 mL of 1,2-dichloroethane at room temperature was added 0.354 mL (0.500 mmol) of acetyl chloride dropwise, and the mixture was left for 3 h. After evaporation to dryness, the residue was dried under vacuum and transferred to an NMR tube. The NMR spectra in $CDCl_3$ were assigned to a mixture of four components: dithioacetate **1**, dithiol **2**, *N*-(thiomethyl)(acetylthio)-

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(9) At lower temperature, splitting of several peaks due to slow interconversion of conformers was observed.

acetic acid amide (7), and *N*-[(acetylthio)methyl]thioglycolic acid amide (8).

The NMR data were as follows: (1) δ 2.37 (s), 2.40 (s), 3.60 (s), 4.65 (d, J = 6.4 Hz); (2) δ 2.19 (t, J = 6.3 Hz), 2.58 (t, J = 8.7 Hz), 3.30 (d, J = 6.3 Hz), 4.40 (dd, J_{SH} = 8.7 Hz, J_{NH} = 6.2 Hz); (7) δ 2.40 (s), 2.54 (t, J = 8.7 Hz), 3.60 (s), 4.36 (dd, J_{SH} = 8.7 Hz, J_{NH} = 6.2 Hz); (8) δ 2.16 (t, J = 6.3 Hz), 2.40 (s), 3.33 (d, J = 6.3 Hz), 4.69 (d, J = 6.4 Hz).

Integration over appropriate peaks indicated that the reaction mixture contained 1, 2, 7, and 8 in the ratio 20:37.5:37.5:5.

2,9-Bis(*p*-methoxyphenyl)-1,3,8,10-tetrathiacyclotetradecane-5,12-diene (11). Crude **10** (0.40 g, 0.0030 mol) obtained by hydrolysis of **9** in 1.2 N methanolic hydrogen chloride[8] was mixed with 0.42 g (0.003 mol) of anisaldehyde in 150 mL of methylene chloride. One drop of boron trifluoride etherate was added, and the mixture was kept overnight at room temperature. The precipitate was filtered, washed with ethanol, and recrystallized from large amounts of pyridine. The product (0.6 g, 75% yield) melted at 244 °C; mass spectrum (11 eV), m/e (rel intensity) 476 (<1), 358 (9), 270 (15); an NMR spectrum could not be obtained due to the insolubility of the sample.

Anal. Calcd for $C_{24}H_{28}O_2S_4$: C, 60.5; H, 5.92; S, 26.9. Found: C, 60.4; H, 5.80; S, 26.4.

Acknowledgment. This work was supported by the Swedish Natural Science Research Council and the Royal Physiographic Society in Lund.

Registry No. 1, 71831-11-3; 2, 71831-12-4; 3, 71831-13-5; 4, 71831-14-6; 7, 71831-15-7; 8, 71831-16-8; 9, 71831-17-9; 10, 55443-61-3; 11, 71831-18-0; *N*-(chloromethyl)chloroacetamide, 3659-52-7.

Supplementary Material Available: The crystallographic data for 4 [fractional coordinates (Table I), bond distances (Table II), and bond angles (Table III)] (2 pages). Ordering information is given on any current masthead page.

Aldehyde Syntheses. Study of the Preparation of 9,10-Anthracenedicarboxaldehyde

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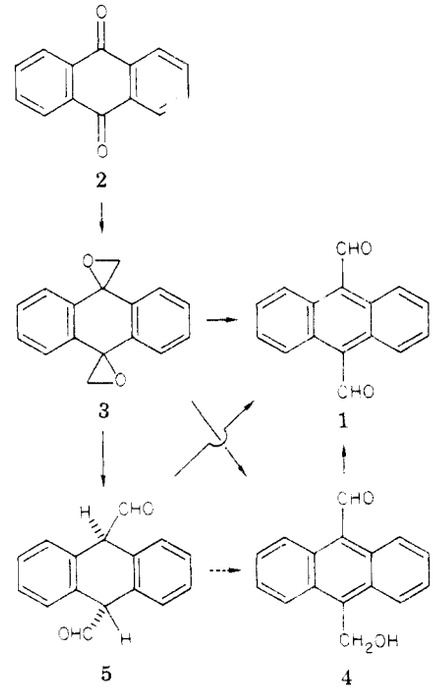
Received May 8, 1979

9,10-Anthracenedicarboxaldehyde (1) is the key intermediate for the synthesis of compounds with biological activity.[2] None of the three reported methods for the synthesis of 1 is convenient or economical. One method[3] involves a low-yield multistep synthesis starting from anthraquinone (2). The other two methods employ respectively dichloromethylation of anthracene[4] and lithiation of 9,10-dibromoanthracene[3] in their synthetic sequences. Since anthraquinone (2) and its substituted derivatives are readily available, a new practical synthesis of 1 from 2 has been sought.

Results and Discussion

We have developed new high-yield three-step syntheses of 1 starting from 2. *trans*-Dispiro[oxirane-2,9′(10′*H*)-anthracene-10′,2″-oxirane] (3)[5] was prepared in 94% yield by the reaction of anthraquinone with dimethylsulfonium methylide which was generated in situ by reacting trimethylsulfonium iodide with sodium hydride in dimethyl sulfoxide. The epoxide functions of 3 may open in two different modes depending on reaction conditions. Under mild and selective conditions, the epoxide moieties of 3 open in a stepwise fashion leading to the formation of 10-hydroxymethyl-9-anthraldehyde (4); for example, the rearrangement of 3 with lithium bromide in acetonitrile at 60 °C gave 4 in quantitative yield. Secondarily, the addition of dilute boron trifluoride etherate solution into a solution of 3 in ether at −45 °C also gave 4 but in 52% yield. Under more drastic conditions, however, both epoxide functions of 3 open simultaneously leading to *trans*-9,10-dihydro-9,10-anthracenedicarboxaldehyde (5); for example, the addition of an etheral solution of 3 to a dilute boron trifluoride etherate solution at 0 °C gave 5 in 95% yield. Furthermore, the treatment of 3 with boron trifluoride etherate at room temperature led to the formation of 1 in low yield (Scheme I).

Scheme I



The structure of 5 was determined by single-crystal X-ray methods.[6] The stereochemistry of the two aldehyde functions is trans. The center of the molecule coincides with a crystallographic inversion center, and the central ring is an extremely distorted chair form with torsion angles of approximately 4°. In agreement with our expectation, both NMR and IR spectra of 5 were similar but different from those of its cis isomer,[7] which was synthesized by oxidation of *cis*-9,10-dihydro-9,10-ethanoanthracene-11,12-diol with potassium periodate.

The oxidation of 4 by dimethyl sulfoxide in the presence of a sulfur trioxide–pyridine complex and triethylamine[8] at room temperature gave 1 in 95% yield.

Attempts to rearrange 5 to 4 with triethylamine in ether or with lithium bromide in acetonitrile led to the formation

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(7) R. G. Child, S. A. Lang, Jr., V. J. Lee, and Y. Lin, in preparation. NMR ($CDCl_3$) δ 4.92 (d, J = 2.2 Hz, 2), 7.40 (s, 8), 9.40 (d, J = 2.2 Hz, 2); IR (KBr) 2800, 1720, 1480, 1450, 1380, 1300, 1240, 1120, 1010, 772, 755, 682 cm^{-1}.
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