Synthesis of 1,2,4-Triazole and Thiazole Analogs of Ketoconazole

Liang-Fu Huang, Jang-Woo Kim and Ludwig Bauer*

Department of Medicinal Chemistry, M/C 781, College of Pharmacy, University of Illinois at Chicago
833 South Wood Street, Chicago, Illinois 60612-7231

George Doss

Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065-0900
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The synthesis of 1,2,4-triazole and thiazole analogs of ketoconazole is described in which one of the α azole ring carbons is linked to C-2 of the ketal by means of a three methylene tether. Lithiation of 1-methyl-1,2,4-triazole and thiazole and subsequent alkylation with 2-(2,4-dichlorophenyl)-2-(3-iodopropyl)-1,3-dioxolane produced, after an aqueous acidic workup, 2,4-dichlorophenyl 3-[5-(1-methyl-1,2,4-triazolyl) and 2-thiazolyl]propyl ketones, respectively. Ketalization with glycerol furnished the corresponding diastereomeric pairs of *cis* and *trans* 1,3- dioxolanes. The reaction of 2,4-dichlorophenyl 3-[5-(1-methyl-1,2,4-triazolyl)]propyl ketone with 3-mercapto-1,2-propanediol produced the corresponding diastereomeric *cis* and *trans* hydroxymethyl 1,3-oxathiolanes. The diastereomeric racemates were separated by column chromatography and their stereochemistry established by nOe nmr experiments. Some of these racemic *cis* ketal alcohols were converted by benzyl bromide to the corresponding benzyl ethers. Several of these racemic *cis*-ketals were reacted, first with methanesulfonyl chloride, then with 1-acetyl-4-(4-hydroxyphenyl)piperazine, to furnish the title compounds.

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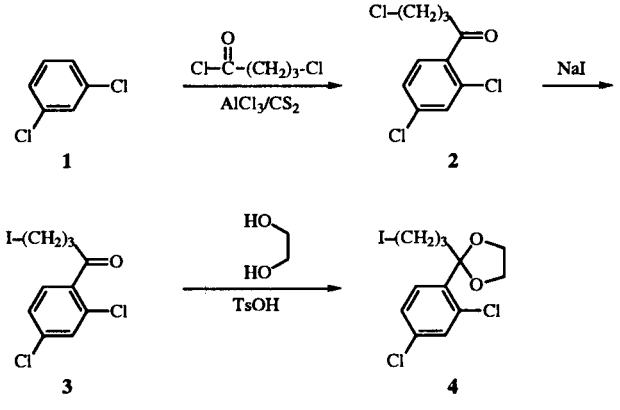
Syntheses of several analogs of ketoconazole, a broad spectrum antifungal agent [1,2], were designed in which the ketal, with its piperazinophenyl side chain, is attached by means of a three-methylene tether to either C-5 of 1-methyl-1,2,4-triazole or C-2 of thiazole. Precursor 2,4-dichlorophenyl 3-[5-(1-methyl-1,2,4-triazolyl) and 2-thiazolyl]propyl ketones, **7** and **15**, respectively, were synthesized by the method used to prepare 4-chlorophenyl 3-(2-imidazolyl)propyl ketone [3]. That particular synthetic sequence utilized the substitution of 1-methyl-2-lithioimidazole by 2-(4-chlorophenyl)-2-(3-iodopropyl)-1,3-dioxolane, which in turn became available from commercial 1-(4-chlorophenyl)-4-chloro-1-butanone. For reasons as yet not understood, alkylation of 1-methyl-2-lithioimidazole by the 2,4-dichlorophenyl analog **4** could not be achieved under a variety of conditions including changes in solvents, temperatures and modes of addition. On the contrary, **4** did successfully alkylate the lithio derivatives of 1-methyl-1,2,4-triazole and thiazole.

1-(2,4-Dichlorophenyl)-4-chloro-1-butanone (**2**) and the Corresponding Iodo Ketal **4** (Scheme 1).

The successful Friedel Crafts acylation of 1,3-dichlorobenzene (**1**) with commercially available 4-chlorobutanoyl chloride provided the chloro ketone **2** whose isolation and purification required attention. During high vacuum distillation, considerable decomposition of **2** took place as evident by ^{1}H nuclear magnetic resonance (nmr) spectra of the distillate. In a separate experiment, it was found that **2** decomposes extensively above 180°. Therefore, **2** was purified by (more tedious) column chromatography on silica gel. The pure ketone thus obtained was an amber oil which was quite stable at 25°.

Scheme 1

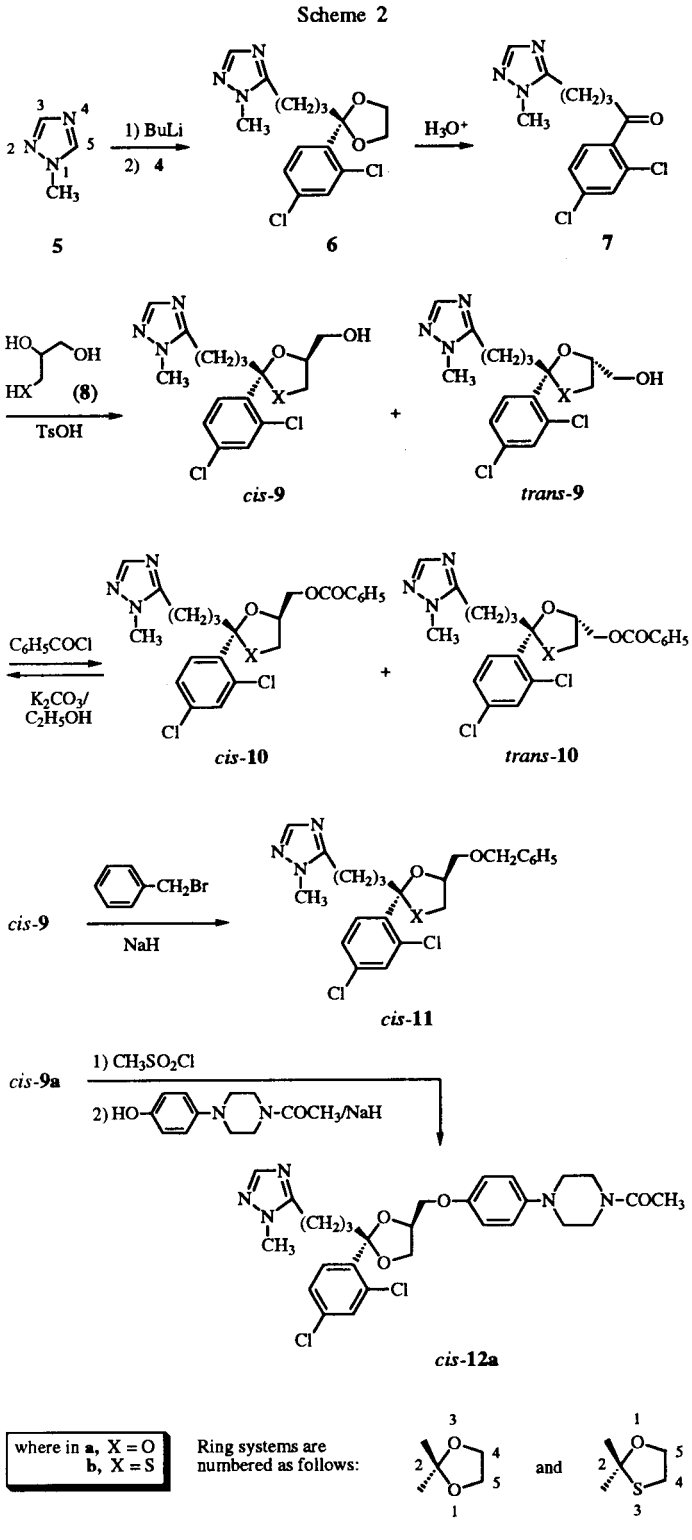


The most successful conversion of **2** to the corresponding iodo ketal **4** followed the route established for the synthesis of the 4-chlorophenyl 2-imidazolyl analog [3]. Of the two alternatives, the reaction of **2** first with iodide ion, followed by ketalization (with ethylene glycol) was preferred to the one in which **2** is ketalized first, followed by nucleophilic displacement by iodide ion [3]. For the conversion of **2** to **4**, one chromatographic separation can be avoided: impure **2** can be reacted with iodide ion to form crude iodo compound **3**, which has to be chromatographed prior to the next step. Use of crude **3** for ketalization with ethylene glycol greatly diminishes the yield of pure **4**.

Synthesis of a 1,2,4-Triazole Analog of Ketoconazole (Scheme 2).

1-Methyl-1,2,4-triazole (**5**) was made unequivocally from 1-amino-1,2,4-triazole by literature methods [6-9]. Lithiation with butyllithium takes place as expected on

Scheme 2



C-5 of **5** [4]. Alkylation with **4** afforded the 5-substituted triazole **6** in respectable yield. Acid-catalyzed hydrolysis of the ketal provided ketone **7**. As anticipated, ketalization of **7** with glycerol (**8a**) [10,11] furnished the expected mixture of *cis*- and *trans*-**9a**, in the ratio of about 3:1 (88%). When **7** was condensed with 3-mercapto-1,2-propanediol (**8b**) according to our method [11], the major product was a mixture of the *cis* and *trans* 1,3-oxathiolanes **9b** (3.3:1, 42%). As before, the *cis* nomenclature is retained for those racemates in which the *alkyl* groups are on the same side of the ketal ring [1,10,11]. Each of these diastereomeric ketals and hemithioketals (from **9a** and **9b**) represents a racemic mixture.

Separation of the *cis* and *trans* racemic alcohols **9** was achieved by means of column chromatography on silica gel. However, the separation of these types of alcohols becomes frequently more efficient if carried out *via* the corresponding benzoates [10]. In these systems, it is almost impossible to predict if alcohols or benzoates are more likely to be separated efficiently. However, since these esters are formed (and hydrolyzed) in good yields, any diversion involving the benzoates did not substantially diminish the yield of pure alcohols. It is important to separate these diastereomers at the alcohol (or ester) stage, since later separations, for example as ethers (*e.g.*, *cis* and *trans* ketoconazole) on silica gel or alumina proved to be highly inefficient [1,2]. Starting from pure racemic *cis*-**9a**, we were able to synthesize the corresponding *cis* *O*-benzyl ether **11a**, which was isolated as a gum and was characterized by microanalytical and spectral data. Similarly, pure *cis*-**9b** was converted to the *cis* *O*-benzyl ether **11b**. To synthesize the ketoconazole analog, *cis*-**9a** was converted to the methanesulfonate by means of methanesulfonyl chloride, followed by displacement of the sulfonate by the anion of 1-acetyl-4-(4-hydroxyphenyl)piperazine to form *cis*-**12a**.

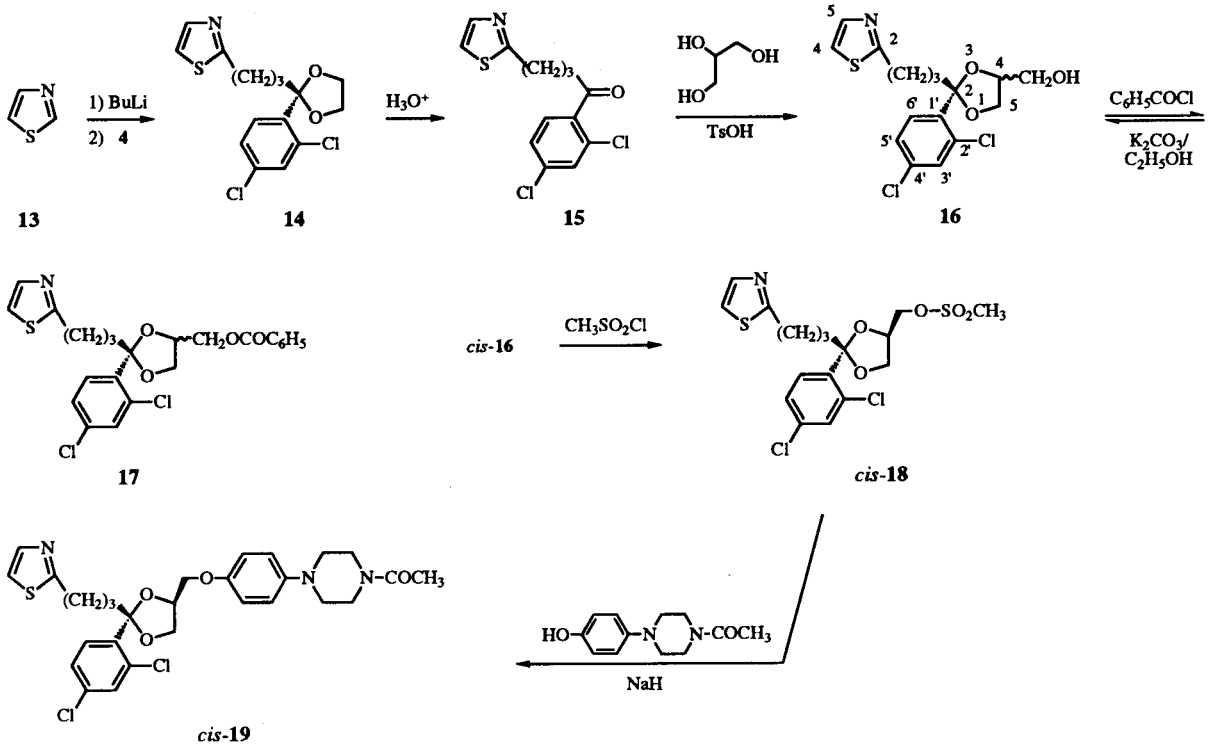
Synthesis of a 2-Thiazole Analog of Ketoconazole (Scheme 3).

Lithiation of thiazole at C-2 is well documented, but relatively few examples have been reported involving alkylations to prepare 2-alkyl derivatives [5]. The reaction of thiazole (**13**) with butyllithium, and subsequent reaction with iodo ketal **4** formed **14**. Acid-catalyzed hydrolysis of the ketal liberated ketone **15**. Subsequent ketalization with glycerol in the presence of 4-toluenesulfonic acid, with azeotropic removal of water, gave rise to a mixture of racemic *cis*- and *trans*-**16** (3.3:1) in overall yield of 65%. Separation of *cis* and *trans* alcohols **16** was achieved, *via* their benzoates, **17**. Base-catalyzed hydrolysis of the *cis*-benzoates provided pure *cis*-**16**. After the reaction of *cis*-**16** with methanesulfonyl chloride to form **18**, displacement with the requisite phenol provided one of the target ketoconazole analogs *cis*-**19**.

Nmr Analyses and Determination of Stereochemistry.

Since considerable ^1H and ^{13}C nmr data for 1,2,4-triazoles [6-9,17], thiazoles [12] and ketoconazole becomes [14] have

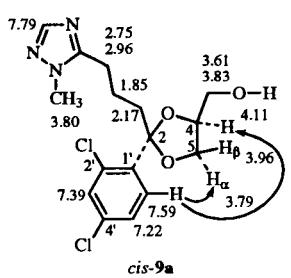
Scheme 3



been published, this discussion centers around the determination of stereochemistry as well as unequivocal assignments of certain ambiguous chemical shifts. Five ketal alcohols (*cis*- and *trans*-**9a**, *cis*- and *trans*-**16** and *cis*-**9b**) were subjected to an in-depth analysis of their ^1H and ^{13}C chemical shifts (Tables 1 and 2) and to nuclear Overhauser enhancement (nOe) experiments. The crucial nOe experiments involved the *ortho*-proton of the 2,4-dichlorophenyl ring (H-6') and the methine proton of the ketal (H-4) and that of the hemithioketal (H-5) in certain *cis* isomers.

From the line pattern and the size of the coupling constants, it was relatively straightforward to assign chemical shifts to the three ring protons of the 2,4-dichlorophenyl ring [14-16]). The distinct ^1H nmr parameters for our series of compounds are as follows (in deuteriochloroform): δ 7.21-7.23 (dd, H-5'), 7.39-7.40 (d, H-3'), 7.52-7.59 (d, H-6'); $J_{3',5'}$ = 2.0-2.1, $J_{5',6'}$ = 8.3-8.5 Hz. These ^1H nmr data compare well with those published recently for a number of related compounds: δ 7.24-7.27 (H-5'), 7.42-7.48 (H-3'), 7.52-7.60 (H-6'); $J_{3',5'}$ = 2.0 Hz, $J_{5',6'}$ = 8.5 Hz [15]. Upon irradiation of H-6' of the 2,4-dichlorophenyl ring, nOe enhancements were observed for the methine ketal proton resonances (H-4) of 1,3-dioxolanes in *cis*-**9a** and *cis*-**16** (around δ 4.11) and H-5 of the 1,3-oxathiolane of *cis*- **9b** (δ 4.29). Moreover, nOe's were also observed between H-6' and the 5α-H ketal ring protons (around δ 3.79) of *cis*-**9a** and *cis*-**16**, but not for 4α-H of the hemithioketal in *cis*-**9b**. By contrast, irradiation of H-6' of *trans*-**9b** and *trans*-**16** showed no nOe effects on the ketal methine signals (around δ 4.36), but significant nOe's of the 5α-H ketal ring proton signals around δ 3.58. Thus, reasonable nOe's between H-6' and the ketal methine proton (H-4 of *cis*-**9a**, *cis*-**9b** and H-5 of *cis*-**16**) proved their stereochemistry. These data are incorporated into the diagrams below for *cis*- and *trans*- **9a**.

The closely-related ^1H and ^{13}C chemical shifts of the ketal methylene group (O-CH_2-CH-) and that of the exocyclic hydroxymethyl group (CH-CH_2-OH) were distinguished by means of HMQC (one-bond ^1H-^{13}C correlation) and HMBC (long-range ^1H-^{13}C) experiments. By virtue of their spatial proximity, there were nOe's between H-6' and the 5α-H ketal ring proton of *cis*- and *trans*-**9a** and *cis*- and *trans*-**16**, hence the ^1H chemical shifts of 5β-H's became known. These experiments enabled us to distinguish between the ^1H (and eventually ^{13}C) chemical shifts of the



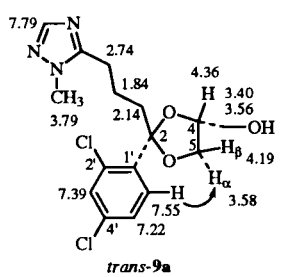


Table 1

Selected Carbon-13 Chemical Shifts of Azolyl-[$(CH_2)_a$-$(CH_2)_b$-$(CH_2)_c$-Ketals *or* Ketones [a,b,c]

Compound	Azolyl C-2	Azolyl C-3	Azolyl C-4	Azolyl C-5	*N*-Me	Tether $(CH_2)_a$	Tether $(CH_2)_b$	Tether $(CH_2)_c$	1,3-Dioxolanes *or* 1,3-Oxathiolanes C-2	C-4	C-5	CH_2-OR at C-4	CH_2-OR at C-5	C=O
2	--	--	--	--	--	39.7	26.7	44.3	--	--	--	--	--	200.7
3	--	--	--	--	--	6.1	27.5	43.3	--	--	--	--	--	200.4
4	--	--	--	--	--	6.7	27.8	38.4	109.3	64.7	64.7	--	--	--
5 [d]	--	151.9	--	143.5	36.1	--	--	--	--	--	--	--	--	--
6	--	150.1	--	155.2	35.0	25.5	21.3	36.7	109.5	64.6	64.6	--	--	--
cis-**9a**	--	149.9	--	155.3	35.1	25.2	21.3	35.9	110.3	76.4	65.5	62.4	--	--
trans-**9a**	--	150.1	--	155.2	35.1	25.5	21.3	37.3	110.2	78.0	66.4	62.7	--	--
cis-**9b**	--	149.9	--	155.0	35.1	25.0	22.4	39.7	95.9	34.1	83.9	--	62.4	--
trans-**9b**	--	150.2	--	154.9	35.1	24.8	23.2	39.4	95.0	34.4	83.0	--	63.6	--
cis-**10a**	--	150.2	--	155.1	35.0	25.5	21.2	36.7	110.6	73.4	66.3	64.5	--	166.3
trans-**10a**	--	150.2	--	155.1	35.0	25.5	21.2	37.5	110.6	75.3	66.4	63.1	--	166.0
cis-**11a**	--	150.1	--	155.3	35.0	25.5	21.3	36.7	110.2	74.4	70.7	66.9	--	--
cis-**11b**	--	150.2	--	155.2	35.0	25.6	22.7	40.3	96.0	35.9	81.9	--	70.6	--
cis-**12a**	--	150.2	--	155.2	35.0	25.6	21.3	36.7	110.5	73.8	68.8	66.9	--	169.0
13	152.8	--	143.4	118.7	--	--	--	--	--	--	--	--	--	--
13 [e]	153.8	--	143.3	119.7	--	--	--	--	--	--	--	--	--	--
14	170.9	--	142.2	118.1	--	33.1	24.0	36.7	109.8	64.6	64.6	--	--	--
15	170.9	--	142.4	118.3	--	32.2	24.1	41.7	--	--	--	--	--	201.2
cis-**16**	171.5	--	142.4	118.5	--	33.0	24.4	36..4	110.7	76.6	65.9	63.1	--	--
trans-**16**	170.8	--	142.2	118.1	--	32.9	23.9	37.4	110.3	77.9	66.2	62.7	--	--
cis-**17**	170.7	--	142.2	118.1	--	33.0	23.9	36.7	110.6	73.4	66.3	64.6	--	166.3
trans-**17**	170.8	--	142.2	118.1	--	33.0	23.9	37.5	110.7	75.3	66.4	63.2	--	166.1
cis-**18**	170.4	--	142.2	118.1	--	32.8	23.8	36.6	111.0	72.9	68.7	65.8	--	--
cis-**19**	170.8	--	142.2	118.1	--	33.0	23.9	36.8	110.5	73.7	68.9	67.0	--	169.1

[a] Spectra determined in deuteriochloroform and shifts are reported in ppm (δ) downfield from Me_4Si. [b] Azolyl is either 5-(1-methyl-1,2,4- triazolyl) or 2-thiazolyl, and the ketal is either a 1,3-dioxolane *or* a 1,3-oxathiolane. [c] Benzenoid chemical shifts are not listed. [d] Chemical shifts have been reported in deuteriochloroform, δ 142.7 (C-5), 150.7 (C-3), 35.0 (*N*-Me), Ref. 12. [e] Values recorded in DMSO-d_6, Ref. 13.

Table 2

Selected Proton Chemical Shifts of Azolyl-[$(CH_2)_a$-$(CH_2)_b$-$(CH_2)_c$]-Ketals *or* Ketones [a,b]

Compound	Azolyl H-3 *or* [H-2]	Azolyl H-4	Azolyl H-5	*N*-Me	Tether $(CH_2)_a$	Tether $(CH_2)_b$	Tether $CH_2)_c$	1,3-Dioxolanes H-4	H-5	CH_2-OR at C-4	1,3-Oxathiolanes H-5	H-4	CH_2-OR at C-5	OH [c]
2	--	--	--	--	3.66	2.21	3.14	--	--	--	--	--	--	--
3	--	--	--	--	3.30	2.23	3.09	--	--	--	--	--	--	--
4	--	--	--	--	3.19	1.91	2.21	3.78, 4.05		--	--	--	--	--
5 [d]	7.94	--	8.08	3.95	--	--	--	--	--	--	--	--	--	--
6	7.78	--	--	3.81	2.76	1.85	2.21	3.79, 4.06		--	--	--	--	--
7	7.78	--	--	3.86	2.86	2.20	3.08	--	--	--	--	--	--	--
cis-**9a**	7.79	--	--	3.80	2.75, 2.96	1.85	2.17	4.11	3.79, 3.96	3.61, 3.83	--	--	--	4.64
trans-**9a**	7.76	--	--	3.79	2.74	1.84	2.14	4.36	3.58, 4.19	3.40, 3.56	--	--	--	2.24
cis-**9b**	7.79	--	--	3.78	2.72, 2.80	1.78, 1.95	2.30	--	--	--	4.29	2.87, 3.15	3.80, 4.06	4.69
cis-**10a**	7.74	--	--	3.79	2.72	1.86	2.20	4.32	3.87, 3.98	4.47	--	--	--	--
trans-**10a**	7.78	--	--	3.79	2.75	1.86	2.17	4.55	3.74, 4.21	4.27, 4.45	--	--	--	--
cis-**11a**	7.77	--	--	3.75	2.75	1.84	2.17	4.13	3.50-3.87		--	--	--	--
cis-**11b**	7.74	--	--	3.74	2.72	1.71, 2.02	2.32	--	--	--	4.28	2.89	3.73	--
cis-**12a**	7.76	--	--	3.76	2.76	1.88	2.21	4.31	3.99, 4.09	3.86, 3.96	--	--	--	--
13	[8.87]	7.97	7.41	--	--	--	--	--	--	--	--	--	--	--
13 [e]	[8.73]	7.83	7.27	--	--	--	--	--	--	--	--	--	--	--
13 [f]	[9.15]	7.97	7.75	--	--	--	--	--	--	--	--	--	--	--
14	--	7.65	7.17	--	3.03	1.86	2.21	3.78, 4.05		--	--	--	--	--
15	--	7.67	7.20	--	3.04	2.23	3.12	--	--	--	--	--	--	--
cis-**16**	--	7.66	7.18	--	3.03, 3.17	1.88	2.19	4.10	3.79, 3.95	3.66, 3.82	--	--	--	2.50
trans-**16**	--	7.64	7.18	--	3.02	1.85	2.16	4.36	3.58, 4.19	3.40, 3.57	--	--	--	2.03

Table 2 (continued)

Selected Proton Chemical Shifts of Azolyl-[$(CH_2)_a$-$(CH_2)_b$-$(CH_2)_c$]-Ketals *or* Ketones [a,b]

Compound	Azolyl			*N*-Me	Tether			1,3-Dioxolanes			1,3-Oxathiolanes			OH [c]
	H-3 *or* [H-2]	H-4	H-5		$(CH_2)_a$	$(CH_2)_b$	$(CH_2)_c$	H-4	H-5	CH_2-OR at C-4	H-5	H-4	CH_2-OR at C-5	
cis-**17**	--	7.62	7.14	--	3.01	1.90	2.23	4.32	3.86, 3.98	4.48	--	--	--	--
trans-**17**	--	7.66	7.17	--	3.04	1.89	2.19	4.56	3.74, 4.21	4.26, 4.44	--	--	--	--
cis-**18**	--	7.65	7.17	--	3.03	1.88	2.22	4.28	3.83, 3.94	4.30	--	--	--	--
cis-**19**	--	7.65	7.16	--	3.03	1.89	2.22	4.31	3.99, 4.11	3.86, 3.96	--	--	--	--

[a] Spectra determined in deuteriochloroform and shifts are reported in ppm (δ) downfield from TMS. [b] Azolyl is either 5-(1-methyl-1,2,4- triazolyl) or 2-thiazolyl, and the ketal is either a 1,3-dioxolane or a 1,3-oxathiolane. [c] The chemical shifts of the alcohol proton resonances vary. [d] In deuteriochloroform, the chemical shifts have been reported at δ 8.10, 7.83, 3.87, Ref 17. [e] Spectrum reported in deuteriochloroform, Ref 13. [f] Spectrum taken in DMSO-d_6, Ref 13.

ring (5-CH_2) and exocyclic (CH_2-OH) methylene protons. In other compounds in Tables 1 and 2, some of the assignments are made by analogy.

Although assignments of ^{1}H chemical shifts of the three ring protons of the 2,4-dichlorophenyl ring (attached at C-2 of a 1,3-dioxolane) are straightforward, [14-16], some controversy surrounds the unambiguous assignments of the ^{13}C chemical shifts associated with the three quaternary carbons of that ring. Using three bond correlations (HMBC) between the first methylene on the ketal [$(CH_2)_c$] and C-1', ^{13}C chemical shifts were established unequivocally for C-1' and the full compliment of such shifts for *cis*-**9a** are: δ 126.8 (C-5'), 129.6 (C-6'), 131.2 (C-3'), 132.7 (C-2'), 134.7 (C-4'), 137.3 (C-1'); and for *trans*-**9a**, the shifts are δ 127.0 (C-5'), 128.9 (C-6'), 131.2 (C-3'), 132.5 (C-2'), 134.7 (C-4'), 138.2 (C-1'). In a related study, similar ranges were reported, δ 126.9-127.5 (C-5'), 129.3-129.9 (C-6'), 131.1-131.5 (C-3'), 132.6-133.0 (C-2'), 132.9-135.3 (C-1'), 135.6-136.5 (C-4') [15]. The chemical shifts of C-1' and C-4' tend to be relatively close and needed to be established independently.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were obtained in deuteriochloroform solutions, using either a Varian XL-300 or a Varian Unity 500 MHz spectrometer. Chemical shifts were recorded in ppm (δ) downfield from tetramethylsilane and are listed in Tables 1 and 2. Research chemicals were purchased from Aldrich Chemical Co. Milwaukee, WI, and were used as supplied, unless specified otherwise. Aldrich grade 60 Å silica gel (200-400 mesh) was used for column chromatography. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

General Work-up Procedures.

Most of the reactions could be followed by tlc. Thin layer chromatograms (tlc) were run on silica gel (impregnated with a 254 nm fluorescent indicator) on either glass, or aluminum or polyester plates, layer thickness 250μm, particle size <60μm, pore size 60Å (Aldrich). Spots were visualized by iodine vapor and/or uv light. In working up mixtures containing acetals, the reaction is always poured into a saturated aqueous sodium bicarbonate solution so as to maintain a *p*H of 8, or higher. Unless the product was acidic, the "usual" work-up procedure consisted of extracting the organic product into dichloromethane or ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate solution, then with brine, dried (sodium sulfate) and the solvent(s) removed, *in vacuo*, at the lowest possible temperature, particularly if the reaction had been conducted at relatively low temperatures. Evaporation or distillation of solvents, *in vacuo*, implies their removal by means of a rotary evaporator at the water pump (20-30 torr) at about 40°.

1-(2,4-Dichlorophenyl)-4-chloro-1-butanone (**2**).

To a stirred mixture of 1,3-dichlorobenzene (73.5 g, 57.1 ml, 0.5 mole) and aluminum chloride (133.0 g, 1.0 mole) in dry carbon disulfide (300 ml) was added 4-chlorobutanoyl chloride (62 ml, 0.55 mole), dropwise (30 minutes). After 5 hours at room temperature, the reaction mixture was poured slowly into ice-water (1 l, caution: exothermic!). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 400 ml). The combined extracts were washed with water, 20% sodium hydroxide and then with brine, dried (sodium sulfate) and evaporated, *in vacuo*, to provide the crude product (105 g) as an oil.

Vacuum distillation of some of the crude product (12.0 g) provided an amber oil (7.0 g, 49%), bp 130-135° (1 torr) whose ^{1}H nmr spectrum indicated about 90% purity, as evidenced by many extraneous signals. These signals increased markedly when a sample was heated (30 minutes) at 180-200°. More than 70% of **2** decomposed if such heating continued for 1.5 hours. Column chromatography of **2** (12.0 g) on silica gel (150 g) and elution with petroleum ether-ethyl acetate (50:1) provided pure **2** (7.6 g, 53%, based on **1**) as a colorless oil; tlc: R_f = 0.50 (petroleum ether-ethyl acetate, 20:1).

Anal. Calcd. for $C_{10}H_9Cl_3O$: C, 47.75; H, 3.61. Found: C, 47.96; H, 3.52.

2-(2,4-Dichlorophenyl)-2-(3-iodopropyl)-1,3-dioxolane (**4**).

A mixture of **2** (4.3 g, 17.0 mmoles) and sodium iodide (7.65 g, 51.0 mmoles) in butanone (50 ml) was refluxed (3 hours), cooled and filtered. The filtrate was evaporated, *in vacuo*, and the residue partitioned between saturated sodium bicarbonate solution (50 ml) and ethyl acetate (150 ml). The organic layer was separated and worked up to furnish 2-(2,4-dichlorophenyl)-2-(3-iodopropyl)-1,3-dioxolane (**3**) as a red oil (5.63 g, 96%). Chromatography on silica

gel, (eluted by petroleum ether-ethyl acetate, 30:1) provided an amber oil; tlc: R_f = 0.50 (petroleum ether-ethyl acetate, 20:1), which was used immediately in the next step.

A stirred mixture of **3** (8.4 g, 24.5 mmoles), ethylene glycol (8.5 g, 137 mmoles) and 4-toluenesulfonic acid monohydrate (1.8 g, 9.5 mmoles) was refluxed in benzene (100 ml) with azeotropic removal of water (7 hours). After cooling, the mixture was poured into saturated sodium bicarbonate solution (100 ml). After the usual workup, the crude oil was chromatographed on silica gel (elution with petroleum ether-ethyl acetate, 30:1) to furnish **4** (8.15 g, 86%) as an amber oil; tlc: R_f = 0.50 (petroleum ether-ethyl acetate, 20:1).

Anal. Calcd. for $C_{12}H_{13}Cl_2IO_2 \cdot 0.3CH_3CO_2C_2H_5$: C, 38.34; H, 3.75. Found: C, 38.50; H, 3.57. The presence of this amount of ethyl acetate was confirmed by the ^1H nmr spectrum of the analytical sample.

2-(2,4-Dichlorophenyl)-2-{3-[1-methyl-5-(1,2,4-triazolyl)]-propyl]}-1,3-dioxolane (**6**).

To a stirred solution of 1-methyl-1,2,4-triazole (**5** [6-9], 3.0 g, 36.0 mmoles) in dry tetrahydrofuran (200 ml), blanketed by nitrogen, at -55°, a 2.5 *M* solution of butyllithium in THF (15.20 ml, 38.0 mmoles) was added dropwise. After 1 hour, a solution of **4** (15.3 g, 39.53 mmoles) in dry tetrahydrofuran (20 ml) was added (3 minutes). After 1 hour at -55°, and 2 hours at room temperature, the reaction was quenched with saturated sodium bicarbonate solution (3 ml). Solvents were removed, *in vacuo*, and the mixture worked up, as usual (dichloromethane). Flash chromatography on silica gel (240 g) provided unreacted **4** (6.0 g), (elution by ethyl acetate-hexane, 7:3, R_f = 0.65), followed by **6**, eluted by dichloromethane-methanol (19:1, R_f = 0.13) as a pale yellow oil (7.1 g, 86%, based on recovered **4**).

Anal. Calcd. for $C_{15}H_{17}Cl_2N_3O_2$: C, 52.65; H, 5.01; N, 12.28. Found: C, 52.41; H, 4.92; N, 12.53.

1-(2,4-Dichlorophenyl)-4-[1-methyl-5-(1,2,4-triazolyl)]-1-butanone (**7**).

A solution of **6** (8.50 g, 24.8 mmoles) in methanol (70 ml) containing 2 *M* aqueous hydrochloric acid (40 ml, 80 mmoles) was refluxed (4 hours). After cooling to 25°, the *p*H was adjusted to 9 (2 *M* sodium hydroxide). Solvents were removed, *in vacuo*, and the residue was extracted with dichloromethane (2 x 200 ml). After the usual workup and column chromatography (150 g silica gel), the pale yellow oil (5.6 g, 76%) was eluted with dichloromethane-methanol (19:1; R_f = 0.71).

Anal. Calcd. for $C_{13}H_{13}Cl_2N_3O$: C, 52.37; H, 4.39; N, 14.09. Found: C, 52.38; H, 4.44; N, 14.24.

cis- And *trans*-{2-(2,4-Dichlorophenyl)-2-{3-[1-methyl-5-(1,2,4-triazolyl)]propyl}-4-(benzoyloxymethyl)}-1,3-dioxolane (**10a**).

A mixture of **7** (3.0 g, 10.06 mmoles), glycerol (2.94 ml, 3.71 g, 42.45 mmoles) and 4-toluenesulfonic acid monohydrate (2.93 g, 15.09 mmoles) was refluxed (3 hours) in benzene (80 ml), with continuous azeotropic removal of water (Dean-Stark trap). The reaction mixture was cooled to room temperature and was poured into saturated sodium bicarbonate (200 ml). The products was extracted with dichloromethane (3 x 200 ml) and worked up as usual. The crude yellow oil (5.05 g) consisted of a mixture of *cis* and *trans*-**9a**, about 3:1, based on the integration of the ketal methine ^1H nmr signals, δ 4.36 and 4.11 for *cis*-**9a** and *trans*-**9a**, respectively. Elution from silica gel (120 g) with ethyl acetate-ethanol (19:1) provided a mixture of *cis*- and *trans*-**9a** (3.30 g, 88%). Better separation of these isomers was possible *via* the corresponding benzoates.

Benzoyl chloride (2.06 g, 17.73 mmoles) was added to a stirred ice-cold solution of *cis* and *trans*-**9a** (3.30 g, 8.86 mmoles) in dichloromethane (100 ml) and pyridine (3.59 ml, 44.32 mmoles). After 1 hour at 0°, the reaction mixture was stirred for 30 minutes at room temperature. The mixture was poured into saturated sodium bicarbonate solution (60 ml) and extracted with dichloromethane (3 x 150 ml) and worked up as usual to furnish a yellow oil (7.95 g). Column chromatography on silica gel (200 g), eluting with ethyl acetate-dichloromethane (1:1), provided pure *cis*-**10a** as a colorless gum (2.80 g, 66%); tlc, R_f = 0.21 (ethyl acetate-dichloromethane, 3:2).

Anal. Calcd. for $C_{23}H_{23}Cl_2N_3O_4$: C, 57.99; H, 4.87; N, 8.82. Found: C, 57.84; H, 4.90; N, 8.66.

Continued elution with ethyl acetate-dichloromethane (3:2) led to pure *trans*-**10a**, as a colorless gum (0.70 g, 17%) which crystallized at room temperature; mp 86-87°; tlc, R_f = 0.14 (ethyl acetate-dichloromethane, 3:2).

Anal. Calcd. for $C_{23}H_{23}Cl_2N_3O_4$: C, 57.99; H, 4.87; N, 8.82. Found: C, 58.13; H, 4.87; N, 8.86.

cis- And *trans*-{2-(2,4-Dichlorophenyl)-2-{3-[1-methyl-5-(1,2,4-triazolyl)]propyl}-4-(hydroxymethyl)}-1,3-dioxolane (**9a**).

cis-Benzoate **10a** (2.30 g, 4.83 mmoles) was hydrolyzed (1.5 hours) by potassium carbonate (1.33 g, 9.66 mmoles) in boiling aqueous ethanol (50 ml containing 3 ml water). Solvents were removed *in vacuo*, and the product (2.09 g) isolated in the usual manner (dichloromethane). After chromatography on silica gel (60 g) and elution with ethyl acetate-hexane (8:1), there was obtained *cis*-**9a** as a pale yellow oil (1.65 g, 92%); tlc, R_f = 0.42 (ethyl acetate-ethanol, 9:1).

Anal. Calcd. for $C_{16}H_{19}Cl_2N_3O_3$: C, 51.63; H, 5.14; N, 11.29. Found: C, 51.49; H, 5.16; N, 11.19.

In a similar hydrolysis, *trans*-**10a** (0.40 g, 0.84 mmole) was boiled in aqueous ethanol (15 ml containing 1 ml water) containing potassium carbonate (0.23 g, 1.67 mmoles) for 1.5 hours. The alcohol (0.27 g, 86%) was isolated, as above, being eluted from silica gel (30 g) as a pale yellow oil (ethyl acetate-ethanol, 8:1, R_f = 0.25).

Anal. Calcd. for $C_{16}H_{19}Cl_2N_3O_3$: C, 51.63; H, 5.14; N, 11.29. Found: C, 51.60; H, 5.17; N, 11.20.

cis-{2-(2,4-Dichlorophenyl)-2-{3-[1-methyl-5-(1,2,4-triazolyl)]-propyl}-4-(benzyloxymethyl)}-1,3-dioxolane (**11a**).

To a stirred solution of *cis*-**9a**, (0.333 g, 0.89 mmoles) in anhydrous tetrahydrofuran (20 ml) was added sodium hydride (0.071 g of 60% suspension in mineral oil, 1.77 mmoles) at 25°. After 15 minutes, benzyl bromide (0.211 ml, 1.77 mmoles) was added and the reaction mixture stirred 10 hours at 25°. Solvents were removed, *in vacuo*, and the brown oil was extracted by dichloromethane and worked up as usual. The yellow oil (0.65 g) was chromatographed (silica gel, 30 g) and elution with ethyl acetate-hexane, (7:3, R_f = 0.28) afforded a colorless gum (0.33 g, 81%).

Anal. Calcd. for $C_{23}H_{25}Cl_2N_3O_3$: C, 59.75; H, 5.45; N, 9.09. Found: C, 59.74; H, 5.41; N, 9.01.

1-Acetyl-4-{4-[[*cis*-2-(2,4-dichlorophenyl)-2-[3-[1-methyl-5-(1,2,4-triazolyl)]propyl]-1,3-dioxolan-4-yl)]methyleneoxy]-phenyl}piperazine (**12**).

To an ice-cold solution of *cis*-**9a** (0.31 g, 0.83 mmole) in anhydrous pyridine (20 ml), methanesulfonyl chloride (0.135 ml, 1.66

mmoles) was added dropwise (7 minutes). The reaction mixture was stirred at 0° (2 hours), then at 25° (1 hour), diluted with dichloromethane (150 ml). After washing the reaction mixture with 1 *M* potassium hydroxide (2 x 20 ml) and, then with water (2 x 20 ml), the organic layer was dried (magnesium sulfate). Removal of solvents, *in vacuo*, provided a yellow oil (0.369 g, 98%) which was used immediately in the next step.

To a stirred solution of 1-acetyl-4-(4-hydroxyphenyl)piperazine [2] (0.365 g, 1.66 mmoles) in dimethylformamide (15 ml) was added sodium hydride (0.066 g, 60%, in mineral oil, 1.66 mmoles]. After 1 hour at 40°, a solution of the crude *cis*-sulfonate, (0.369 g, 0.83 mmole) in DMF (4 ml) was added and the mixture stirred at 70° (5 hours). The reaction was cooled and quenched by the addition of 5% potassium hydroxide solution (40 ml) and the product extracted into dichloromethane (3 x 70 ml). The extract was washed with water (2 x 30 ml), dried (magnesium sulfate) and the solvent removed, *in vacuo*. The residue (1.95 g) was chromatographed (60 g silica gel) and elution with ethyl acetate-acetone (7:3) gave unreacted *cis*-sulfonate (0.11 g) followed by *cis*-**12**, as a yellow oil (0.231 g, 70%, based on recovered sulfonate); tlc, $R_f = 0.20$ (ethyl acetate-acetone, 7:3).

Anal. Calcd. for $C_{28}H_{33}Cl_2N_5O_4$: C, 58.54; H, 5.79; N, 12.19. Found: C, 58.73; H, 6.03; N, 11.81.

cis- And *trans*-{2-(2,4-Dichlorophenyl)-2-{3-[1-methyl-5-(1,2,4-triazolyl)]propyl}-5-(hydroxymethyl)}-1,3-oxathiolane (**9b**).

A mixture of **7** (2.0 g, 6.7 mmoles), **8b** (95%, 2.29 g, 20 mmoles) and 4-toluenesulfonic acid monohydrate (2.56 g, 20 mmoles) was refluxed in benzene (50 ml) with azeotropic removal of water (7 hours). The reaction mixture was cooled and quenched by pouring into saturated sodium bicarbonate solution (150 ml). The usual workup (dichloromethane) provided a gum, which consisted of a mixture of *cis*- and *trans*-**9b** (3.3:1, based on the integration of the signal at 4.19 and 4.52, arising from H-5 of 1,3-oxathiolane of *cis*- and *trans*-**9b**, respectively). Elution from a column of silica gel (90 g) with ethyl acetate afforded an unidentified mixture (2.77 g) and with ethyl acetate-methanol (19:1) yielded pure *cis*-**9b** (0.513 g, 20%) as a colorless gum, followed by a mixture of *cis*- and *trans*-**9b** (1.3:1, 0.59 g). The total yield of *cis*- and *trans*-**9b** was 42%; tlc: $R_f = 0.53$ for *cis*, and 0.51 for *trans* isomers (ethyl acetate-methanol, 10:1).

Anal. Calcd. for *cis*-$C_{16}H_{19}Cl_2N_3O_2S \cdot 0.2CH_3CO_2C_2H_5$: C, 49.71; H, 5.12; N, 10.35. Found: C, 49.42; H, 4.94; N, 10.06. The presence of ethyl acetate was confirmed (^{1}H nmr spectrum).

cis-{2-(2,4-Dichlorophenyl)-2-[3-(1-methyl-5-(1,2,4-triazolyl))-propyl]-5-(benzyloxy)methyl}-1,3-oxathiolane (**11b**).

The benzylation was carried out in the same manner as described for *cis*-**11a**, using *cis*-**9a** (0.39 g, 1.0 mmole), sodium hydride (0.08 g, 2.0 mmoles), benzyl bromide (0.238 ml, 2.0 mmoles) in tetrahydrofuran (15 ml) for 10 hours. After chromatography (silica gel, ethyl acetate-methanol, 10:1), there was isolated *cis*-**11b** (0.344 g, 72%) as a gum; $R_f = 0.72$.

Anal. Calcd. for $C_{23}H_{25}Cl_2N_3O_2S$: C, 57.74; H, 5.27; N, 8.78. Found: C, 57.90; H, 5.23; N, 8.41.

2-(2,4-dichlorophenyl)-2-[3-(2-thiazolyl)propyl]-1,3-dioxolane (**14**).

A stirred cold (-50°) solution of **13** (5.0 g, 58.73 mmoles) in anhydrous tetrahydrofuran (250 ml) was flushed with dry nitrogen (5 minutes) before a solution of 2.5 *M* solution of butyllithium in THF (28.2 ml, 70.5 mmoles) was added, dropwise. After 1 hour at -50°, **4** (25.0 g, 64.6 mmoles in 40 ml tetrahydrofuran) was added (10 minutes). The mixture was allowed to stand at -50° (1 hour) and then at 25° (24 hours). After quenching with saturated sodium bicarbonate solution (5 ml), the mixture was worked up, as described for **6**. Flash chromatography on silica gel (250 g) provided first (ethyl acetate-hexane, 7:3) **4** (3.75 g), then (ethyl acetate-hexane, 3:7) **14** (13.14 g, 70% based on recovered **4**) as a pale yellow oil; tlc, $R_f = 0.50$ (ethyl acetate-hexane, 2:3).

Anal. Calcd. for $C_{15}H_{15}Cl_2NO_2S$: C, 52.33; H, 4.39; N, 4.07. Found: C, 52.26; H, 4.38; N, 4.30.

1-(2,4-Dichlorophenyl)-4-(2-thiazolyl)-1-butanone (**15**).

A solution of **14** (11.3 g, 32.8 mmoles) was hydrolyzed in boiling ethanol (100 ml) containing 2 *M* hydrochloric acid (50 ml). After 4 hours, the ketone **15** was isolated as described for **7**. After chromatography (250 g, silica gel) and elution with ethyl acetate-hexane (2:3), there was isolated **15** as a pale yellow oil (8.51 g, 86%).

Anal. Calcd. for $C_{13}H_{11}Cl_2NOS$: C, 52.01; H, 3.69; N, 4.67. Found: C, 52.28; H, 3.80; N, 4.48.

cis- And *trans*-{2-(2,4-Dichlorophenyl)-2-[3-(2-thiazolyl)-propyl]-4-(benzoyloxymethyl)}-1,3-dioxolane (**17**).

A mixture of **8a** (2.93 ml, 3.70 g, 40 mmoles), **15** (3.0 g, 9.99 mmoles) and *p*-toluenesulfonic acid monohydrate (3.88 g, 19.99 mmoles) in benzene (80 ml) was refluxed for 4 hours, with continuous removal of water as an azeotropic mixture by means of a Dean-Stark trap. During refluxing the reaction mixture, disappearance of ketone was monitored by tlc. After a work-up similar to that described for the formation of **9a**, *cis*- and *trans*-**16** were isolated as an oil (4.0 g, *cis*:*trans* isomers, 3.3:1, based on the integration of the ketal methine ^{1}H nmr signals, δ 4.07 and 4.39 for *cis*- and *trans*-**16**, respectively). Attempts to separate by column chromatography on silica gel (120 g) failed. Elution with ethyl acetate furnished a mixture of these isomers (2.80 g, 75%).

To a stirred ice-cold solution of a mixture of *cis* and *trans* alcohols, (**16**, 2.80 g, 7.48 mmoles) and pyridine (3.03 ml, 37.40 mmoles) in dichloromethane (30 ml) was added benzoyl chloride (1.74 ml, 14.96 mmoles). After 1 hour at 0°, the reaction mixture was allowed to warm up to 25°. After 30 minutes, the mixture was worked up as described for **10**. Elution from silica gel (200 g) by ethyl acetate-hexane (2:3) yielded pure *cis*-**17** (2.28 g, 64%) and, then, *trans*-**17** (0.74 g, 21%) as colorless gums; tlc, for *cis*-**17**, $R_f = 0.30$; for *trans*-**17**, $R_f = 0.21$ (ethyl acetate-hexane, 2:3).

Anal. Calcd. for $C_{23}H_{21}Cl_2NO_4S$: C, 57.75; H, 4.42; N, 2.93. Found for *cis*-**17**: C, 57.61; H, 4.39; N, 2.85. Found for *trans*-**17**: C, 57.74; H, 4.39; N, 2.80.

cis- And *trans*-{2-(2,4-Dichlorophenyl)-2-[3-(2-thiazolyl)-propyl-4-(hydroxymethyl)}-1,3-dioxolane (**16**).

Following the procedure established for the hydrolysis of **10**, *cis*-**17** (2.16 g, 4.52 mmoles) was boiled (3 hours) in 50 ml of ethanol containing 3 ml of water and potassium carbonate (1.25 g, 9.04 mmoles), and worked up as described for the isolation of **9a**. Column chromatography on silica gel (50 g) and elution with ethyl acetate-hexane (2:3) provided the alcohol as a pale yellow oil (1.65 g, 98%); tlc, $R_f = 0.11$ (ethyl acetate-hexane, 2:3).

Anal. Calcd. for $C_{16}H_{17}Cl_2NO_3S$: C, 51.34; H, 4.58; N, 3.74. Found: C, 51.09; H, 4.61; N, 3.65.

A similar hydrolysis of *trans*-**17**, (0.36 g, 0.75 mmole) in 15 ml of ethanol and water (1 ml) was added potassium carbonate (0.21 g, 1.52 mmoles), provided after chromatography, a pale yellow oil (eluted with ethyl acetate, 0.237 g, 84%); tlc, R_f = 0.29 (ethyl acetate).

Anal. Calcd. for $C_{16}H_{17}Cl_2NO_3S$: C, 51.34; H, 4.58; N, 3.74. Found: C, 51.21; H, 4.50; N, 3.59.

cis-{2-(2,4-Dichlorophenyl)-2-[3-(2-thiazolyl)propyl]-4-(methanesulfonyloxymethyl)}-1,3-dioxolane (**18**).

To an ice-cold solution of *cis*-**16** (0.47 g, 1.27 mmoles) in dichloromethane (25 ml) and anhydrous pyridine (0.21 ml) at 0° was added methanesulfonyl chloride (0.15 ml, 1.90 mmoles) dropwise (7 minutes). After stirring at 0° (2 hours), the mixture was allowed to return to room temperature and was stirred for another hour. After washing with 5% aqueous potassium hydroxide solution (2 x 20 ml) and then with water (2 x 20 ml) the organic layer was dried (magnesium sulfate) and the solvent was removed, *in vacuo*, to provide a yellow oil (0.558 g, 97%). The oily compound was purified by column chromatography (on silica gel, ethyl acetate) to afford pure *cis*-**18** (0.51 g, 89%).

Anal. Calcd. for $C_{17}H_{19}Cl_2NO_5S_2$: C, 45.14; H, 4.23; N, 3.10. Found: C, 45.18; H, 4.15; N, 3.01.

1-Acetyl-4-{4-[[*cis*-2-(2,4-dichlorophenyl)-2-[3-(2-thiazolyl)-propyl]-1,3-dioxolan-4-yl)]methyleneoxy]phenyl}piperazine (**19**).

To a solution of 1-acetyl-4-(4-hydroxyphenyl)piperazine [2] (0.16 g, 0.71 mmole) in dimethylformamide (15 ml) was added sodium hydride (0.028 g, 0.71 mmole). After stirring the mixture for 1 hour at 40°, *cis*-**18** (0.16 g, 0.35 mmole) was added and the mixture stirred at 70° (10 hours). Upon cooling, 5% potassium hydroxide solution (40 ml) was added and the mixture extracted with dichloromethane (2 x 100 ml) and the extract washed with water (30 ml). The organic layer was dried, the solvent removed, *in vacuo*, to provide a yellow oil (0.25 g). Elution from a column of silica gel (25 g) with ethyl acetate gave a yellow oil (0.131 g, 64%); tlc, R_f = 0.13 (ethyl acetate).

Anal. Calcd. for $C_{28}H_{31}Cl_2N_3O_4S \cdot 0.25H_2O$: C, 57.88; H, 5.46; N, 7.23. Found: C, 57.80; H, 5.62; N, 7.23.

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