The Synthesis and Antitrichomonad Activity of 2-Substituted 4,8-Dithiaspiro[2.5]octanes (Dithianes)[1]

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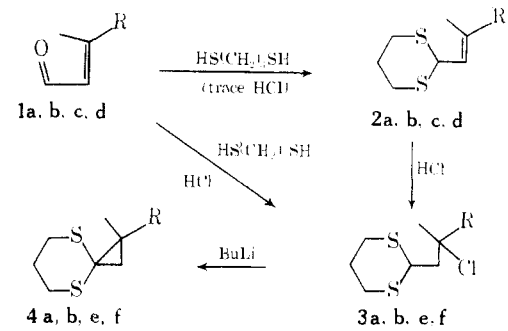
1,3-Dithianes have been alkylated with iodo-*n*-alkanes in the presence of 1 equiv of BuLi to afford the corresponding 2-(ω-chloroalkyl)-1,3-dithianes which on further treatment with BuLi were cyclized to form cycloalkyl-1,3-dithianes.[2] As an extension of this reaction sequence we now report the preparation of a number of monosubstituted cyclopropyl-1,3-dithianes (Scheme I).

Condensation of citral (**1c**) and 1,3-propanedithiol in AcOH containing a trace of alcoholic HCl gave the unsaturated thioacetal (**2c**) which was converted to the dichlorodithiane **3e** with excess HCl. Alternatively, **3e** was obtained directly by condensing **1c** and 1,3-propanedithiol with excess HCl. Reaction of **3e** with 1 equiv of BuLi effected monodehydrohalogenation to give the 2-spirocyclopropyl-1,3-dithiane (**4e**).

The scope of this type of reaction was extended to include other α,β-unsaturated aldehydes. Reaction of β-methylcrotonaldehyde (**1a**) or dihydrocitral (**1b**) with 1,3-propanedithiol and a trace of HCl gave the corresponding alkenyl-substituted dithianes **2a** or **2b**. Excess HCl converted **2a** and **2b** to the β-chloroalkyl-substituted dithianes **3a** and **3b**, respectively, which, on treatment with BuLi, were cyclized to the corresponding spiro derivatives **4a** and **4b**. By the same reaction sequence the polyunsaturated aldehyde, farnesal (**1d**), was transformed *via* **2d** and **3f** to afford the spirane **4f**.

Scheme I



a, R = CH_3

b, R = $(CH_2)_3CH(CH_3)_2$

c, R = $(CH_2)_2CH{=}C(CH_3)_2$

d, R = $(CH_2)_2CH{=}C(CH_3)(CH_2)_2CH{=}C(CH_3)_2$

e, R = $(CH_2)_3C(Cl)(CH_3)_2$

f, R = $(CH_2)_3\overset{CH_3}{\overset{|}{C}}(Cl)(CH_2)_3C(Cl)(CH_3)_2$

The structures of **4a**, **b**, **e**, **f** are compatible with their ir, mass spectra, and nmr data. In particular, the nmr spectra show the expected shifts for the cyclopropane methylene protons,[3] a singlet at 0.95 ppm, whereas the precursors **3a**, **b**, **e**, **f** exhibit a doublet at 2.14 ppm.

To determine the antitrichomonad activity, mice were subcutaneously infected with *Trichomonas vaginalis* and the substance was infiltrated into the same area.[4] The results are given in Table I. Metronidazole, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, which was used as the reference compound, exhibited a CD_{50} of 100 μg/ml. The most active compound of the series was 2-(2-chloro-2,6-dimethylheptyl)-1,3-dithiane (**3b**) with a CD_{50} of 5 μg/ml. Interestingly enough cyclization of **3b** to the corresponding cyclopropyl derivative **4b** destroyed the activity. In contrast, 2-(2-chloro-2-methylpropyl)-1,3-dithiane (**3a**) was inactive with a CD_{50} of >1000 while the corresponding cyclopropyl derivative **4a** showed moderate activity with a CD_{50} of 19. None of the compounds were active orally in this experimental infection.

Table I

Physical Properties and *Trichomonas vaginalis* Activity of the 1,3-Dithianes

Compd	Method	Yield, %	Bp (mm) or mp, °C	$n^{25}D$ or recrystn solvent	Formula	Analyses	*T. vaginalis* CD_{50}, μg/ml[a]
2a	I	70	62 (0.02)	1.5449	$C_8H_{14}S_2$	C, H	>1000
2b	I	75	117 (0.07)	1.5469	$C_{13}H_{22}S_2$	C, H	>1000
2c	I	80	119 (0.03)	1.5432	$C_{13}H_{24}S_2$	C, H	>1000
2d	I	70	162 (0.02)	1.5429	$C_{18}H_{30}S_2$	C, H	>1000
3a	II (III)	95 (60)	77 (0.02)	1.5458	$C_8H_{15}ClS_2$	C, H	>1000
3b	II (III)	85 (55)	115 (0.02)	1.5223	$C_{13}H_{25}ClS_2$	C, H	5
3e	II (III)	97 (60)	67–68	Pet ether	$C_{13}H_{24}Cl_2S_2$	C, H, Cl, S	104
3f	II (III)	80 (65)	97–98	EtOH	$C_{18}H_{33}Cl_3S_2$	C, H, S	>1000
4a	IV	90	52 (0.05)	1.5465	$C_8H_{14}S_2$	C, H	19
4b	IV	80	115 (0.02)	1.5120	$C_{13}H_{24}S_2$	C, H	>1000
4e	IV	85	120 (0.03)	1.5346	$C_{13}H_{23}ClS_2$	C, H, Cl, S	>1000
4f	IV	65	59–61	Pet ether	$C_{18}H_{32}Cl_2S_2$	C, H	>1000

[a] The CD_{50} for metronidazole was 100 μg/ml.

(1) Presented in part by one of us (J. P. O'B.) at the Division of Medicinal Chemistry Section, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

(2) D. Seebach, N. R. Jones, and E. J. Corey, *J. Org. Chem.*, **33**, 300 (1968).

(3) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1964, p 83.

(4) E. Grunberg and E. Titsworth, Antimicrobial Agents and Chemotherapy—1965, American Society for Microbiology, Ann Arbor, Mich., 966, pp 1478–480.