of THF was added at -78 °C and stirring was continued at this temperature for 2 h. Methanol (0.5 mL) was added, and the mixture was allowed to reach room temperature. Extractive workup, drying, evaporation of the solvent, and column chromatography yielded 510 mg of **14a** (1.55 mmol, 89%) as an orange oil: IR (CCl_4) ν 1720 cm^{-1}; ^1H NMR (60 MHz) δ 7.9–6.0 (m, 5 H, 7-H, 8-H, 10-H, 11-H, 12-H), 5.58 (s, 1 H, 14-H), 3.65 (s, 3 H, 15-OCH_3), 2.45 (q, 2 H, 13-CH_2, J = 7 Hz), 2.2–2.0 (m, 2 H, 4-H), 1.98 (s, 3 H, 9-CH_3), 1.70 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 4 H, 2-H, 3-H), 1.17 (t, 3 H, 13-CCH_3), 1.05 (s, 6 H, 1-CH_3); MS, m/e 328 (M^+); exact mass calcd for $C_{22}H_{32}O_2$ 328.2402, found 328.2405.

20-Nor-13-ethylretinal (15a). To 68 mg (1.8 mmol) of $LiAlH_4$ in 5 mL of diethyl ether was added 510 mg (1.55 mmol) of **14a** in 5 mL of diethyl ether at -65 °C. The mixture was stirred at -30 °C for 2 h and hydrolyzed with 1 mL of saturated NH_4Cl solution. The precipitate was filtered off and washed with diethyl ether. The crude alcohol obtained after drying of the filtrate and evaporation of the solvent was dissolved in 40 mL of diethyl ether, and 5.2 g (0.06 mol) of activated manganese dioxide was added. After the mixture had been stirred for 15 h, the manganese dioxide was removed by filtration, and the solvent was evaporated. Purification of the crude aldehyde by column chromatography provided 225 mg of **15a** (0.75 mmol, 49%) as a yellow oil. The product was analyzed by HPLC and consisted out of 55% 13-*cis*- and 45% 9-*cis*,13-*cis*-**15a**: IR (CCl_4, 13-*cis*-**15a**): ν 1670 cm^{-1}. ^1H and ^{13}C NMR: see paragraph at the end of the paper about supplementary material. UV: see Table II. MS: m/e 298 (M^+); exact mass calcd for $C_{21}H_{30}O$ 298.2297, found 298.2300.

Methyl 20-Nor-13-*tert*-butylretinoate (14b). A suspension of 434 mg (2.28 mmol) of copper(I) iodide in 4 mL of THF was treated with 2.9 mL of *tert*-butyllithium (4.55 mmol, 15% solution in pentane) at -30 °C. After addition of 522 mg (1.75 mmol) of **13** in 4 mL of THF at -78 °C and stirring at this temperature for 2 h, 0.5 mL of methanol was added. Workup was carried out as described for **14a** and furnished 483 mg of **14b** (1.35 mmol, 77%) as an orange oil: IR (CCl_4) ν 1725 cm^{-1}; ^1H NMR (60 MHz) δ 7.0–6.0 (m, 5 H, 7-H, 8-H, 10-H, 11-H, 12-H), 5.83 and 5.67 (2 × s, 1 H, 14-H), 3.65 and 3.60 (2 × s, 3 H, 15-OCH_3), 2.2–2.0 (m, 2 H, 4-H), 1.97 (s, 3 H, 9-CH_3), 1.70 (s, 3 H, 5-CH_3), 1.7–1.5 (m, 2 H, 2-H, 3-H), 1.23 and 1.20 (2 × s, 9 H, 13-CCH_3), 1.03 (s, 6 H, 1-CH_3); MS, m/e 356 (M^+). Exact mass calcd for $C_{24}H_{36}O_2$ 356.2715, found 356.2707.

20-Nor-13-*tert*-butylretinal (15b). The reduction of 483 mg (1.35 mmol) of **14b** in 5 mL of diethyl ether with 61 mg (1.6 mmol) of $LiAlH_4$ in 5 mL of diethyl ether and the reoxidation with 4.3 g (0.05 mol) of activated manganese dioxide was carried out as described for **15a**, yielding 260 mg of **15b** (0.80 mmol, 59%) as a yellow oil. The composition of the product mixture was determined by HPLC: 33% 9-*cis*,13-*cis*- and 67% 13-*cis*-**15b**; IR (CCl_4, 13-*cis*-**15b**) ν 1670 cm^{-1}. ^1H and ^{13}C NMR: see paragraph at the end of the paper about supplementary material. UV: see Table II. MS: m/e 326 (M^+); exact mass calcd for $C_{23}H_{34}O$ 326.2610, found 326.2622.

Acknowledgment. Gifts of chemicals by the BASF AG (Ludwigshafen) are gratefully acknowledged. N.K. thanks the Fonds der Chemischen Industrie for a dissertation scholarship.

Supplementary Material Available: Tables of ^1H and ^{13}C NMR data for compounds **10** and **15** (6 pages). Ordering information is given on any current masthead page.

Chemistry of N-Heterocyclic Sulfur Compounds. Reaction of 2,5-Dimercapto-1,3,4-thiadiazoles with 1,ω-Dibromoalkanes. Synthesis of Tetrathia[(*n* + 2).(*n* + 2)](2,5)-1,3,4-thiadiazolophanes and Dithia[(*n* + 1).(*n* + 1)](3,5)-1,3,4-thiadiazolinophanedithiones

Sebastiano Pappalardo,* Francesco Bottino, and Corrado Tringali

Dipartimento di Scienze Chimiche, Università di Catania, 95125 Catania, Italy

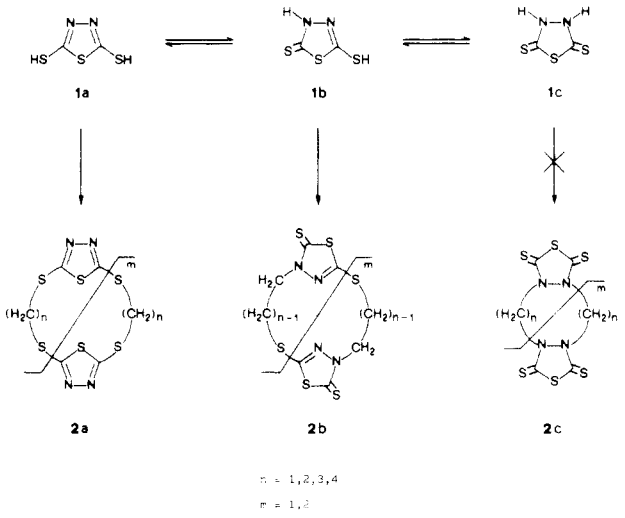
Received March 21, 1986

The base-catalyzed reaction of 2,5-dimercapto-1,3,4-thiadiazole (**1**) with 1,ω-dibromoalkanes $Br(CH_2)_nBr$ (n = 1–4) has been investigated. Model experiments on the alkylation of 2-mercapto-5-(methylthio)-1,3,4-thiadiazole (**3**) with 1,ω-dibromoalkanes and 2,5-bis[(chloroalkyl)thio]-1,3,4-thiadiazoles, as well as on the dialkylation of **1** with 2-[(chloroalkyl)thio]-5-(methylthio)-1,3,4-thiadiazoles, have shown that both **3** and **1** undergo regioselective S-alkylation under basic conditions. However, the heterocyclization of **1** with 1,ω-dibromoalkanes and 2 equiv of KOH, carried out in EtOH under high dilution conditions, not only gave the expected S,S-bridgehead 2:2 macrocycles **2a** (m = 1; n = 1, 2, 4), i.e., tetrathia[(n + 2).(n + 2)](2,5)-1,3,4-thiadiazoles, but also the S,N-bridgehead 2:2 macrocycles **2b** (m = 1; n = 2, 3), i.e., dithia[(n + 1).(n + 1)](3,5)-1,3,4-thiadiazolinophanedithiones. Furthermore, the high-dilution reaction of **1** with CH_2Br_2 and triethylamine gave 1,3,9,11,17,19-hexathia[3.3.3](2,5)-1,3,4-thiadiazolinophane (**19**) (**2a**: m = 2; n = 1), while the use of 1 equiv of KOH under moderate dilution resulted in the formation of the macrocyclic isomer 1,8,15-trithia[2.2.2](3,5)-1,3,4-thiadiazolinophane-4,11,18-trithione (**20**) (**2b**: m = 2; n = 1). The product distribution appears to be strongly dependent on the experimental conditions used, the nature and amount of base, the length of the dibromide, and its strength as an electrophilic agent. Several competing mechanisms have been ascertained to occur in the base-catalyzed heterocyclization of **1** with 1,ω-dibromoalkanes. The proposed reaction pathways gain support from the study of appropriate model reactions and from the isolation and identification of the involved key intermediates. ^{13}C NMR spectroscopy has been extensively used to firmly establish the structures of the compounds obtained.

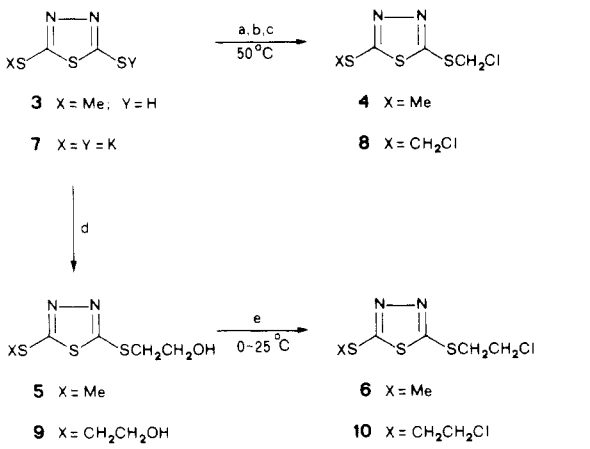
In the light of potential biological[1] and analytical[2,3] interest in disubstituted 1,3,4-thiadiazoles, as well as the limited examples of 1,3,4-thiadiazole inclusion in a macrocyclic framework,[4] recently we described the synthesis

0022-3263/87/1952-0405$01.50/0

Chart I



Scheme I[a]



[a] (a) MeONa/MeOH; (b) $PhCH_2(Et)_3N^+Br^-$; (c) $BrCH_2Cl$; (d) $BrCH_2CH_2OH/KOH/EtOH/\Delta$; (e) $SOCl_2/Py$.

of a series of macrocyclic compounds containing 2,5-dithio-1,3,4-thiadiazole moieties connected by 1,2-, 1,3-, and 1,4-bis(methylene)benzenes.[5]

As an extension of these studies, we report here our results on the base-catalyzed reaction of 2,5-dimercapto-1,3,4-thiadiazole (1) with 1,ω-dibromoalkanes of general formula $Br(CH_2)_nBr$ (n = 1–4). The reaction of 1 with CH_2Br_2 has been the subject of a preliminary communication.[6]

Since dithiol 1 theoretically can exist in any of three tautomeric forms **1a**, **1b**, and **1c**, many cyclization modes can be envisaged in these reactions, which might afford a variety of symmetrical and/or unsymmetrical macrocycles. Chart I shows the three possible symmetrical structures **2a–c** that can in principle be obtained when 1 is treated with dibromoalkanes in alkaline medium.

Actually, from these reactions we have isolated macrocycles of type **2a** (m = 1, 2; n = 1, 2, 4) and/or **2b** (m = 1,2; n = 1, 2, 3), with no evidence for the formation of macrocycles of type **2c**. The cyclic nature of the compounds obtained has been confirmed by their ^1H NMR and mass spectra. In some cases, however, these spectral data alone afforded little assistance in the structural assignment of macrocycles. Since ^{13}C NMR spectroscopy has been shown to provide a powerful tool for distinguishing between substitution on sulfur and/or nitrogen in heterocyclic thiols capable of thiol–thione tautomerism,[7] we have extensively used this technique to firmly establish the structures of all the compounds obtained. For those macrocycles whose ^{13}C NMR spectra were precluded by solubility problems, an independent stepwise synthesis was achieved; alternatively, the structural assignment was made by comparison of their ^1H NMR spectra with those of suitable acyclic or cyclic model compounds of well-established structure.

The product distribution in the reaction of 1 with 1,ω-dibromoalkanes in alkaline medium appears to depend on many factors; among these, the experimental conditions used, the nature and amount of base, the length of the dibromide, and its strength as an electrophilic agent. These data are consistent with the occurrence of several competing reaction pathways. The proposed mechanisms gain support from the study of appropriate model reactions and from the isolation and full characterization of the involved key intermediates.

Results and Discussion

A. Preliminary Observations. Despite the demonstrated preponderance of the 2-mercapto-5-thione structure **1b** (Chart I) both in the solid state[8] and solution,[9] direct alkylation of 1 with alkyl halides in alkaline medium has been reported to give regioselective S-alkylation.[2]

In agreement with the literature data,[2] a ^{13}C NMR analysis of the products of *monoalkylation* of 2-mercapto-5-(methylthio)-1,3,4-thiadiazole (**3**) with $Br(CH_2)_nBr$ (n = 1–4) and 2,5-bis[(chloroalkyl)thio]-1,3,4-thiadiazoles (e.g., **8** and **10**), as well as the products of *dialkylation* of 1 with 2-[(chloroalkyl)thio]-5-(methylthio)-1,3,4-thiadiazoles (e.g., **4** and **6**) has established that *both 1 and 3 undergo regioselective S-alkylation under basic conditions.*

The required (chloroalkyl)thio heterocycles **4**, **6**, **8**, and **10** were synthesized as shown in Scheme I. 2-[(chloromethyl)thio]-5-(methylthio)-1,3,4-thiadiazole (**4**) was obtained in good yield by treating the sodium salt of **3** with a large excess of $BrCH_2Cl$ (20:1) in the presence of benzyltriethylammonium bromide, acting as a phase-transfer

(1) (a) Maffii, G.; Testa, E.; Ettorre, R. *Il Farmaco, Ed. Sci.* **1958**, *13*, 187. Testa, E.; Gallo, G. G.; Fava, F.; Weber, G. *Gazz. Chim. Ital.* **1958**, *88*, 812. (c) Ciotti, M. M.; Humphreys, S. R.; Venditti, J. M.; Kaplan, N.; Goldin, A. *Cancer Res.* **1960**, *20*, 1195.

(2) Sandström, J. *Adv. Heterocycl. Chem.* **1968**, *9*, 165.

(3) (a) Gregorowicz, S.; Klima, Z. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3880. (b) Rao, Y. R. *Indian J. Chem.* **1969**, *7*, 836. (c) Gajendragad, M. R.; Agarwala, U. *Indian J. Chem.* **1975**, *13*, 1331; *Aust. J. Chem.* **1975**, *28*, 763; *J. Inorg. Nuclear Chem.* **1975**, *37*, 2429. (d) Osman, M. M.; Makhyoun, M. A.; Tadros, A. B. *Bull. Soc. Chim. Fr.* **1980**, 451. (e) Fabretti, A. C.; Franchini, G. C.; Peyronel, G. *Spectrochim. Acta* **1980**, *36A*, 517; *Transition Met. Chem. (Weinheim, Ger.)* **1982**, *7*, 105. (f) Fabretti, A. C.; Franchini, G. C.; Malavasi, W.; Peyronel, G. *Polyhedron* **1985**, *4*, 989.

(4) (a) Borodkin, V. F.; Kolesnikov, N. A. *Khim. Geterotsikl. Soedin.* **1971**, 194; *Chem. Abstr.* **1971**, *75*, 35981w. (b) Kolesnikov, N. A.; Maizlish, V. E.; Borodkin, V. F. URSS Pat. 505 654, March 1976; *Chem. Abstr.* **1976**, *85*, 78136y. (c) Bottino, F.; Pappalardo, S. *Org. Magn. Reson.* **1981**, *16*, 1.

(5) Bottino, F.; Pappalardo, S. *Tetrahedron* **1982**, *38*, 665.

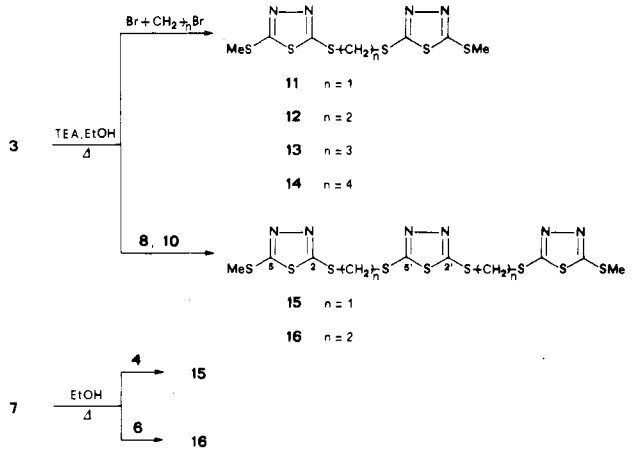
(6) Pappalardo, S.; Bottino, F.; Tringali, C. *Heterocycles* **1984**, *22*, 1339.

(7) (a) Still, I. W. J.; Plavac, N.; McKinnon, D. M.; Chauhan, M. S. *Can. J. Chem.* **1976**, *54*, 1660. (b) Bartels-Keith, J. R.; Burgess, M. T.; Stevenson, J. M. *J. Org. Chem.* **1977**, *42*, 3725. (c) Fujita, E.; Nagao, Y.; Seno, K.; Takao, S.; Miyasada, T.; Kimura, M.; Watson, W. H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 914.

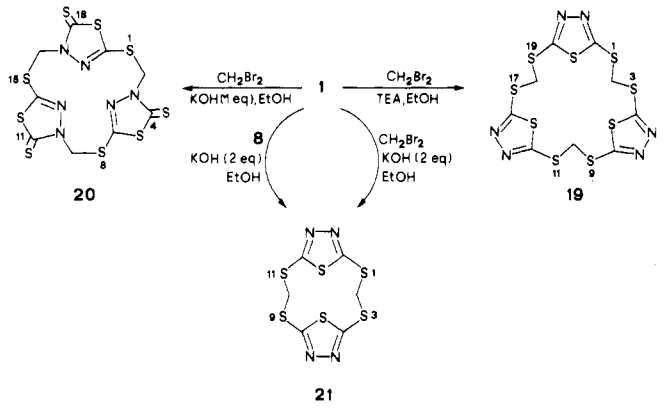
(8) Bats, J. W. *Acta Crystallogr., Sect. B* **1976**, *B32*, 2866.

(9) (a) Sheinker, Y. N.; Postovskii, I. Y.; Voronina, N. M. *Zh. Fiz. Khim.* **1959**, *33*, 302. (b) Thorn, G. D. *Can. J. Chem.* **1960**, *38*, 1439. (c) Stanovnik, B.; Tišler, M. *Croat. Chem. Acta* **1965**, *37*, 17.

Scheme II



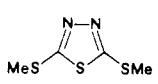
Scheme III



catalyst.[10] Treatment of **3** with 2-bromoethanol and KOH in EtOH, followed by chlorination of the 2-(hydroxyethyl)thia intermediate **5** with $SOCl_2$ in anhydrous pyridine, afforded 2-[(chloroethyl)thio]-5-(methylthio)-1,3,4-thiadiazole (**6**) in a 45% overall yield. 2,5-Bis[(chloromethyl)thio]-1,3,4-thiadiazole (**8**)[10] and 2,5-bis[(chloroethyl)thio]-1,3,4-thiadiazole (**10**) were prepared in good yield from 2,5-dimercapto-1,3,4-thiadiazole dipotassium salt (**7**) by similar routes (Scheme I).

Condensation of **3** with 0.5 equiv of $Br(CH_2)_nBr$ (n = 1–4) in EtOH in the presence of triethylamine (TEA) produced acyclic dimers **11–14** in excellent yield, while treatment of **3** with 0.5 equiv of dichlorides **8** and **10** in the same conditions afforded acyclic trimers **15** and **16**, respectively (Scheme II). The use of KOH instead of TEA did not greatly influence the yields of compounds **11–16**. Compounds **15** and **16** were also synthesized by dialkylation of **7** with 2 equiv of **4** and **6**, respectively.

The structures of all new compounds were unequivocally assigned by ^{13}C NMR spectroscopy, using the chemical shifts of the quaternary carbons in models 2,5-bis(methylthio)-1,3,4-thiadiazole (**17**) (165.5 ppm) and 3,4-dimethyl-1,3,4-thiadiazolidine-2,5-dithione (**18**) (180.3 ppm) as standards for substitution on sulfur or on nitrogen, respectively. The analytical, physicochemical, and spectral data of compounds **11–16** are summarized in Table I.

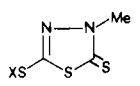


17

18

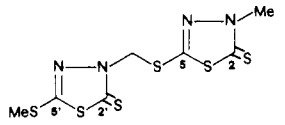
B. Reaction of 1 with Dibromomethane. When **1** was treated with 1 equiv of CH_2Br_2 and TEA in EtOH under high-dilution conditions, 1,3,9,11,17,19-hexathia-[3.3.3](2,5)-1,3,4-thiadiazolophane (**19**)[11] was isolated in low yield (6%) (Scheme III). The molecular weight of **19** was ascertained by mass spectrometry, and the symmetrical macrocyclic structure was confirmed by NMR spectroscopy. The methylene protons in **19** showed up as a sharp singlet at δ 5.22, while the quaternary carbons gave a single peak at 164.7 ppm.

The use of 1 equiv of KOH instead of TEA resulted in the formation of the macrocyclic isomer 1,8,15-trithia-[2.2.2](3,5)-1,3,4-thiadiazolinophane-4,11,18-trithione (**20**) (15%). The symmetrical structure was deduced by the sharp singlet of the methylene protons at δ 5.09, while convincing evidence for the thiol–thione structure **20** was provided by comparison of the ^{13}C chemical shift values of the two magnetically nonequivalent endocyclic carbon atoms in the heterocyclic subunits of **20** (155.6 and 188.5 ppm) with those in models **23** (157.6 and 186.7 ppm) and **24** (151.1, 158.0, 185.7, and 186.8 ppm).



22 X = H

23 X = Me



24

Model **24** was synthesized in three steps from **3**, according to Scheme IV. Treatment of **3** with 40% formaldehyde in EtOH gave 3-(hydroxymethyl)-5-(methylthio)-1,3,4-thiadiazoline-2-thione (**25**) (82%), which was converted (63%) to 3-(chloromethyl)-5-(methylthio)-1,3,4-thiadiazole-2-thione (**26**) by treatment with $SOCl_2$ in CH_2Cl_2. Subsequent condensation of **26** with 3-methyl-5-mercapto-1,3,4-thiadiazoline-2-thione (**22**)[12] in EtOH and TEA afforded the desired model **24** (85%).

It is worth noting that the bridged methylenes in **20** experience a remarkable shielding as compared to the methylene chemical shifts in acyclic model **24**, with proton and carbon upfield shifts of 0.76 and 13.2 ppm, respectively, probably due to the anisotropic effect of the juxtaposed heterocyclic moieties.

As far as the genesis of macrocycle **20** is concerned, it is likely that the reaction of the ambifunctional monoanion **27**, generated by addition of 1 equiv of KOH to **1**, with CH_2Br_2 gives first a mixture of intermediates 2-[(bromomethyl)thio]-5-mercapto-1,3,4-thiadiazole (**28**) and 3-(bromomethyl)-5-mercapto-1,3,4-thiadiazoline-2-thione (**29**)[13] (Scheme V). Both **28** and **29** might undergo (in their thiol–thione tautomeric forms **28b** and **29a**) self-condensation to macrocycle **20** *in the absence of base*, the latter having been supposedly consumed to promote the first step.

(10) Goralski, C. T.; Burk, G. A. *J. Org. Chem.* **1977**, *42*, 3094.

(11) The nomenclature of Vögtle and Neumann (Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5847) is employed for all macrocyclic compounds.

(12) Busch, M.; Ziegele, E. *J. Prakt. Chem.* **1899**, *60*, 51.

(13) Competitive N-alkylation can occur when the alkylating species is strong enough as electrophilic agent. As a matter of fact, diazomethane and 5-phenyl-1,3,4-thiadiazoline-2-thione give a mixture of *N*- and *S*-methyl derivatives.[14] On the other hand, substitution on the endocyclic nitrogen is the rule when stronger electrophilic agents, such as formaldehyde[15] or acyl chlorides,[7c] are used. These observations can be rationalized in terms of the hard–soft acid–base principle.[16]

(14) Sandström, J.; Wennerbeck, I. *Acta Chem. Scand.* **1966**, *20*, 57.

(15) Rhada Vakula, T.; Srinivasan, W. R. *Indian J. Chem.* **1969**, *7*, 583.

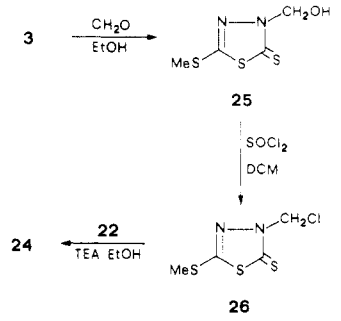
(16) Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977.

Table I. Analytical, Physicochemical, and Spectral Data of S-Alkylated Derivatives 11–16

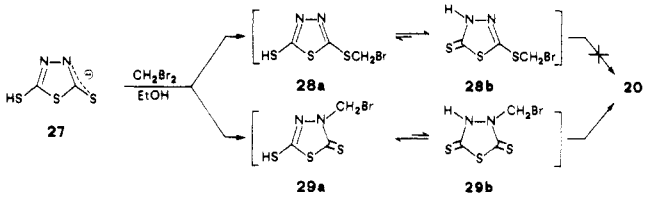
compd	mp, °C	recryst solvent	yield, %	formula (MW)	N% calcd	N% found	M^{+g}	^{1}H NMR[a,b] SCH_3	^{1}H NMR[a,b] methylene(s)	^{13}C NMR[a] SCH_3	^{13}C NMR[a] methylene(s)	^{13}C NMR[a] C_2	^{13}C NMR[a] C_5	^{13}C NMR[a] $C_{2'} = C_{5'}$
11	77–78	MeOH	88	$C_7H_8N_4S_6$ (340.57)	16.45	16.38	340 (5.5)	2.85 (s)[c]	5.20 (s)[c]	16.5[c]	37.7[c]	167.8[c]	162.6[c]	
12	127–128	EtOH	85	$C_8H_{10}H_4S_6$ (354.60)	15.80	15.75	354 (0.2)	2.83 (s)[c]	3.83 (s)[c] 2.33 (p)[d]	16.3[c] 16.5	33.2[c] 32.6	166.9[c]	163.7[c]	
13	53–54	Me_2CO–hexane	73	$C_9H_{12}N_4S_6$ (368.62)	15.20	15.33	368 (4.4)	2.75 (s)	3.43 (t)[d]		28.6	167.1	164.2	
14	76–77.5	EtOH	81	$C_{10}H_{14}N_4S_6$ (382.65)	14.64	14.77	382 (1.3)	2.72 (s)	1.82 (m) 3.27 (m)	16.4	33.4 27.6	166.8	164.4	
15	110–112	AcOEt	65[e]	$C_{10}H_{10}N_6S_9$ (502.83)	16.71	16.59	502 (0.1)	2.73 (s)	5.15 (s)	16.5	38.5	168.7	162.1	164.5
16	113–114	AcOEt	51[f]	$C_{12}H_{14}N_6S_9$ (530.88)	15.83	15.96	530 (0.2)	2.84 (s)	3.49 (s)	16.4	33.4	167.6	163.6	164.8

[a] Unless otherwise stated, chemical shifts refer to Me_2SO-d_6 solutions. [b] The multiplicities of the signals are indicated in parentheses. [c] In $CDCl_3$. [d] J = 6 Hz. [e] By treatment of **3** with **8** and TEA. [f] By dialkylation of **7** with **6**. [g] m/z (relative intensity).

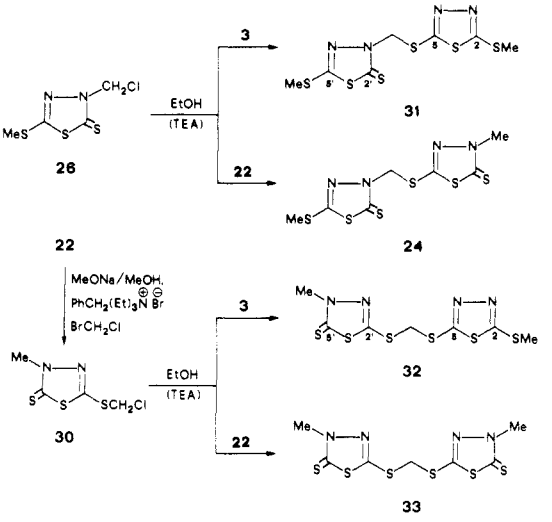
Scheme IV



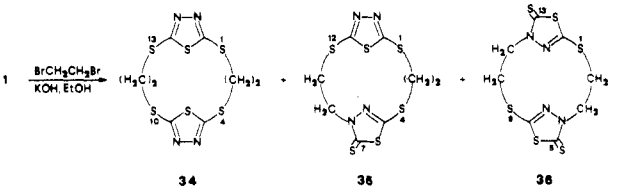
Scheme V



Scheme VI



Scheme VII



In order to make a choice between the two alternative pathways (Scheme V), the *N*- and *S*-chloromethyl model isomers **26** and **30**, in which substitution of methyl groups for NH and SH hydrogens forces each molecule in the thiol–thione form, were subjected to a reactivity test with isomeric thiols **3** and **22**, chosen on purpose because of their different nature and reactivity.[17] The results obtained, summarized in Scheme VI, have shown that both **26** and **30** undergo a ready and regioselective nucleophilic displacement by thiol sulfur (as in **22**) to afford derivatives **24** and **33**, respectively, *even in the absence of base*, while their reactions with thione sulfur (as in **3**) require extended time in the absence of base with only partial conversion to the corresponding *S*-alkyl derivatives **31** and **32**. Moreover, the *N*-chloromethyl derivative **26** is found to be much more reactive than the *S*-chloromethyl isomer **30**.[19] These data strongly support the suggestion that macrocycle **20** is produced via self-condensation of the extremely reactive *N*-bromomethyl intermediate **29a**.

When the high-dilution reaction of **1** and CH_2Br_2 was carried out in the presence of 2 equiv of KOH, 1,3,9,11-tetrathia[3.3](2,5)-1,3,4-thiadiazolophane (**21**) was obtained (25%). Although no ^{13}C NMR spectra could be determined for this compound, structure **21** was assigned on the basis of a chemical shift comparison of its methylene protons (δ 5.27) with those of models **11** (δ 5.20) and **19** (δ 5.22). To further confirm the assignment made, macrocycle **21** was independently synthesized by condensation of equimolar amounts of **7** and **8** under highly dilute conditions (Scheme III).

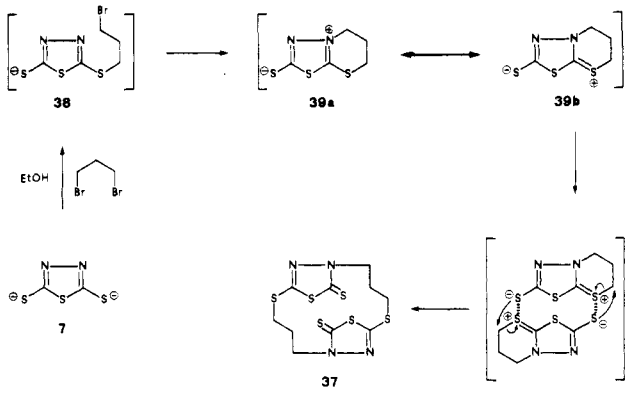
C. Reaction of 1 with 1,2-Dibromomethane. Reaction of **1** with 1,2-dibromoethane and KOH in refluxing EtOH produced a mixture of cyclic dimers **34–36** (Scheme VII), which could be separated by careful fractional crystallization. The product distribution is greatly de-

(17) ^{13}C NMR spectra show that **3** (very stable in the air) exists predominantly in the thione form. Conversely, **22** exists in the thiol form, as shown by its spontaneous oxidation to 5,5′-dithiobis(3-methyl-1,3,4-thiadiazoline-2-thione),[18] mp 139–140 °C (AcOEt); ^{1}H NMR (Me_2SO-d_6) δ 3.80 (s, NCH_3); ^{13}C NMR (Me_2SO-d_6) δ 38.7 (NCH_3), 153.7 ($C_5 = C_{5'}$), and 186.8 ($C_2 = C_{2'}$).

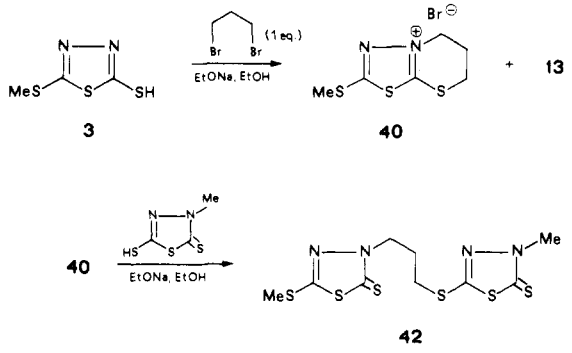
(18) Anthoni, U.; Dahl, B. M.; Eggert, H.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 71.

(19) For the interesting and unexpected reactivity of related *N*-chloromethyl heterocycles see: ref 15; Kristinsson, H.; *Abstracts of Papers*; 8th International Congress of Heterocyclic Chemistry, Graz, Austria, August 23–28, 1981; p 257.

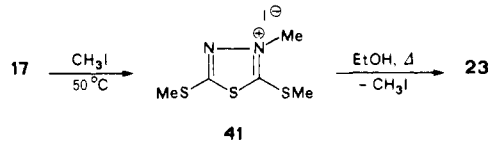
Scheme VIII



Scheme IX



Scheme X



pendent on the experimental conditions used. When the reaction was carried out under high-dilution conditions and dipotassium salt **7** ws used, 1,4,10,13-tetrathia[4.4](2,5)-1,3,4-thiadiazolophane (**34**) was isolated (12%) as the major cyclic product, along with minor amounts of unsymmetrical 1,4,12-trithia[4](2,4)-1,3,4-thiadiazolino[3](2,5)-1,3,4-thiadiazolinophane-7-thione (**35**) and of 1,9-dithia[3.3](3,5)-1,3,4-thiadiazolinophane-5,13-dithione (**36**). Instead, reaction of equimolar amounts of **1**, 1,2-dibromoethane, and KOH (1 equiv) in moderate EtOH solution at reflux for 24 h, followed by the addition of a second equivalent of KOH, gave dimer **36** as the predominant cyclic product (15%).

The structures of cyclic isomers **34–36** were assigned on the basis of their ^{1}H NMR spectral patterns. The ethylene bridges in the least soluble macrocycle **34** showed up as a sharp singlet at δ 3.48 in Me_2SO-d_6 at 120 °C, while those in dithione **36** appeared as an AA′BB′ system centered at δ 4.57 (two sets of signals resembling two distorted triplets at δ 4.94 and 4.21) using $C_6D_5NO_2$ as solvent. In unsymmetrical monothione **35** the signal pattern (in Me_2SO-d_6) was more complex and spin-decoupling experiments were used to firmly establish the attributions. A low-field multiplet at δ 4.58 was easily assigned to the N-linked methylene group, representing the AA′ part of an AA′XX′ system; by irradiation on this signal, a dramatic simplification occurs at δ 3.72, indicating the resonance position of the S-linked methylene group (XX′ part) of the S,N-ethylene bridge. Conversely, irradiating at δ 3.72, the signal at δ 4.58 modifies to a broad singlet. A complex multiplet centered at δ 3.61 and partly overlapped with the signal at δ 3.72 was unaffected by these irradiations and could be assigned to the S,S-bridgehead ethylene (AA′BB′ system). Of course, irradiation of the higher field signal did not affect the signals of the other ethylene bridge.

Structure **35** was further confirmed by ^{13}C NMR spectroscopy, showing the quaternary carbons as four distinct peaks at 154.3, 166.5, 167.3, and 185.7 ppm.

D. Reaction of 7 with 1,3-Dibromopropane. The high-dilution reaction of **7** with 1,3-dibromopropane in refluxing EtOH gave 1,10-dithia[4.4](3,5)-1,3,4-thiadiazolinophane-6,15-dithione (**37**) *as the only cyclic product in unusually high yield* (45%) as compared with other reactions in this series.

Structure **37** was easily assigned by NMR spectroscopy. The ^{1}H NMR spectrum in Me_2SO-d_6 displayed three different signals for the methylenes at δ 4.24 (N-CH_2), 3.39 (S-CH_2), and 2.44 (central CH_2), while the ^{13}C NMR spectrum showed the expected two peaks for quaternary carbons at 186.3 (C_6=S = C_{15}=S) and 161.5 (C_8—S = C_{17}—S) ppm, in addition to three peaks for the methylenes at 50.2 (N—CH_2), 27.3 (S—CH_2), and 21.5 (central CH_2) ppm. The proton and carbon chemical shift values in structure **37** are consistent with those observed for the open-chain analogue **42**, whose synthesis is described below (Scheme IX).

The genesis of **37** can be envisioned as proceeding via the bromothiolate intermediate **38**, which quickly undergoes intramolecular quaternization to give the bicyclic thiadiazolium salt **39** (Scheme VIII). Zwitterionic **39** can be considered as an hybrid of two mesomeric forms **39a** and **39b**, the latter having more importance since it can find further stabilization by "self-association". Thus, two molecules of **39b**, suitably oriented by the strong electrostatic interactions between opposite charges,may then combine by nucleophilic attack of the thiolate functionalities on the S-linked methylene groups, followed by the cleavage of the six-membered dihydrothiazine rings to produce macrocyclic dithione **37**.

Consistent with this scheme is the reaction of **3** with dibromopropane. Using conditions similar to those used for the preparation of **37** (high dilution, 1:1 molar ratio of the reagents, and EtONa as the base), the bicyclic thiadiazolium salt **40** was obtained in 31% yield, along with the expected *S*-alkyl derivative **13** (60%) (Scheme IX).

Salt **40** is volatile under MS conditions and gives a nice parent peak at *m/z* 284, accompanied by the characteristic M + 2 peak of equal intensity. The ^{1}H NMR spectrum of **40** is consistent with the assigned structure, and its ^{13}C NMR spectrum well compares to that of model 2,5-bis-(methylthio)-3-methyl-1,3,4-thiadiazolium iodide (**41**), obtained in 75% yield by treatment of **17** with an excess of CH_3I (Scheme X). On heating in absolute EtOH, salt **41** smoothly decomposes by loss of CH_3I to give 3-methyl-5-(methylthio)-1,3,4-thiadiazoline-2-thione (**23**).[20]

Finally, bicyclic thiadiazolium cation **40** reacted with mercaptide **22** at the S-linked methylene group to give the N-substituted 1,3,4-thiadiazoline-2-thione **42** (Scheme IX), while no detectable nucleophilic attack had occurred at the N-linked methylene group. Ring-opening reactions induced by nucleophilic reagents have been recently re-

(20) Brown and Teitei[21] have previously demonstrated the facile isomerization of 4,6-dimethoxypyrimidine with CH_3I to give 1-methyl-4-methoxy-1,6-dihydro-6-oxopyrimidine as the major product and 1,4-dihydro-6-methoxy-1-methyl-4-oxopyrimidine. Similarly, 1-alkyl-5-phenyltetrazoles are converted into 2-alkyl isomers on heating with alkyl iodide, presumably by quaternary salt formation followed by elimination of alkyl iodide to give the thermodinamically more stable isomer.[22]

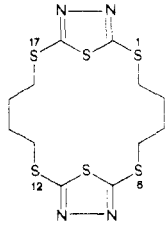
(21) Brown, D. J.; Teitei, T. *Aust. J. Chem.* **1964**, *17*, 567.

(22) Butler, R. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 323.

ported for related bridgehead nitrogen pyridinium cations.[23]

These model experiments provide clear evidence that bicyclic thiadiazolium salt **39** is the precursor of macrocyclic dithione **37**. A similar reaction pathway could also account for the formation of macrocyclic dithione **36** from dithiol **1** and 1,2-dibromoethane.

E. Reaction of 1 with 1,4-Dibromobutane. When 1,4-dibromobutane was subjected to the dipotassium salt of **1** in refluxing EtOH, 1,6,12,17-tetrathia[6.6](2,5)-1,3,4-thiadiazolophane (**43**) was isolated (12%), and no other cyclic products were detected. Structure **43** was assigned by ^{1}H NMR and mass spectrometry, whereas the limited solubility of **43** precluded the possibility to record its ^{13}C NMR spectrum.



43

Experimental Section

General Comments. Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WP-80 NMR spectrometer. Chemical shifts are quoted in ppm (δ) from Me_4Si. Coupling constants (J) are reported in hertz. For ^{13}C NMR spectra a pulse length of 3 μs (90° pulse = 12 μs) and a pulse delay of 5 s were used in order to obtain satisfactory signal/noise ratio for quaternary carbons sandwiched between three heteroatoms. Mass spectra (MS) were determined on a LKB 9000S instrument or a Hewlett-Packard Model 5985 GC/MS spectrometer, obtained at 70 eV (except where noted), and herewith recorded as m/z (assignment, relative intensity). Elemental analyses were obtained commercially. 2,5-Dimercapto-1,3,4-thiadiazole (**1**), 2,5-dimercapto-1,3,4-thiadiazole dipotassium salt (**7**), and 1,ω-dibromoalkanes were purchased for Aldrich Chemical and used without further purification. The following compounds are known and were prepared by standard methods or slight variation thereof.

2-Mercapto-5-(methylthio)-1,3,4-thiadiazole (3): mp 136–137 °C (H_2O) (lit.[4c] mp 136–137 °C); ^{1}H NMR ($CDCl_3$) δ 2.63 (s, SCH_3, 3 H) and 11.34 (br s, NH, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.5 (SCH_3), 160.7 (C_5), and 189.2 (C_2).

2,5-Bis[(chloromethyl)thio]-1,3,4-thiadiazole (8): mp 63–64 °C (Et_2O) (lit.[10] mp 63–64 °C); ^{1}H NMR ($CDCl_3$) δ 5.21 (s, SCH_2Cl); ^{13}C NMR ($CDCl_3$) δ 46.9 (SCH_2Cl) and 163.1 ($C_2 = C_5$).

2,5-Bis(methylthio)-1,3,4-thiadiazole (17): bp 95 °C (0.3 mm) [lit.[9b] bp 87–88 °C (0.05 mm)]; ^{1}H NMR ($CDCl_3$) δ 2.62 (s, SCH_3); ^{13}C NMR ($CDCl_3$) δ 16.0 (SCH_3) and 165.5 ($C_2 = C_5$).

3,4-Dimethyl-1,3,4-thiadiazoline-2,5-dithione (18): mp 167–168 °C (EtOH) (lit.[9b] mp 168–169 °C); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, NCH_3); ^{13}C NMR ($CDCl_3$) δ 36.3 (NCH_3) and 180.2 ($C_2 = C_5$).

2-Mercapto-4-methyl-1,3,4-thiadiazoline-5-thione (22): mp 65–66 °C (Et_2O) (lit.[12] mp 65–66 °C); ^{1}H NMR ($CDCl_3$) δ 3.84 (s, NCH_3); ^{13}C NMR ($CDCl_3$) δ 38.3 (NCH_3), 148.0 (C_2), and 186.1 (C_5).

2-(Methylthio)-4-methyl-1,3,4-thiadiazoline-5-thione (23): mp 81–82 °C (EtOH) (lit.[12] mp 81–82 °C); ^{1}H NMR ($CDCl_3$) δ 2.62 (s, SCH_3, 3 H) and 3.84 (s, NCH_3, 3 H); ^{13}C NMR (Me_2CO-d_6) δ 15.8 (SCH_3), 39.0 (NCH_3), 157.6 (C_2), and 186.3 (C_5).

2-[(Chloromethyl)thio]-5-(methylthio)-1,3,4-thiadiazole (4). To a solution of sodium methoxide (0.378 g, 7 mmol) in absolute MeOH (10 mL) was added **3** (1.15 g, 7 mmol) by portion. The solution was heated with stirring on a water bath for 15 min and concentrated in vacuo to dryness. Bromochloromethane (10 mL) containing benzyltriethylammonium bromide (0.2 g) was then added, and the resulting slurry was stirred for 3 h at 50 °C. The sodium bromide formed was filtered off, and the filtrate was evaporated in vacuo to leave a thick oil, which was chromatographed on silica gel (*n*-hexane–ether (3:2) as the eluent) to afford white crystals of **4**: 1.15 g, 75%; mp 39–40 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 2.79 (s, SCH_3, 3 H) and 5.23 (s, SCH_2Cl, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.2 (SCH_3), 47.3 (SCH_2Cl), 160.2 (C_5), and 168.8 (C_2); MS, m/z 212 (M^+, 29). Anal. Calcd for $C_4H_5ClN_2S_3$: C, 22.58; H, 2.37; N, 13.17. Found: C, 22.41; H, 2.40; N, 13.11.

2-[(Chloroethyl)thio]-5-(methylthio)-1,3,4-thiadiazole (6). To a solution of **3** (1.15 g, 7 mmol) in EtOH (10 mL) containing 85% KOH (0.46 g, 7 mmol) was added 2-bromoethanol (0.87 g, 7 mmol) in one portion. The mixture was heated at reflux for 1 h with stirring. After cooling, the potassium bromide formed was filtered off and washed with EtOH. The solvent was removed in vacuo to leave a residue, which was extracted with AcOEt and dried over Na_2SO_4. Evaporation of the solvent afforded crude 2-[(hydroxyethyl)thio]-5-(methylthio)-1,3,4-thiadiazole (**5**) (1.1 g, 76%) as a thick oil, which was used for the next step without further purification. It was dissolved in dry pyridine (5 mL) and treated at 0 °C with an excess of thionyl chloride (2 mL). The mixture was stirred for 2 h while the temperature was raised to 25 °C. The solvent and excess $SOCl_2$ were removed in vacuo, and the residue was partitioned between cold water and $CHCl_3$. The organic extract was washed with dilute $NaHCO_3$ solution and then with 1 N HCl and water and dried over anhydrous Na_2SO_4. On evaporation of the solvent, the oily residue was chromatographed on silica gel (eluent *n*-hexane–ether, 5:1) to give **6** as white needles: 0.72 g, 60%; mp 49–50 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, SCH_3, 3 H), and 3.72 [m (A_2B_2 system), SCH_2CH_2Cl, 4 H]; ^{13}C NMR ($CDCl_3$) δ 16.2 (SCH_3), 35.5 (SCH_2CH_2Cl), 42.0 (SCH_2CH_2Cl), 163.1 (C_2), and 167.0 (C_5); MS, m/z 226 (M^+, 12). Anal. Calcd for $C_5H_7ClN_2S_3$: C, 26.48; H, 3.11; N, 12.35. Found: C, 26.73; H, 3.03; N, 12.44.

2,5-Bis[2-(hydroxyethyl)thio]-1,3,4-thiadiazole (9). To a suspension of **7** (6.78 g, 30 mmol) in EtOH (50 mL) was added 2-bromoethanol (7.5 g, 60 mmol) in a single portion. The mixture was heated at reflux under stirring for 2 h. The potassium bromide formed was filtered off, and the filtrate was evaporated to leave a crystalline material, which upon recrystallization from aqueous EtOH gave diol **9** as white scales (5.8 g, 81%): mp 82–83 °C; ^{1}H NMR (Me_2CO-d_6) δ 3.37 (t, J = 4.5, SCH_2CH_2OH, 4 H), 3.79 (q, J = 4.5, SCH_2CH_2OH, 4 H), and 4.26 (t, J = 4.5, OH, 2 H); ^{13}C NMR (Me_2CO-d_6) δ 37.1 (SCH_2CH_2OH), 60.7 (SCH_2CH_2OH), and 165.8 ($C_2 = C_5$); MS, m/z 238 (M^+, 10). Anal. Calcd for $C_6H_{10}N_2O_2S_3$: C, 30.23; H, 4.23; N, 11.75. Found: C, 30.11; H, 4.15; N, 11.82.

2,5-Bis[2-(chloroethyl)thio]-1,3,4-thiadiazole (10). To a chilled solution of **9** (0.714 g, 3 mmol) in anhydrous pyridine (2 mL) was added dropwise an excess of thionyl chloride (1.5 mL). The mixture was stirred for 2 h while the temperature was raised to 25 °C. Usual workup afforded an oily residue, which was chromatographed on silica gel (*n*-pentane–ether (4:1) as the eluent) to afford dichloride **10** as white prisms: 0.45 g, 55%; mp 61–62 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.72 [m (A_2B_2 system), SCH_2CH_2Cl]; ^{13}C NMR ($CDCl_3$) δ 35.4 (SCH_2CH_2Cl), 42.0 (SCH_2CH_2Cl), and 164.2 ($C_2 = C_5$); MS, m/z 274 (M^+, 12). Anal. Calcd for $C_6H_8Cl_2N_2S_3$: C, 26.18; H, 2.93; N, 10.18. Found: C, 26.32; H, 2.99; N, 10.13.

Monoalkylation of 3 To Produce Compounds 11–16. General Procedure. A mixture of **3** (0.49 g, 3 mmol), the appropriate dihalide (1.5 mmol) and TEA (0.5 mL) in EtOH (10 mL) was heated with stirring on a water-bath for 0.5–3 h. On cooling, the crude derivative was collected by filtration, washed with water, and recrystallized from the stipulated solvent (Table I). The analytical, physicochemical, and spectra data of compounds **11–16** are collected in Table I.

Dialkylation of 7 To Produce Compounds 15 and 16. A mixture of **7** (0.226 g, 1 mmol) and dichloride **4** or **6** (2 mmole) in EtOH (10 mL) was heated at reflux for several hours. General workup afforded acyclic trimers **15** or **16**, identical in all respects with the products of monoalkylation of **3** with **8** or **10**, respectively.

Reaction of 1 with Dibromomethane and TEA To Produce Macrocycle 19. Solutions of **1** (1.5 g, 10 mmol) and dibromo-

(23) Molina, P.; Alajarin, M.; Vilaplana, M. J. *J. Chem. Res., Synop.* 1985, 262.

methane (1.74 g, 10 mmol) in EtOH (100 mL) were dropped into boiling EtOH (1 L) containing TEA (3 mL) during 3 h. The mixture was refluxed with stirring for 24 h, cooled, and filtered. The mother liquor by slow evaporation deposited a white crystalline material, which was collected by filtration and recrystallized from *N*,*N*-dimethylformamide (DMF) to give macrocycle **19** as white prisms: 0.1 g, 6%; mp 215–218 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.22 (s, SCH_2S); ^{13}C NMR (Me_2SO-d_6) δ 39.7 (SCH_2S) and 164.7 ($C_2 = C_5$); MS, m/z 486 (M^+, 34). Anal. Calcd for $C_9H_6N_6S_9$: C, 22.21; H, 1.24; N, 17.16. Found: C, 22.08; H, 1.22; N, 17.03.

Reaction of 1 with Dibromomethane and KOH (1 Equiv) To Produce 20. To a solution of 1 (3 g, 20 mmol) in 70% EtOH (30 mL) containing 85% KOH (1.31 g, 20 mmol) was added dibromomethane (3.48 g, 20 mmol) under stirring. The mixture was heated on a water bath for 1 h and allowed to stir overnight at room temperature. The precipitate obtained was filtered and recrystallized from a large volume of water to give 1,8,15-trithia[2.2.2](3,5)-1,3,4-thiadiazolinophane-4,11,18-trithione (**20**) as pale yellow needles: 0.49 g, 15%; mp 176–179 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.09 (s, SCH_2N); ^{13}C NMR (Me_2SO-d_6) δ 39.5 (SCH_2N), 155.6 (C_5), and 188.5 (C_2); ^{13}C NMR (Me_2SO-d_6) δ 38.3 (SCH_2N), 156.1 (C_5), and 190.9 (C_2); MS, m/z 486 (M^+, 2.7). Anal. Calcd for $C_9H_6N_6S_9 \cdot 1.5H_2O$: C, 21.04; H, 1.77; N, 16.36. Found: C, 20.52; H, 1.76; N, 16.88.

3-(Hydroxymethyl)-5-(methylthio)-1,3,4-thiadiazoline-2-thione (25). A mixture of **3** (0.82 g, 5 mmol) and 40% formaldehyde (0.5 mL) in EtOH (25 mL) was heated on a water bath for 0.5 h. The solvent was removed under reduced pressure and the residue was crystallized from cyclohexane–CH_2Cl_2 to afford **25** as white needles: 0.79 g, 82%; mp 72–74 °C; ^{1}H NMR ($CDCl_3$) δ 2.64 (s, SCH_3, 3 H), 4.25 (t, J = 6, NCH_2OH, 1 H), and 5.65 (d, J = 6, NCH_2OH, 2 H); ^{13}C NMR (Me_2CO-d_6) δ 15.1 (SCH_3), 72.7 (NCH_2OH), 157.1 (C_5), and 187.5 (C_2); MS, m/z 194 (M^+, 8). Anal. Calcd for $C_4H_6N_2OS_3$: C, 24.73; H, 3.11; N, 14.42. Found: C, 24.55, H, 3.15; N, 14.30.

3-(Chloromethyl)-5-(methylthio)-1,3,4-thiadiazoline-2-thione (26). A solution of **25** (0.58 g, 3 mmol) in CH_2Cl_2 (20 mL) was treated with an excess of thionyl chloride (2 mL). The mixture was gently refluxed with stirring for 5 h. Usual workup afforded an oily residue, which was chromatographed on silica gel (eluent *n*-pentane–ether, 4:1) to give **26** as colorless prisms: 0.4 g, 63%; mp 66.5–68 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 2.67 (s, SCH_3, 3 H) and 5.94 (s, NCH_2Cl); ^{13}C NMR ($CDCl_3$) δ 15.2 (SCH_3), 55.3 (NCH_2Cl), 157.6 (C_5), and 187.4 (C_2); MS, m/z 212 (M^+, 100). Anal. Calcd for $C_4H_5ClN_2S_3$: C, 22.58; H, 2.37; N, 13.17. Found: C, 22.75; H, 2.31; N, 13.25.

[(3-Methyl-2-thioxo-1,3,4-thiadiazolin-5-yl)thio][5-(methylthio)-2-thioxo-1,3,4-thiadiazolin-3-yl]methane (24). A mixture of **22** (82 mg, 0.5 mmol) and **26** (106 mg, 0.5 mmol) in EtOH (5 mL) containing a few drops of TEA was refluxed with stirring for 0.5 h. The general workup afforded compound **24** as light yellow prisms: 145 mg, 85%; mp 114–115 °C (AcOEt); ^{1}H NMR (Me_2SO-d_6) δ 2.62 (s, SCH_3, 3 H), 3.80 (s, NCH_3, 3 H), and 5.85 (s, SCH_2N, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 15.1 (SCH_3), 38.5 (NCH_3), 151.2 (C_2), 158.0 ($C_{5'}$), 185.7 ($C_{2'}$), and 186.8 (C_5); MS, m/z 340 (M^+, 17). Anal. Calcd for $C_7H_8N_4S_6$: C, 24.69; H, 2.37; N, 16.45. Found: C, 24.82; H, 2.39; N, 16.52.

2-[(Chloromethyl)thio]-4-methyl-1,3,4-thiadiazoline-5-thione (30). To a solution of sodium methoxide (0.27 g, 5 mmol) in absolute MeOH (10 mL) was added **22** (0.82 g, 5 mmol) in small portions. The mixture was stirred at room temperature for 15 min. After removal in vacuo of the solvent, bromochloromethane (10 mL) containing benzyltriethylammonium bromide (0.1 g) was added to the residue, and the resulting slurry was stirred for 4 h at 50 °C. The sodium bromide formed was filtered off, and the filtrate was evaporated in vacuo to leave a crystalline material, which was chromatographed on silica gel (*n*-pentane–ether (4:1) as the eluent) to give **30** as pale yellow prisms: 0.83 g, 78%; mp 81–82.5 °C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, NCH_3, 3 H) and 5.05 (s, SCH_2Cl, 2 H); ^{13}C NMR (Me_2CO-d_6) δ 39.2 (NCH_3), 48.2 (SCH_2Cl), 147.9 (C_2), and 182.1 (C_5); MS, m/z 212 (M^+, 100). Anal. Calcd for $C_4H_5ClN_2S_3$: C, 22.58; H, 2.37; N, 13.17. Found: C, 22.47; H, 2.34; N, 13.23.

[[2-(Methylthio)-1,3,4-thiadiazol-5-yl]thio][5-(methylthio)-2-thioxo-1,3,4-thiadiazolin-3-yl]methane (31). A mixture of **3** (82 mg, 0.5 mmol) and **26** (106 mg, 0.5 mmol) in EtOH (5 mL) containing a few drops of TEA was refluxed for 0.5 h. The general workup afforded compound **31** as white needles: 150 mg, 88%; mp 82–83 °C (MeOH); ^{1}H NMR (Me_2SO-d_6) δ 2.57 (s, $C_{5'}$—SCH_3, 3 H), 2.77 (s, C_5—SCH_3, 3 H), and 5.90 (s, SCH_2N, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 15.1 ($C_{5'}$—SCH_3), 16.4 (C_5—SCH_3), 53.6 (SCH_2N), 157.9 ($C_{5'}$), 160.3 (C_2), 170.5 (C_5), and 185.5 ($C_{2'}$); MS, m/z 340 (M^+, 8). Anal. Calcd for $C_7H_8N_4S_6$: C, 24.69 H, 2.37; N, 16.45. Found: C, 24.58; H, 2.33; N, 16.55.

[[2-(Methylthio)-1,3,4-thiadiazol-5-yl]thio][(4-methyl-5-thioxo-1,3,4-thiadiazolin-2-yl)thio]methane (32). A mixture of **30** (212 mg, 1 mmol), **3** (164 mg, 1 mmol), and TEA (0.2 mL) in EtOH (10 mL) was refluxed with stirring for 1 h. The general workup afforded compound **32** as pale yellow needles: 0.24 g, 70%; mp 95–96.5 °C (MeOH); ^{1}H NMR (Me_2SO-d_6) δ 2.76 (s, SCH_3, 3 H), 3.78 (s, NCH_3, 3 H), and 5.06 (s, SCH_2S, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 16.4 (SCH_3), 38.5 (NCH_3 and SCH_2S), 152.8 ($C_{2'}$), 161.6 (C_2), 169.0 (C_5), and 185.6 ($C_{5'}$); MS, m/z 340 (M^+, 10). Anal. Calcd for $C_7H_8N_4S_6$: C, 24.69; H, 2.37; N, 16.45. Found: C, 24.55; H, 2.44; N, 16.40.

Bis[(4-methyl-5-thioxo-1,3,4-thiadiazolin-2-yl)thio]methane (33). A mixture of **22** (82 mg, 0.5 mmol) and **30** (106 mg, 0.5 mmol) in EtOH (5 mL) containing a few drops of TEA was refluxed with stirring for 0.5 h. The general workup afforded compound **33** as light yellow prisms: 100 mg, 59%; mp 157–158 °C (AcOEt); ^{1}H NMR (Me_2SO-d_6) δ 3.80 (s, NCH_3, 6 H) and 4.99 (s, SCH_2S, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 37.7 (NCH_3), 152.6 (C_2), and 185.7 (C_5); MS, m/z 340 (M^+, 22). Anal. Calcd for $C_7H_8N_4S_6$: C, 24.69; H, 2.36; N, 16.45. Found: C, 24.81; H, 2.31; N, 16.38.

Reaction of 7 with Dibromomethane. General Procedure. Solutions of **7** (2.26 g, 10 mmol) and dibromomethane (1.74 g, 10 mmol) in EtOH (500 mL) were dropped separately but synchronously from two dropping funnels into boiling EtOH (1 L) over 8 h, under mechanical stirring. The mixture was refluxed for 24 h and cooled. The precipitate obtained was collected by filtration, washed thoroughly with water, dried, and recrystallized from DMF to give 1,3,9,11-tetrathia[3.3](2,5)-1,3,4-thiadiazolophane (**21**) as white prisms: mp 265–267 °C; 0.4 g, 25%; ^{1}H NMR (Me_2SO-d_6, 120 °C) δ 5.27 (s, SCH_2S); MS, m/z 324 (M^+, 100). Anal. Calcd for $C_6H_4N_4S_6$: C, 22.21; H, 1.24; N, 17.26. Found: C, 22.38; H, 1.28; N, 17.36.

Macrocycle **21** was also obtained in ca. 45% yield by reaction of **7** and **8** in EtOH under high-dilution conditions.

Reaction of 7 with 1,2-Dibromomethane. The above general procedure was followed except for the substitution of 1,2-dibromoethane (10 mmol). The amorphous material that separated from the reaction mixture was filtered off. The mother liquor by concentration (ca. 100 mL) gave a solid, which was collected by filtration and thoroughly extracted with $CHCl_3$. The solvent was evaporated to give a powder, which on recrystallization from DMF afforded crystals of 1,4,12-trithia[4](2,4)-1,3,4-thiadiazolino[3](2,5)-1,3,4-thiadiazolophane-7-thione (**35**): 90 mg, 5%; mp 209–211 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.61 [m, (AA′BB′ system), SCH_2CH_2S, 4 H], 3.72 [m (XX′ part of an AA′XX′ system) SCH_2CH_2N, 2 H], and 4.58 [m (AA′ part of an AA′XX′ system), SCH_2CH_2N, 2 H]; ^{13}C NMR (Me_2SO-d_6) δ 34.0 (SCH_2CH_2S), 39.5 (SCH_2CH_2N), 52.6 (SCH_2CH_2N), 154.3 (C_5), 166.5 (C_{13} or C_{16}), 167.3 (C_{16} or C_{13}), and 185.7 (C_7); MS, m/z 352 (M^+, 76). Anal. Calcd for $C_8H_8N_4S_6$: C, 27.25; H, 2.29; N, 15.89. Found: C, 27.52; H, 2.40; N, 16.03.

The less soluble residue was recrystallized from dimethyl sulfoxide to give 1,4,10,13-tetrathia[4.4](2,5)-1,3,4-thiadiazolophane (**34**) as white needles: 0.2 g, 12%, mp 262–263 °C; ^{1}H NMR (Me_2SO-d_6, 120 °C) δ 3.48 (s, SCH_2CH_2S); MS, m/z 352 (M^+, 71). Anal. Calcd for $C_8H_8N_4S_6$: C, 27.25; H, 2.29; N, 15.89. Found: C, 27.13; H, 2.18; N, 15.74.

From the mother liquor crude crystals of 1,9-dithia[3.3]-(3,5)-1,3,4-thiadiazolinophane-5,13-dithione (**36**) deposited after some time, which were collected by suction filtration and recrystallized twice from DMF: 53 mg, 3%; mp 277–280 °C; ^{1}H NMR ($C_6D_5NO_2$) δ 4.57 [m (AA′BB′ system), NCH_2CH_2S]; MS (18 eV), m/z 352 (M^+, 52). Anal. Calcd for $C_8H_8N_4S_6$: C, 27.25; H, 2.29; N, 15.89. Found: C, 27.44; H, 2.25; N, 15.97.

Macrocyclic dithione **36** was obtained as the major cyclic product by the following procedure: a solution of 1,2-dibromoethane (0.75 g, 4 mmol) in EtOH (10 mL) was slowly added to a boiling solution of **1** (0.6 g, 4 mmol) and 85% KOH (0.26 g, 4

mmol) in EtOH (50 mL) under stirring. The solution was refluxed for 24 h, then a second portion of KOH (0.26 g, 4 mmol) was added, and the mixture was refluxed for additional 2 h. The mixture was filtered until hot to remove crude **34** (ca. 5%), and the filtrate was kept overnight in a refrigerator. The crystalline precipitate that deposited was collected by filtration, washed with water, and recrystallized from DMF to give **36** in 15% yield.

Reaction of 7 with 1,3-Dibromopropane. The general procedure was followed except for the substitution of 1,3-dibromopropane (10 mol). After removal of ca. 500 mL of solvent from the reaction mixture, the residue was kept overnight in a refrigerator. The crystalline material that precipitated was collected by filtration and recrystallized from DMF to give 1,10-dithia[4.4](3,5)-1,3,4-thiadiazolinophane-6,15-dithione (**37**) as yellowish prisms: 0.85 g, 45%; mp 210–212 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.44 (m, $SCH_2CH_2CH_2N$, 4 H), 3.39 (dd, J = 5.5 $SCH_2CH_2CH_2N$, 4 H), and 4.24 (t, J = 5.5, $SCH_2CH_2CH_2N$, 4 H); ^{13}C NMR (Me_2SO-d_6) δ 21.5 ($SCH_2CH_2CH_2N$), 27.3 ($SCH_2CH_2CH_2N$), 50.2 ($SCH_2CH_2CH_2N$), 161.5 (C_8 = C_{17}), and 186.3 (C_6 = C_{15}); MS (18 eV), m/z 380 (M^+, 5). Anal. Calcd for $C_{10}H_{12}N_4S_6$: C, 31.55; H, 3.18; N, 14.72. Found: C, 31.68. H, 3.12, N, 14.45.

4,5-Dihydro-1,3-thiazino[2,3-*b*][1,3,4]thiadiazolium Bromide (40). Solutions of 2-mercapto-5-(methylthio)-1,3,4-thiadiazole sodium salt (0.31 g, 1.68 mmol), generated from **3** by treatment with 1 equiv of EtONa, and 1,3-dibromopropane (0.34 g, 1.68 mmol) in absolute EtOH (10 mL) were dropped separately but synchronously from two dropping funnels into absolute EtOH (10 mL) under stirring. The solution was heated at reflux for 17 h. After cooling, the mixture was concentrated to dryness and extracted with benzene. Evaporation of the solvent left crude crystals of **13** (0.17 g, 60%). The residue was extracted several times with hot $CHCl_3$. Concentration of the chloroform solution gave a crystalline material, which did not redissolve in $CHCl_3$. It was recrystallized from EtOH–AcOEt to give white crystals of **40**: 0.15 g, 31%; mp 195–200 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.46 (m, $SCH_2CH_2CH_2N^+$, 2 H), 2.76 (s, SCH_3, 3 H), 3.50 (dd, J = 7.5, $SCH_2CH_2CH_2N^+$, 2 H), and 4.52 (br t, J = 6.5, $SCH_2CH_2CH_2N^+$, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 17.1 (SCH_3), 21.5 ($SCH_2CH_2CH_2N^+$), 28.3 ($SCH_2CH_2CH_2N^+$), 52.0 ($SCH_2CH_2CH_2N^+$), 167.2 (C=N), and 171.6 (C=N^+); MS, m/z 284 (M^+, 9). Anal. Calcd for $C_6H_9BrN_2S_3$: C, 25.26; H, 3.18; N, 9.82. Found: C, 25.04; H, 3.02; N, 10.14.

2,5-Bis(methylthio)-3-methyl-1,3,4-thiadiazolium Iodide (41). A mixture of **17** (1.78 g, 10 mmol) and methyl iodide (2 mL) was heated at 50 °C for 20 h in a stoppered flask. The crystalline quaternary salt was collected by filtration, washed thoroughly with anhydrous Et_2O, and dried: 2.4 g, 75%; ^{1}H NMR (Me_2SO-d_6) δ 2.76 (s, C_5—SCH_3, 3 H), 3.03 (s, C_2—SCH_3, 3 H), and 4.05 (s, NCH_3, 3 H); ^{13}C NMR (Me_2SO-d_6) δ 16.7 (C_5—SCH_3), 20.7 (C_2—SCH_3), 41.9 (NCH_3), 167.9 (C_5), and 177.9 (C_2). Anal. Calcd for $C_5H_9IN_2S_3$: C, 18.75; H, 2.83; N, 8.75. Found: C, 18.85; H, 2.87; N, 8.71.

On heating for several hours in absolute EtOH, salt **41** was converted almost quantitatively to **23**, identical in all respects with an authentic sample.

1-[(3-Methyl-2-thioxo-1,3,4-thiadiazolin-5-yl)thio]-3-[5-(methylthio)-2-thioxo-1,3,4-thiadiazolin-3-yl)]propane (42). A mixture of salt **40** (142 mg, 0.5 mmol), thiol **22** (82 mg, 0.5 mmol), and EtONa (34 mg, 0.5 mmol) in absolute EtOH (10 mL) was heated at reflux under stirring for 17 h. The solvent was evaporated in vacuo to give a residue, which was extracted with benzene and chromatographed on silica gel, eluting with cyclohexane–ethyl acetate (5:1) to afford **42** as a pale yellow oil: 83 mg, 45%; ^{1}H NMR ($CDCl_3$) δ 2.33 (p, J = 7, $SCH_2CH_2CH_2N$, 2 H), 2.61 (s, SCH_3, 3 H), 3.20 (t, J = 7, $SCH_2CH_2CH_2N$, 2 H), 3.83 (s, NCH_3, 3 H), and 4.42 (t, J = 7, $SCH_2CH_2CH_2N$, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.4 (SCH_3), 27.6 ($SCH_2CH_2CH_2N$), 32.9 ($SCH_2CH_2CH_2N$), 38.7 (NCH_3), 49.3 ($SCH_2CH_2CH_2N$), 154.8, 157.3 (C—S), and 185.9, 186.0 (C=S); MS (18 eV), m/z 368 (M^+, 16). Anal. Calcd for $C_9H_{12}N_4S_6$: C, 29.32; H, 3.28; N, 15.20. Found: C, 29.17; H, 3.33; N, 15.27.

Reaction of 7 with 1,4-Dibromobutane. The general procedure was followed except for the substitution of 1,4-dibromobutane (10 mmol). General workup afforded 1,6,12,17-tetrathia[6.6](2,5)-1,3,4-thiadiazolophane (**43**) as colorless prisms: 0.24 g, 12%; mp 206–208 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.96 (m, SCH_2CH_2, 8 H), and 3.30 (m, SCH_2CH_2, 8 H); MS (18 eV), m/z 408 (M^+, 100). Anal. Calcd for $C_{12}H_{16}N_4S_6$: C, 35.27; H, 3.95; N, 13.71. Found: C, 35.38; H, 3.87; N, 13.85.

Acknowledgment. We thank the Ministero della Pubblica Istruzione (Fondi 60%) for partial financial support of this work and Prof. L. Mandolini for stimulating discussions.

Registry No. 1, 1072-71-5; **3**, 6264-40-0; **4**, 96993-48-5; **5**, 103639-76-5; **6**, 105784-95-0; **7**, 4628-94-8; **8**, 62601-22-3; **9**, 103639-76-5; **10**, 105784-96-1; 11, 91021-38-4; **12**, 105784-97-2; **13**, 105784-98-3; **14**, 105784-99-4; **15**, 105785-00-0; **16**, 105785-01-1; **17**, 7653-69-2; **18**, 2245-12-7; **19**, 91021-39-5; **20**, 91021-35-1; **21**, 91021-36-2; **22**, 29546-26-7; **23**, 33682-80-3; **24**, 91021-40-8; **25**, 90567-39-8; **26**, 105785-02-2; **30**, 105785-03-3; **31**, 105785-04-4; **32**, 105785-05-5; **33**, 105785-06-6; **34**, 105785-07-7; **35**, 105785-08-8; **36**, 105785-09-9; **37**, 105785-10-2; **40**, 105785-11-3; **41**, 104249-18-5; **42**, 105785-12-4; **43**, 105817-44-5; CH_2BrCl, 74-97-5; $HOCH_2CH_2Br$, 540-51-2; CH_2Br_2, 74-95-3; $Br(CH_2)_2Br$, 106-93-4; $Br(CH_2)_3Br$, 109-64-8; $Br(CH_2)_4Br$, 110-52-1; CH_2O, 50-00-0; CH_3I, 74-88-4.

Structure and Stereochemistry of Psorospermin and Related Cytotoxic Dihydrofuranoxanthones from *Psorospermum febrifugum*

A. M. Habib, David K. Ho, S. Masuda, T. McCloud, K. S. Reddy, M. Aboushoer, A. McKenzie, S. R. Byrn, Ching-Jer Chang, and John M. Cassady*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

Received June 26, 1986

Chemical studies of the cytotoxic extract of the plant *Psorospermum febrifugum* (Guttiferae) have led to the reisolation of the antileukemic xanthone psorospermin (**1**) and the discovery of a series of novel bioactive analogues. These analogues include 3′,4′-deoxypsorospermin (**2**), 3′,4′-deoxypsorospermin-3′,4′-diol (**3**), 3′,4′-deoxy-4′-chloropsorospermin-3′-ol (**4**), and O^5-methyl-3′,4′-deoxypsorospermin-3′-ol (**8**). The absolute stereochemistry of **1** was assigned by ORD, ^{1}H NMR, and X-ray studies of **1** and the epimeric epoxytubaic acids (**13a**, **13b**) and epoxyrotenones (**11a**, **11b**). The structures and stereochemistry of **2**–**4** and **8** were established by analysis of MS and ^{1}H NMR data and chemical correlation.

The observation that the extracts of the tropical African plant *Psorospermum febrifugum* Spach. (Guttiferae) exhibited cytotoxic and in vivo antitumor activity in the P388 mouse leukemia assay has stimulated a detailed study to determine the components responsible for these effects. Bioassay-directed chemical studies have led to the isolation

0022-3263/87/1952-0412$01.50/0