Synthesis of Diastereomeric Ketoconazole Analogs [1].

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Syntheses of *trans*-isomers of ketoconazole, and the corresponding des-acetyl, 1-methyl-, 1-formyl and 1-methanesulfonyl analogs were investigated. These isomers, along with the corresponding *cis*-diastereomers were characterized by their carbon-13 nmr spectra.

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Of the many 1-substituted imidazoles and 1,2,4-triazoles used as oral antifungal agents [2], one of the most potent for human use is *cis*-ketoconazole (**3a**). While many *cis* analogs of **3a** have been reported in which the 1-piperazinyl substituent, R, runs the gamut of virtually every conceivable type of alkyl, aryl, heteroaryl, aralkyl and acyl group [3], there is a paucity of syntheses of the corresponding *trans*-isomers.

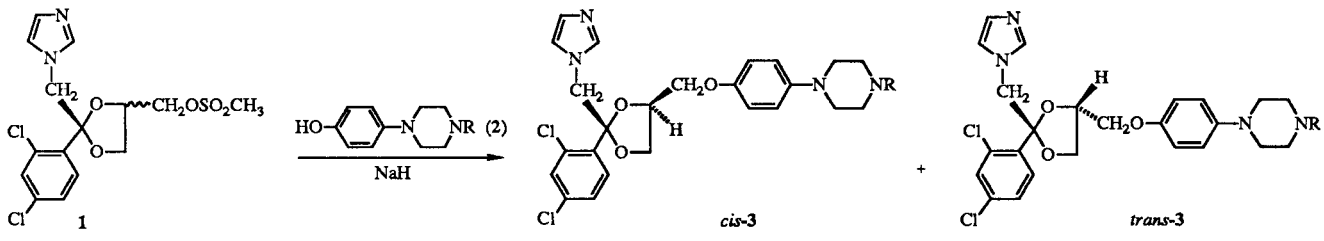
The availability of *cis*- and *trans*-{2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl}-methyl methanesulfonates **1** [4] provides good precursors for the synthesis of diastereomers, **3a-3e**. Although detailed preparations of some of these compounds are reported, others are barely mentioned in patents, and in many instances no physical data are provided. Their ^{13}C nmr spectra are now reported. Since only several characteristic chemical shifts allow one to distinguish between *cis* and *trans* isomers in simpler 2,2,4-trisubstituted 1,3-dioxolanes of type **1** [4], it was of interest to establish if this premise holds for *cis* and *trans* ketoconazole, des-acetyl-ketoconazole, as well as for their methyl, formamido and methanesulfonamido analogs **3a-3e**.

Two major routes of synthesis of these compounds are elaborated on. It would seem that the displacement of the sulfonate in **1** by an appropriate piperazino-substituted phenol should be a versatile route to the ether of **3**.

While such displacements lead to stereochemically pure products, the yield of **3** is frequently low. These reactions are best carried out in such non-hydroxylic solvents as *N,N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) with sodium hydride to generate the phenoxide ion. However, other nucleophiles, particularly if the N-1 amino group in piperazine is a secondary or tertiary amine, could compete with phenoxide ion in these nucleophilic displacements. However, by acylating N-1 of the piperazine **2** (by forming an amide or sulfonamide) the reaction to form **3** is improved.

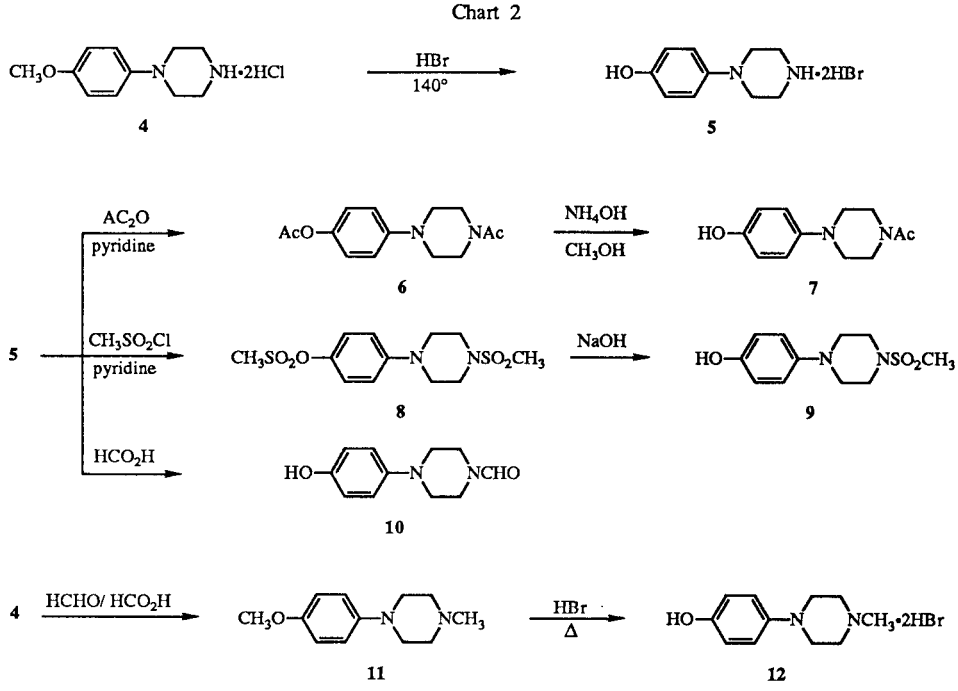
We prepared a number of piperazino phenols to use in such displacements. Some of these preparations were modifications of literature methods but frequently represent an improvement of published procedures (Chart 2).

Chart 1



where, **a**, R = $COCH_3$
b, R = SO_2CH_3
c, R = H
d, R = CH_3
e, R = CHO

Chart 2



Commercially available 4-(1-piperazinyl)anisole dihydrochloride (**4**) is readily cleaved by hydrobromic acid to form the phenol **5** [6]. This amino phenol is stable as a salt but tends to darken and decompose as the free base. Acetylation of **5** with excess acetic anhydride in pyridine readily forms the ester-amide **6** which is transformed by methanolic ammonia to the more stable phenolic amide **7**.

Although the synthesis of the sulfonamide **9** has been described by Heeres [3b] the following procedure furnishes a cleaner product, in better yield. The reaction of **5** with excess methanesulfonyl chloride forms **8**. This sulfonamido sulfonate is preferentially hydrolyzed by hot aqueous sodium hydroxide to produce the phenolic sulfonamide **9**. Direct formylation of **5** leads to the *N*-formyl derivative **10**, apparently without forming the formyl ester.

cis And *trans*-ketoconazole (**3a**) can be synthesized readily from {2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl}methyl methanesulfonates, (**1**) [4] and 1-(4-hydroxyphenyl)-4-acetylpiperazine **7** [3a]. Furthermore, the reactions of *cis*- and *trans*-**1** with **9** and **10** proceeded in good yield to form **3b** and **3e**. However, the reaction of **1** with **12** to form **3d** is not recommended. Alternate methods were sought for the synthesis of **3d**, as well as **3c**. Displacements of **1** with **7** and **10** furnished amides **3a** and **3d**, which were hydrolyzed to **3c**. By conducting these hydrolyses in basic media, the destruction of the acetal was not jeopardized. The secondary amine of **3c** may be transformed to many new groups by either alkylation or acylation to yield sulfonamides, cyanamides, ureas, thioureas, urethans, to mention of few [3].

We found that the Eschweiler-Clark procedure to methylate **3c** to form **3d** worked very well. Acylation with formic acid or methanesulfonyl chloride also afforded **3e** and **3b**, in good yield. In this way the *trans*-ketoconazole analogs can be prepared readily.

The *cis* and *trans* products **3** were characterized by their ^{13}C nmr spectra and as noted before assignments could be made provided that both isomers were available [4]. The chiral C-4 dioxolane carbons showed again the greatest chemical shift differences. Such differences are small, of the order of 1.5 ppm (Table 1). The chemical shift of C-4 of the 1,3-dioxolane ring was farther downfield for the *trans*-isomers of **3**, but this assignment can be made with certainty only if both isomers are available. It should be noted that in the final ketoconazole analogs, the amidic piperazines showed restricted rotation about the amide bond, but not the *N*-methyl or sulfonamide derivatives. Thus in *cis* and *trans* ketoconazole (**3a**) and the *N*-formyl analog **3e** two α-carbon (C-2, C-6) signals were recorded some 5 ppm apart, arising from restricted rotation about the amide bond (on this nmr time scale), see Table 1.

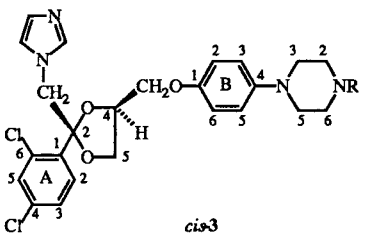
EXPERIMENTAL [4]

1-(4-Hydroxyphenyl)piperazine Dihydrobromide (**5**).

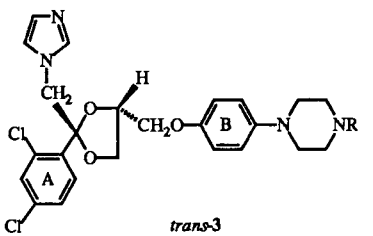
1-(4-Methoxyphenyl)piperazine dihydrochloride (Lancaster Chemical Co., **4** 37.4 g, 0.142 mole) was refluxed with 48% hydro-

Table 1

Carbon-13 Chemical Shifts of *cis*- and *trans*-3



cis-3



trans-3

Compound	R	MP (°C)	1,3-dioxolane					C=O	CH_3	1-Imidazolyl			Halo-subst Ring A						*O*-Aryl-*N* (Ring B)				Piperazine			
			2	4	5	2-CH_2	4-CH_2			2	4	5	1	2	3	4	5	6	4'	3'	2'	1'	3(5)	3(5)	2(6)	6(2)
3a-*cis*	$COCH_3$	145-146	108.0	74.7	67.6	51.2	67.5	168.9	21.3	138.7	128.4	121.3	127.2	129.4	131.3	132.9	134.5	135.8	145.7	115.2	118.7	152.8	51.0	50.6	46.3	41.4
3a-*trans*	$COCH_3$	Glass	107.9	75.8	67.3	51.9	67.3	168.6	21.1	138.4	128.4	120.6	126.7	129.2	130.7	132.5	135.2	135.3	145.5	115.0	118.4	152.5	50.7	50.3	46.1	41.2
3b-*cis*	SO_2CH_3	110-111	108.0	74.8	67.7	51.3	67.6	–	34.4	138.9	128.5	121.2	127.2	129.5	131.4	133.0	134.8	134.8	145.4	115.3	119.1	153.1	50.6	50.6	46.0	46.0
3b-*trans*	SO_2CH_3	112-115	108.2	76.1	67.6	52.3	67.6	–	34.4	138.5	128.7	121.5	127.0	129.4	131.1	131.7	132.8	135.6	145.4	115.3	119.0	153.1	50.6	50.6	46.0	46.0
3c-*cis*	H	168-169	107.9	74.7	67.6	51.2	67.6	–	–	138.7	128.5	121.0	127.1	129.4	131.2	132.9	134.5	135.7	146.6	115.0	118.0	152.1	51.7	51.7	46.2	46.2
3c-*trans*	H	Gum	108.2	76.1	67.7	52.3	67.7	–	–	138.7	128.7	120.8	127.0	129.4	131.0	132.8	135.6	135.6	146.6	115.2	118.1	152.4	51.4	51.4	46.0	46.0
3d-*cis*	CH_3	114-115	107.6	74.5	67.4	50.9	67.2	–	45.8	138.4	128.2	120.8	126.8	129.2	130.9	132.6	134.4	135.4	145.8	114.9	117.6	151.9	54.9	54.9	50.0	50.0
3d-*trans*	CH_3	99-100	108.1	76.0	67.6	52.2	67.6	–	46.0	138.6	128.6	120.8	126.9	129.4	130.9	132.7	135.5	135.5	146.1	115.1	117.8	152.1	55.1	55.1	50.2	50.2
3e-*cis*	CHO	151-152	108.0	74.7	67.6	51.2	67.5	160.6	–	138.7	128.5	121.1	127.2	129.4	131.3	132.9	134.6	135.8	145.6	115.2	119.1	153.0	51.7	50.6	45.6	40.0
3e-*trans*	CHO	165-166	107.9	75.8	67.2	51.9	67.2	160.4	–	138.3	128.4	120.6	126.7	129.2	130.7	132.4	135.2	135.3	145.4	115.0	118.7	152.7	51.3	50.2	45.3	39.7

bromic acid (150 ml) for 4 hours. The reaction was cooled, filtered to remove some black solid, and concentrated *in vacuo*. The brown gummy residue was triturated with hot ethanol and the colorless solid (44.0 g, 88%) filtered and dried, mp 286-289°, lit [6] mp 291-293°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.45 (br s, NH(CH_2)$_2$), 3.54 (br s, ArN(CH_2)$_2$), 6.83, 7.23 (m, AA'BB' arom H's), 9.15, 10.00 (two br exchangeable singlets); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 41.6, 48.9, (piperazine carbons), 116.2, 120.3, 137.5, 154.9 (aromatic carbons).

1-Acetyl-4-(4-hydroxyphenyl)-piperazine (**7**).

This method represents a modification of the literature preparation [3b]. A mixture of **5** (5.0 g, 0.014 mole) and pyridine (3.3 g, 0.042 mole) in acetic anhydride (15 ml) was stirred at room temperature under nitrogen for 12 hours. The resulting suspension was diluted with water (25 ml) and the solution carefully neutralized by dropwise addition of 12 *N* sodium hydroxide (ice-cooling). The resultant gelatinous precipitate was extracted into chloroform (2 x 50 ml), the combined extracts dried (magnesium sulfate), and solvents evaporated, *in vacuo*, to give 1-(4-acetoxyphenyl)-4-acetylpiperazine (**6**) as a brown gum which was used without further purification; ^{1}H nmr (deuteriochloroform): δ 2.12 (s, 3H, amide CH_3), 2.25 (s, 3H, ester CH_3), 3.10 (m, 4H, ArN(CH_2)$_2$), 3.60, 3.75 (two m's for 2H, each, NCH_2's), 6.70-6.90 (m's of AA'BB; system for four aromatic H's).

A solution of **6** in methanol (30 ml) was stirred with concentrated ammonium hydroxide (5 ml) for 12 hours at room temperature. The colorless solid which had precipitated proved to be a mixture of **6** and **7** (tlc, silica gel, chloroform-ethyl acetate, 1:1). Additional concentrated ammonium hydroxide (2 ml) was added and stirring continued for 2 hours. The product **7** (930 mg, 30%) was collected and was washed with a little methanol, mp 177-178°, lit [3b] mp 181.3°. The combined methanol filtrate and washings were concentrated, *in vacuo*, and the resultant purple solid was recrystallized from ethanol to furnish a second batch of **7**, (980 mg, another 32%); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.02 (s, 3H, CH_3), 2.87, 2.94 (m's, 4H, NCH_2's), 3.54 (m, 4H, ArN(CH_2)$_2$), 6.66-6.81 (AA'BB, 4H, arom), 8.90 (s, 1H, OH).

1-Formyl-4-(4-hydroxyphenyl)piperazine (**10**).

A mixture of 1-(4-hydroxyphenyl)piperazine dihydrobromide (5.0 g, 0.014 mole), sodium carbonate (1.5 g, 0.014 mole - which appears to be necessary to neutralize hydrogen bromide) and formic acid (90%, 4.0 ml, 0.071 mole) was refluxed in toluene (150 ml) for 18 hours, with azeotropic removal of water. Solvents were removed, *in vacuo*, and the residue suspended in methylene chloride. After washing with saturated sodium bicarbonate solution, the product (2.9 g, 100%) was filtered, washed with water and dried, mp 215°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.85-2.95, 3.35-3.52 (m's, 4H, piperazine CH_2's), 6.64, 6.80 (AA'BB', 4H, Ar), 8.04 (s, 1H, CHO), 8.89 (s, 1H, OH); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 39.3, 44.8, 50.1, 51.2, 115.4, 118.7, 143.9, 151.5, 160.7 (C=O). When **10** was reacted with **1e** in the synthesis of **3e**, the latter gave an excellent microanalysis.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.35; H, 6.71; N, 13.38.

1-(4-Hydroxyphenyl)-4-(methanesulfonyl)piperazine (**9**).

To a stirred solution of **5** (5.0 g, 0.014 mole) in pyridine (30 ml) at 0-5° was added dropwise methanesulfonyl chloride (3.6 g, 0.031 mole). After 30 minutes the reaction was diluted with water (100 ml), and the precipitate was filtered and washed with water. After drying, *in vacuo*, **8** was obtained as a yellow solid (4.6 g, 97%), mp 188-190°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.94 (s, 3H, NSO_2CH_3), 3.25 (br s, 8H, piperazine CH_2's), 3.32 (s, 3H, OSO_2CH_3), 7.05-7.22 (AA'BB', 4H).

A suspension of **8** (4.6 g, 0.014 mole) was refluxed with 1N aqueous sodium hydroxide solution (30 ml) for 12 hours, after which time the bulk of the material had dissolved to provide a yellow solution. After filtration, the solution was carefully neturalized by the addition of glacial acetic acid. The pale pink solid **9** (3.0 g, quantitative) was filtered, washed with water, and dried, mp 205-206°, lit [3b] mp 204.9°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.91 (s, CH_3), 3.04 (m, SN(CH_2)$_2$), 3.22 (m, ArN(CH_2)$_2$), 6.67-6.82 (AA'BB, 4H, arom), 8.93 (s, OH); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 33.8, 45.4, 49.8, 115.4, 118.5, 143.5, 151.4.

1-(4-Hydroxyphenyl)-4-methylpiperazine Dihydrobromide (**12**).

A mixture of 1-(4-methoxyphenyl)piperazine (5.1 g, 0.027 mole), 90% formic acid (2.2 ml, 0.43 mole) and 35% formaldehyde (2.5 ml, 0.029 ml) in methanol (20 ml) was refluxed for 12 hours. After evaporation of solvents, *in vacuo*, the residue was partitioned between methylene chloride and aqueous saturated bicarbonate. The extract was dried (magnesium sulfate) and solvents evaporated to furnish **11** as a brown solid (5.2 g, 95%), mp 67-70°, which was used in the next step, without further purification; ^{1}H nmr (deuteriochloroform): δ 2.34 (s, 3H, NMe), 2.58, 3.10 (m's, 4H, piperazine H's), 3.76 (s, 3H, OMe), 6.82-6.90 (m, 4H, Ar); ^{13}C nmr (deuteriochloroform): δ 46.1, 50.5, 55.2, 55.5, 114.4, 118.1, 145.7, 153.8.

A solution of **11** (5.2 g, 0.027 mole) was refluxed in 48% hydrobromic acid (70 ml) for 6 hours. After concentration, *in vacuo*, the brown residue was recrystallized twice from ethanol to give **12** (3.0 g, 30%), as an off-white solid, mp 240-244°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.94 (s, 3H, Me), 3.35 & 3.70 (br m, 8H, pip CH2), 6.7-7.3 (m, 4H, Ar), 8.65 (br s, 2H, HN$^+$), 10.4 (br s, 1H, OH).

Anal. Calcd. for $C_{11}H_{18}Br_2N_2O$: C, 37.31; H, 5.12; N, 7.91. Found: C, 37.25; H, 5.01; N, 7.84.

Synthesis of Ketoconazole Analogs.

1-Acetyl-4-{4-[[*trans*-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (*trans*-Ketoconazole, **3a**).

A suspension of sodium hydride (60% in mineral oil, 60 mg, 1.5 mmoles) in dry dimethyl sulfoxide (15 ml) and **7** (300 mg, 1.4 mmoles) was stirred for 1 hour. After the addition of *trans*-**1a** [4] (500 mg, 1.2 mmoles) the stirred mixture was warmed to 60° for 4 hours. The black solution was diluted with water (100 ml) and extracted with methylene chloride (3 x 50 ml). The extract was dried (magnesium sulfate) and the solvent removed, *in vacuo*, providing a brown oil, which was chromatographed over silica gel (20 g) and was eluted with methylene chloride-methanol (95:5). The major component (R_f = 0.7) was collected and the solvents removed to yield *trans*-**3a** (520 mg, 80%) as a pale brown glass.

Anal. Calcd. for $C_{26}H_{28}Cl_2N_4O_4 \cdot 0.5H_2O$: C, 57.79; H, 5.40; N, 10.36. Found: C, 58.00; H, 5.16; N, 10.36.

4-{4-[*trans*-2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (*trans*-Desacetylketoconazole, **3c**).

The *trans*-formamide **3e** (250 mg, 0.48 mmoles) was refluxed in 1-butanol (15 ml) containing 85% potassium hydroxide (0.5 g, 8.9 mmoles) for 24 hours, after which time tlc indicated complete hydrolysis (R_f of starting material, 0.95, of product, 0.3, using methylene chloride-ethanol, 4:1). The solvent was removed, *in vacuo*, and the product was extracted into chloroform. The residue from this extract was chromatographed (silica gel) and was eluted by methylene chloride-ethanol (4:1) as a colorless powder (60 mg, 25%), mp 161-163°.

Anal. Calcd. for $C_{26}H_{28}Cl_2N_4O_4$: C, 58.90; H, 5.36; N, 11.45. Found: C, 58.65; H, 5.59; N, 10.99.

4-{4-[[*cis*-2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (*cis*-**3c**).

A mixture of *cis*-ketoconazole (*cis*-**3a**, 3.6 g, 6.8 mmoles) and powdered 85% potassium hydroxide (2.2 g, 33 mmoles) in 1-butanol (50 ml) was refluxed for 24 hours. After removing solvents, *in vacuo*, the residue was suspended in water and extracted with chloroform (3 x 50 ml), the extract washed with brine, dried (magnesium sulfate), and evaporated to furnish an oily solid which crystallized from ether-petroleum ether to give a pale yellow solid (2.83 g, 85%), mp 168-169°, lit [3b] mp 170.7°.

1-Methyl-4-{4-[[*cis*-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (*cis* **3d**).

A solution of **3c** (1.0 g, 2.04 mmoles), 88% formic acid (0.2 ml, 3.06 mmoles) and 35% aqueous formaldehyde (0.2 ml, 2.04 mmoles) in methanol (10 ml) was refluxed for 12 hours, after which time tlc (silica gel, methylene chloride-ethanol 9:1) indicated consumption of starting material (R_f, 0.2) and the formation of **3d** (R_f, 0.75). Solvents were evaporated, *in vacuo*, the residue washed with saturated sodium bicarbonate solution, extracted with methylene chloride (3 x 40 ml) and dried (magnesium sulfate). The product was originally isolated as gum, which crystallized from methylene chloride-petroleum ether as colorless crystals (1.05 g, 98%), mp 114-115°; ^{1}H nmr (deuteriochloroform): δ 2.34 (s, 3H), 2.55 (m, 4H), 3.11 (m, 4H), 3.30 (m, 1H), 3.72 (m, 2H), 3.86 (m, 1H), 4.40 (m, 3H), 6.70-7.60 (m, 10H).

Anal. Calcd. for $C_{25}H_{28}Cl_2N_4O_3$: C, 59.64; H, 5.60; N, 11.13. Found: C, 59.69; H, 5.67; N, 11.14.

1-Methyl-4-{4-[[*trans*-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (*trans*-**3d**).

A solution of *trans*-**3c** (40 mg, 0.08 mmoles), 90% formic acid (0.06 ml, 1.2 mmoles) and 35% formaldehyde (0.07 ml, 0.82 mmoles) in methanol (5 ml) was refluxed for 18 hours after which time the solvent was removed *in vacuo*. Work-up as for the *cis*-isomer provided a colorless solid (40 mg, 95%) of **3d**, after recrystallization from petroleum ether, mp 99-100°.

Anal. Calcd. for $C_{25}H_{28}Cl_2N_4O_3$: C, 59.64; H, 5.60; N, 11.13. Found: C, 59.54; H, 5.62; N, 11.06.

Attempts to prepare *trans*-**3d** from **1** and **12** resulted in hopeless mixtures containing just small quantities of the required product.

1-Formyl-4-{4-[[*cis*-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (*cis*-**3e**).

A mixture of *cis*-**3c** (2.5 g, 5.1 mmoles) and 88% formic acid (0.9 ml, 20 mmoles) in toluene (100 ml) was refluxed for 18 hours, with azeotropic water removal using a Dean-Stark trap. After cooling, solvents were removed, *in vacuo*, the residue was suspended in saturated aqueous sodium bicarbonate solution (100 ml), and extracted with dichloromethane (3 x 50 ml). After drying (magnesium sulfate) and removal of the solvent, *in vacuo*, the oily residue was triturated with ether to furnish a colorless solid (2.7 g, quantitiative), mp 151-152°, lit [3b] mp 153.4°; ^{1}H nmr (deuteriochloroform): δ 3.00 (m, 4H), 3.26 (m, 1H), 3.48 (m, 2H), 3.69 (m, 4H), 3.84 (m, 1H), 4.40 (m, 3H), 6.7-7.6 (m, 10H), 8.06 (s, 1H, CHO).

Anal. Calcd. for $C_{25}H_{26}Cl_2N_4O_4$: C, 58.03; H, 5.07; N, 10.83. Found: C, 57.95; H, 5.06; N, 10.71.

1-Formyl-4-{4-[[*trans*-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (*trans*-**3e**).

A mixture of sodium hydride (50%, 240 mg, 4.91 mmoles) and **10** (5.06 mg, 2.46 mmoles) in dry DMF (10 ml) was stirred for 5 minutes at room temperature, then *trans*-**1** (1.0 g, 2.46 mmoles) was added, in small portions. The reaction was stirred and warmed to 50° for 2 hours, after which the bulk of the DMF was evaporated, *in vacuo*. The residue was dissolved in methylene chloride (50 ml) and the solution washed with brine (2 x 50 ml), dried (magnesium sulfate) and evaporated to an oil. Chromatography on silica gel using methylene chloride-ethanol (9:1) as eluent, followed by evaporation of the fractions containing *trans*-**3e** (R_f 0.85) furnished a colorless solid (220 mg, 16%), mp 165-166°.

Anal. Calcd. for $C_{25}H_{26}Cl_2N_4O_4$: C, 58.03; H, 5.07; N, 10.83. Found: C, 57.82; H, 5.06; N, 10.47.

1-Methanesulfonyl-4-{4-[[*cis*-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl}piperazine (*cis*-**3b**).

Method A. To a stirred suspension of sodium hydride (60% in mineral oil, 150 mg, 3.7 mmoles) in dry dimethyl sulfoxide (20 ml) was added **9** (630 mg, 2.5 mmoles). After 1 hour, *cis*-**1** (1.0 g, 2.5 mmoles) was added, and stirring continued for 12 hours. The bulk of dimethyl sulfoxide was removed, *in vacuo*, at 70°, and the residue was diluted with water (100 ml). The resultant gummy precipitate was chromatographed on silica gel (30 g), the major fraction (R_f 0.85) being eluted by chloroform-methanol (95:5). The nmr spectrum indicated a mixture of *cis*-**1** and *cis*-**3b** (identical R_f's in this solvent system). This mixture was refluxed overnight in methanolic ammonia (5 ml concentrated ammonium hydroxide, 20 ml methanol) and worked up once more as previously to yield a colorless solid (440 mg, 31%), mp 110-111°, lit [3b] mp 113°.

Method B is an adaptation of Heeres' method [3b]. Methanesulfonyl chloride (1.2 g, 10.9 mmoles) was added dropwise (10 minutes) to a stirred, cooled (0.5°) suspension of *cis*-**3c** (3.87 g, 7.3 mmoles) in pyridine (50 ml). After 2 hours, the bulk of the pyridine was removed, *in vacuo*, and the residue was partitioned between water (200 ml) and chloroform (200 ml). The aqueous layer was extracted further with chloroform (2 x 200 ml), the combined extracts were washed with brine (150 ml), dried (magnesium sulfate), and the solvent was evaporated, *in vacuo*, to give an oil, which crystallized upon standing to a pale yellow solid, (4.5 g, 100%), mp 111-112°, lit [3b] mp 113°.

When this sulfonamide was extracted with methylene chloride

after removal of that solvent, the gum slowly crystallized and possesses the same mp and spectral parameters but analyzed with methylene chloride as solvent of crystallization (also visible in nmr spectra).

Anal. Calcd. for $C_{25}H_{28}Cl_2N_4O_5S \cdot 0.5CH_2Cl_2$: C, 50.21; H, 4.79; N, 9.18. Found: C, 50.43; H, 4.76; N, 9.18.

1-Methanesulfonyl-4-{4-[[*trans*-2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyleneoxy]phenyl} piperazine (*trans*-**3b**).

To a stirred suspension of sodium hydride (60% in mineral oil, 150 mg, 3.7 mmoles) in dry dimethylsulfoxide (20 ml) was added **9** (630 mg, 2.5 mmoles), and the mixture stirred for 1 hour after which time foaming had ceased. After the addition of *trans*-**1** (1.0 g, 2.5 mmoles), the mixture was stirred overnight at room temperature to turn into a black solution. The bulk of the dimethyl sulfoxide was removed under reduced pressure at 70°, and the residue dissolved in water (100 ml). The resultant gummy precipitate was extracted into methylene chloride (3 x 50 ml), and the combined extracts were concentrated to a brown oil which was chromatographed on silica gel (30 g) using methylene chloride-methanol 9:1 as eluent. Fractions containing *trans*-**3b** (R_f 0.8) were combined and the solvent removed to give a yellow gum. Trituration with ether gave 100 mg (7%) of a pale yellow powder, mp 112-115°.

Anal. Calcd. for $C_{25}H_{28}Cl_2N_4O_5S$: C, 52.92; H, 4.97; N, 9.87. Found: C, 52.76; H, 4.99; N, 9.62.

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[1] Support for this work through Research Contract (NO1-8-2900) from NICHHD is most gratefully acknowledged.

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