Ketalizations of Aryl ω-(2-Imidazolyl)alkyl Ketones by Glycerol and 3-Mercapto-1,2-propanediol. Synthesis and Characterization of *cis*- and *trans*-{2-Aryl-2-[ω-(2-imidazolyl)alkyl](1,3-dioxolan-4-yl and 1,3-oxathiolan-5-yl)}methanols [1]

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Aryl 2-[(2-imidazolyl)ethyl or 3-(2-imidazolyl)propyl]ketones were ketalized by glycerol *or* 3-mercapto-1,2-propanediol in boiling benzene in the presence of 4-toluenesulfonic acid to provide the title compounds. The aryl substituents are 4-chloro-, 4-bromo-, 4-fluoro-, or 2,4-dichlorophenyl. While aryl (2-imidazolyl)methyl ketones condensed with glycerol to form *cis*- and *trans*-{2-aryl-2-[(2-imidazolyl)methyl]-4-(hydroxymethyl)}-1,3-dioxolanes, related condensations with 3-mercapto-1,2-propanediol, under similar, or even more stringent reaction conditions, produced no 1,3-oxathiolane analogs, with the starting ketones being recovered. Separation and structure determination of these racemic *cis* and *trans* isomeric products are described. The structure of these stereoisomers was established by means of ^{1}H and ^{13}C nmr correlation and nOe experiments. Selective methylation of the *N*-unsubstituted 2-imidazolyl alcohols with one equivalent sodium hydride and methyl iodide provided the corresponding *N*-methyl alcohols in excellent yields. With excess benzoyl chloride, *N*-unsubstituted 2-imidazolyl alcohols were initially converted to *O,N*-dibenzoates from which the *N*-benzoyl group was easily cleaved by ammonium hydroxide in ethanol to provide benzoate esters.

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Introduction.

Ketalization of aryl ω-(*N*-imidazolyl)alkyl ketones **1** (n is 1 to 3, *Z* is 2- or 4-halo, or 2,4-dihalo) with glycerol (**2**) in boiling benzene in the presence of 4-toluenesulfonic acid (TsOH), with azeotropic removal of water, furnished a mixture of *cis*- and *trans*-1,3-dioxolanes **4** [1-4]. Cognate reactions of **1** (n is 2 or 3) with 3-mercapto-1,2-propanediol (**3**) provided *cis*- and *trans*-1,3- oxathiolanes **6** [3]. No six-membered ketals could be detected. This paper describes the reactions of *C*- analogs **13-15** with **2** and **3** under conditions found favorable for ketal formation. *cis*-Isomers in these series are those in which the two *alkyl* groups at *C*-2 and *C*-4 of **4**, or those at *C*-2 and *C*-5 of **6**, are on the *same* side of the five-membered ketal [2,3].

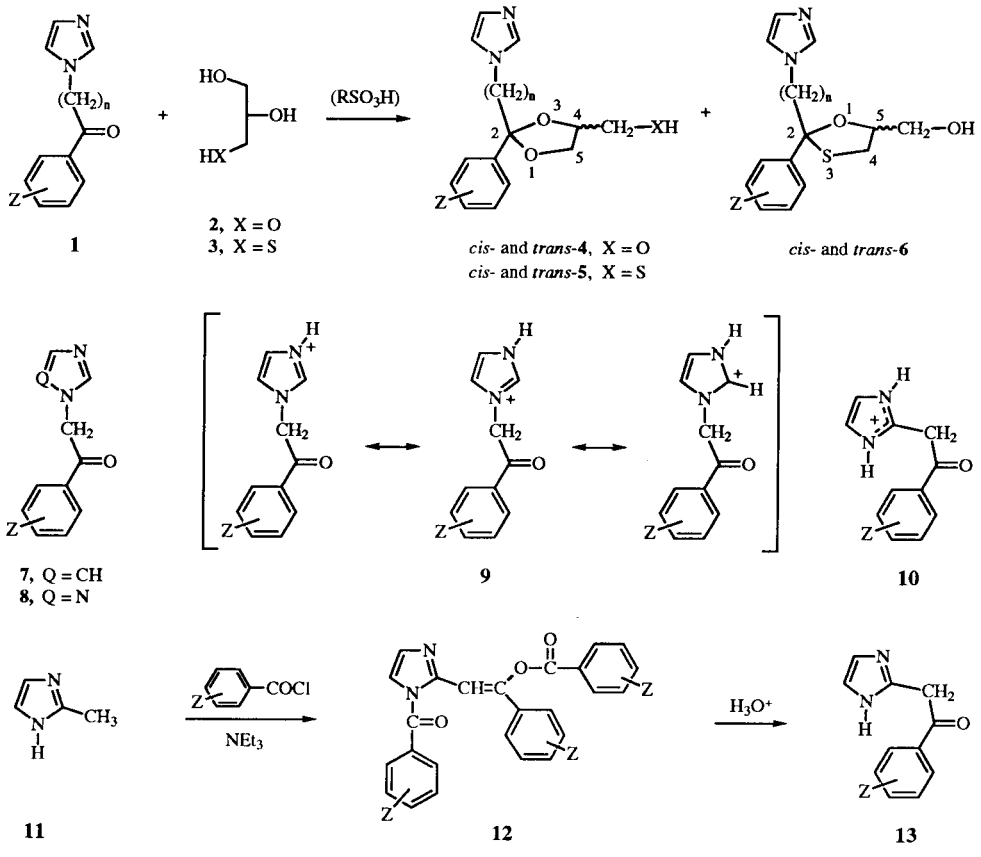
Differences in Reactivities of **7**, **8** and **13** with **2** and **3**.

We have encountered several *N*- and *C*-[(azolyl)methyl] ketones **7**, **8** and **13** which were ketalized by **2**, but not by **3**. Although these ketones reacted with **2** to produce the corresponding 1,3-dioxolanes in an 80-90% yield [1,3], cognate reactions with **3** led to the recovery of starting ketone accompanied by a gum which is insoluble in benzene, ethanol, acetone, chloroform, acetic acid, pyridine and dimethyl sulfoxide. An increase of the reaction time (24-48 hours, from a maximum of 8 hours needed for **2**), temperature (from benzene to boiling xylenes) or concentration of TsOH (up to 10 equivalents) simply speeds the rate of formation of that gum. Independently, it was observed that upon boiling **3** in benzene (or toluene) containing TsOH, a thin gum separated from the reaction mixture which was deemed to be a polymer of **3**.

A structural feature common to **7**, **8** and **13** is that only one methylene group separates the ketone from the azole. In anhydrous acidic media, imidazole in **7** and **13** is present as the resonance-stabilized imidazolium ion, as shown in **9** and **10**, where the positive charge is delocalized primarily over the two imidazole ring nitrogens and the carbon between them. Since acid-catalyzed ketalizations involve a number of oxonium and carbonium ions intermediates, development of such new cationic centers one methylene group from the azolium cation would be greatly discouraged. Thus, while glycerol withstands conditions necessary for ketalization, apparently 3-mercapto-1,2-propanediol polymerizes faster than forming a hemithioketal. As before, [3] when the distance between the ketone and the imidazolium ion was increased from one to two (or more) methylene groups, normal ketalization behavior with **3** resumes.

Synthesis of Aryl ω-(2-Imidazolyl)alkyl Ketones, **13-15**.

Aryl ω-(2-imidazolyl)alkyl ketones were needed in order to study ketalizations with **2** and **3**. The simplest members of this series, 2-phenacylimidazoles **13**, where just one methylene group separates the aromatic ketone from *C*-2 of imidazole, have been prepared by the acylation of 2-methylimidazole (**11**) with aroyl chlorides [5,6]. We applied this literature method to convert **11** to **13**. Using 4-chlorobenzoyl chloride, it was expected that the *N*-H of



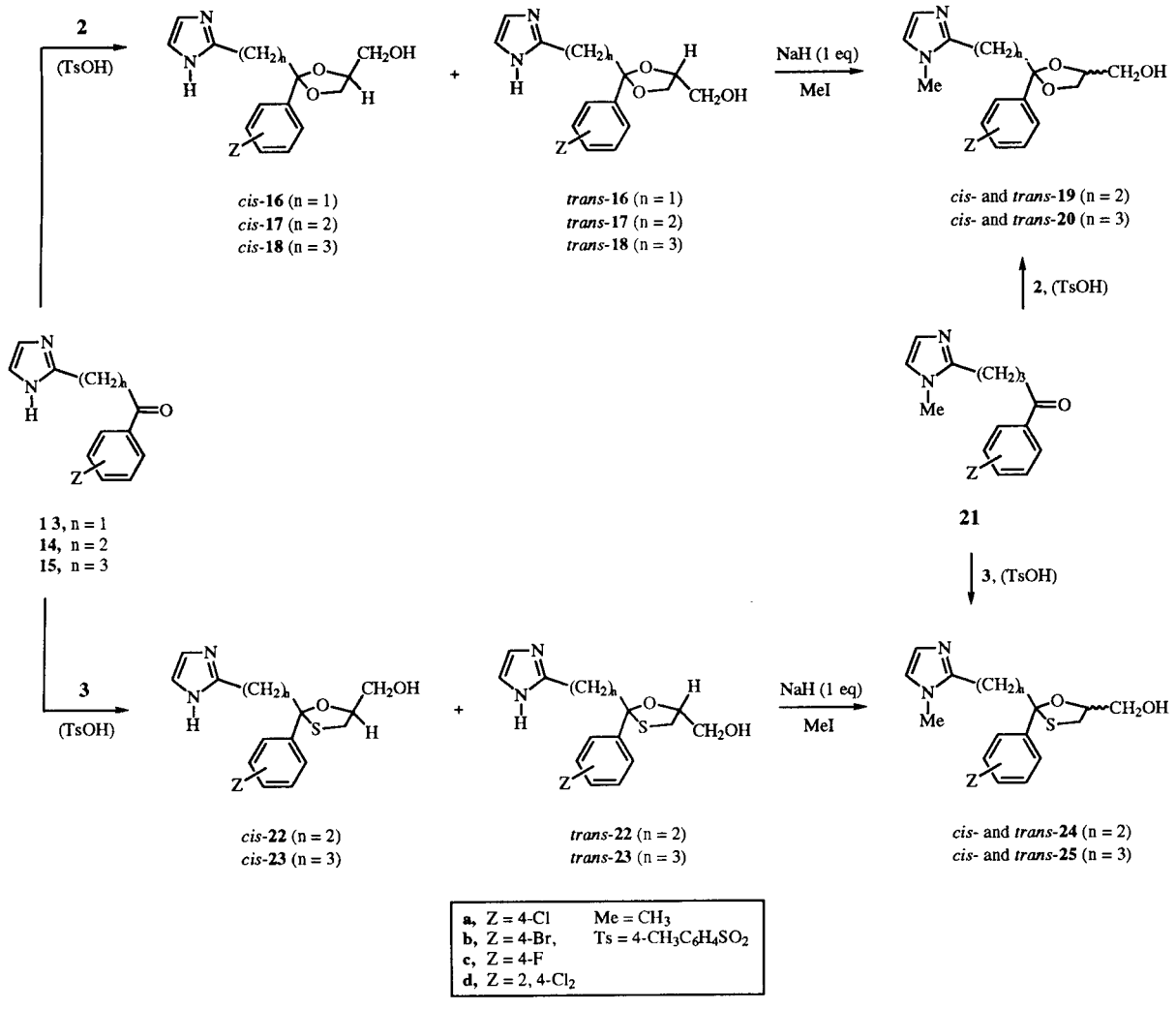
11 was acylated to form 1-(4- chlorobenzoyl)imidazole, *in situ*. The presence of the *N*-benzoyl group does not abrogate the active methylene nature of the 2-methyl group and further reaction with 4-chlorobenzoyl chloride in the presence of triethylamine furnished the *N*-benzoyl enol benzoate **12**. No attempt was made to establish the stereochemistry of **12** but acid-catalyzed hydrolysis provided **13** in excellent overall yields. The ^{1}H and ^{13}C nuclear magnetic resonance (nmr) spectra revealed that **13** exists in solution as a mixture of keto-enol isomers. Homologous ketones **14** and **15** in which two or three methylene groups separate the 2-imidazolyl moiety from the aromatic ketone have just become available recently [7,8].

Reactions of **13-15** with Glycerol (**2**) and 3-Mercapto-1,2-propanediol (**3**).

Normal ketalization of 2-imidazolyl ketones **13-15**, as well as the *N*-methyl derivatives, **21** with **2** furnished a mixture of *cis*- and *trans*-(4-hydroxymethyl)-1,3-dioxolanes **16-18, 20**. In the same vein, **14**, **15**, and **21** reacted with **3** to afford mixtures consisting of *cis*- and *trans*-(5-hydroxymethyl)-1,3-oxathiolanes **22**, **23** and **25**, apparently free from isomeric 4-(mercaptomethyl)-1,3-dioxolanes, the *C*-analogs of **5** (n = 2 or 3). Such by-products had been encountered previously, particularly when the aryl ketone possessed an *o*-substituent (*e.g.*, Z = 2-Cl, or 2,4-Cl_2), and were minimal for reactions involving just *p*-substituted aryl ketones [3].

The majority of crude products were gums, with a tendency to retain solvents, and were purified by extensive column chromatography on silica. When reasonably pure (nmr) we tried to estimate overall yields (in the vicinity of 60-90%) and ratio of isomeric *cis* and *trans* ketals. *cis*-Isomers once again predominated all of the reaction mixtures [1-3] and were usually eluted first from silica gel columns and were easiest to purify. Some times a change from silica gel to alumina columns aided the separations of *cis* and *trans* isomers.

cis And *trans* isomers were checked for purity by microanalysis and their ^{1}H and ^{13}C nmr spectra (Tables 1-3). The yields in Table 3 are strictly those of the pure *cis* and *trans* isomers, after column chromatography. The ratio of *cis* to *trans* isomers was estimated (^{1}H nmr) at the earliest possibility. One needed to search for some relatively clear sets of ^{1}H nmr signals for integration. Since the majority of their ^{1}H nmr spectra consisted virtually of a continuum of overlapping complex sets of multiplets between 1 and 4 ppm, that task became a challenge. The ratios of the methine ^{1}H nmr signals of *cis* and *trans* ketals (H-4 in 1,3-dioxolanes, H-5 in 1,3-oxathiolanes) were usually utilized to provide this information, but other signals were used also.

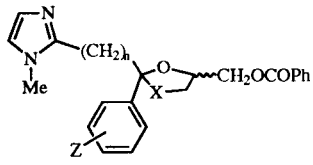


Selective *N*-Methylation of **17**, **18**, **22** and **23**.

Preferential *N*- to *O*-methylation of these imidazolyl alcohols is reported. After adding one equivalent of sodium hydride, followed by one equivalent of methyl iodide, effectively methylates **17**, **18**, **22** and **23** on the imidazole ring nitrogen to form **19**, **20**, **24** and **25**, respectively. It should be noted that a mixture of *cis* and *trans* *N*-methyl ketals is formed when the 1-methyl-2-imidazolyl ketone **21** is ketalized independently by **2** or **3**. In a few instances, it was found that a mixture of *cis* and *trans* (*N*-methyl analogs) separated more readily than (*N*-unsubstituted) imidazolyl alcohols, but the relative ease of separation, *N*-H *versus* *N*-Me compounds, is not predictable.

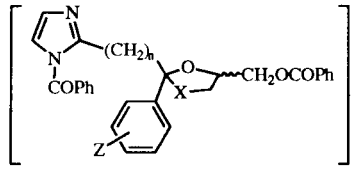
Benzoylation of Various Alcohols.

Separation of *cis* and *trans* alcohols in these series was more effective some times when the alcohols were derivatized as benzoates. If the esters are solids, fractional crystallizations could be used, other times their chromatographic behavior changes substantially to permit better separation. In either case, the esters can always be hydrolyzed back to the alcohol [2,3]. Benzoylation of *N*-methyl alcohols, like **19**, **20**, **24**, and **25** was straightforward and the corresponding *O*-benzoates **26-29** could be prepared. However, benzoylation of *N*-H analogs **16**, **17** and **18**, presented a different problem, since mixtures of *N*-, or *O*-benzoates, as well as *N,O*-dibenzoates are plausible. Fortuitously, the progress of the benzoylation of *N*-H- type of imidazolyl alcohols with benzoyl chloride in dry methylene chloride containing dry pyridine could be monitored by means of thin layer chromatograms (tlc) and ^{1}H nmr spectra. By using an excess of benzoyl chloride, both nucleophilic sites could be acylated to form *N,O*-dibenzoyl derivatives **30**. The structures were substantiated by their ^{1}H nmr spectra but, these (usually gummy) dibenzoyl derivatives were quite sensitive to wet solvents and were partially cleaved during attempted chromatographic separations. It is the *N*-benzoyl group which is partially lost resulting in mixtures of *N,O*-dibenzoyl and *O*-benzoyl derivatives. The *N*-benzoyl group of crude **30** was



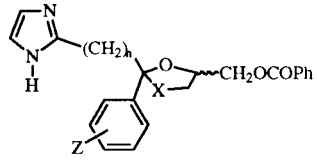
cis- and *trans*-**26** (n = 2), X = O
cis- and *trans*-**27** (n = 3), X = O
cis- and *trans*-**28** (n = 2), X = S
cis- and *trans*-**29** (n = 3), X = S

16, 17, 18, 22 and 23 —PhCOCl→



cis- and *trans*-**30**

—NH_4OH, (C_2H_5OH)→



cis- and *trans*-**31** (n = 1), X = O
cis- and *trans*-**32** (n = 2), X = O
cis- and *trans*-**33** (n = 3), X = O

a, Z = 4-Cl	Me = CH_3
b, Z = 4-Br,	Ph = C_6H_5
c, Z = 4-F	
d, Z = 2, 4-Cl_2	

cleaved efficiently and almost instantly to generate stable *O*-benzoates **31-33** in excellent yields upon treatment with ammonium hydroxide in ethanol at room temperature.

Structure Proofs of *cis*- and *trans*-1,3-Dioxolanes and 1,3-Oxathiolanes.

Extensive ^{13}C chemical shift data on closely related structures have been reported [2,3,9] but relatively sparse ^1H nmr data are available [2,3]. One of the problems complicating the analysis of the ^1H nmr spectra was that the protons of the many methylene systems were magnetically nonequivalent leading to many complex spin systems and thereby also to many overlapping signals. Although ^1H nmr spectra of these ketals were relatively complex, they nevertheless held the key to stereochemical assignments. The ^1H and ^{13}C chemical shift data are presented in Tables 1 and 2. No attempt was made to obtain coupling constants and correlate them with conformations. To establish the stereochemistry, a number of ^1H and ^{13}C chemical shift correlations, as well as nuclear Overhauser enhancement (nOe) experiments were carried out.

As an example of such an in-depth analysis and structure determination, ^1H and ^{13}C nmr spectral data of *cis*-**25b** is discussed. One of the first tasks was to settle the thorny problem of assigning unequivocally ^1H and ^{13}C chemical shifts of H-4, C-4, and H-5, C-5 of this 1,2-disubstituted imidazole. Heteronuclear correlation experiments (HETCOR) linked the following ^1H and ^{13}C signals: δ 6.75 with 120.2, and 6.89 with 126.5. Irradiation of the *N*-methyl ^1H nmr signal of *cis*-**25b** at δ 3.51 caused an 11% nOe of the signal at δ 6.75, thereby establishing that signal to be from H-5. However, irradiation of these *N*-methyl protons did not enhance the intensities of the ^1H nmr signals of the adjacent methylene protons attached at *C*-2.

Other nmr experiments were utilized to pinpoint ^1H and ^{13}C chemical shifts in *cis*-**25b** of the three sets of adjacent methylene groups, $(CH_2)_a$-$(CH_2)_c$-$(CH_2)_b$, which separate the imidazole and ketal rings. The resonances at δ 1.72 and 1.84 arise from the most shielded protons, those of the middle methylene group, $(CH_2)_c$. Selective homonuclear ^1H-^1H decoupling of the $(CH_2)_c$ proton resonances cause *only* the multiplets at δ 2.11 (two protons) and at 2.60, 2.81 (one proton, each) to simplify which identified the chemical shifts of these neighboring protons. HETCOR experiments linked the multiplets at δ 2.11 and at 2.60, 2.81 with the ^{13}C resonances at δ 43.1 and 25.9, respectively. It was perhaps somewhat unexpected that the most shielded protons are attached to the most deshielded carbon. The FLOCK program [11], which establishes long range two to three bond C-H couplings, correlates the ^1H nmr signal at δ 2.11 with the ^{13}C nmr signal of *C*-2 of the 1,3-oxathiolane at δ 98.1 [10] which then means that the ^1H signal at δ 2.11 and the ^{13}C signal at δ 43.1 are associated with $(CH_2)_b$. Thus, the ^1H and ^{13}C chemical shifts at δ 2.60, 2.81 and 25.9 arise from $(CH_2)_a$.

The relative shielded nature of the protons in $(CH_2)_b$ is understandable in terms of the anisotropic effect exerted upon them by the neighboring aromatic 4-bromophenyl group. Apparently, the carbon of that methylene group does not experience the anisotropic effect to the same degree, and is in fact quite deshielded. This is not so surprising in view of inductive effects experienced *via* the σ-network by having three electron-attracting atoms (O, S and an sp^2 aryl carbon) β to the $(CH_2)_b$ carbon. Interestingly, projected ^{13}C chemical shifts [12] for *cis*-**25b** are in good agreement with experimentally determined values (Table 1).

Since a number of related ketones and ketals were available, we examined if similar ketone-ketal chemical shift relationships operated. We found that ^1H and ^{13}C chemical shifts of ketone **21a**, (2-Im)-$(CH_2)_a$-$(CH_2)_c$-$(CH_2)_b$-C=(O)-C_6H_4-Cl(4), correlated well for groups a, c, and b, for ^1H, δ 2.78, 2.18 and 3.10, and for ^{13}C, δ 25.8, 21.8, and 37.4, respectively. Interestingly, HETCOR correlations in the related ethylene glycol ketal, (2-Im)-

Table 1

Selected Carbon-13 Chemical Shifts of 2-Im-$(CH_2)_a$-$(CH_2)_c$-$(CH_2)_b$-Ketal [a,b]

Compound	Imidazole							1,3-Dioxolane *or* 1,3-Oxathiolane					
	C-2	C-4	C-5	*N*-Me	$(CH_2)_a$	$(CH_2)_b$	$(CH_2)_c$	C-2	C-4	C-5	CH_2 at C-4	CH_2 at C-5	C=O
cis-**16a**	142.9	121.4	121.4	—	39.2	—	—	108.8	76.4	65.6	60.8	—	—
trans-**16a**	142.6	121.2	121.2	—	40.1	—	—	109.0	78.5	66.9	62.4	—	—
cis-**17a**	149.0	121.1	121.1	—	22.2	38.4	—	110.0	76.4	65.4	61.6	—	—
trans-**17a**	148.0	121.3	121.3	—	22.7	38.9	—	110.2	78.4	66.8	62.8	—	—
cis-**17d**	148.9	121.0	121.0	—	22.0	35.6	—	109.7	78.3	65.5	61.3	—	—
cis-**18a**	148.4	121.2	121.2	—	27.6	38.7	22.6	110.5	76.6	65.3	62.6	—	—
trans-**18a**	148.2	121.2	121.2	—	27.9	40.0	22.6	110.8	78.2	66.7	62.6	—	—
cis-**19a**	148.5	126.2	120.3	32.6	20.4	37.1	—	109.8	76.9	65.2	61.5	—	—
cis-**20a**	148.2	126.6	120.3	32.6	26.0	38.9	21.7	110.7	76.9	65.4	62.7	—	—
trans-**20a**	148.1	126.9	120.3	32.6	26.5	40.4	21.9	110.5	76.6	66.9	62.8	—	—
cis-**20c**	148.2	126.7	120.3	32.6	26.1	39.1	21.7	110.8	76.8	65.5	62.7	—	—
cis-**22a**	148.4	121.2	121.2	—	24.2	42.2	—	97.9	34.5	83.5	—	62.1	—
trans-**22a**	147.5	121.4	121.4	—	24.3	41.9	—	96.3	34.9	84.1	—	63.9	—
cis-**23a**	148.2	121.1	121.1	—	27.6	42.8	24.2	98.3	34.5	83.6	—	63.5	—
trans-**23a**	148.2	121.1	121.1	—	27.3	41.9	24.6	97.0	35.1	84.2	—	63.5	—
cis-**24a**	148.1	126.6	120.3	32.6	22.4	41.3	—	97.8	34.4	84.2	—	62.3	—
cis-**25a**	147.8	126.6	120.4	32.6	26.0	43.3	23.0	98.1	34.6	84.1	—	62.8	—
trans-**25a**	147.8	126.6	120.5	32.6	26.0	42.4	23.4	96.9	35.2	84.0	—	63.7	—
cis-**25b**	147.7	126.5	120.2	32.5	25.9	43.1	22.9	98.0	34.6	83.9	—	62.6	—
cis-**25b**[c]	136.2	122.3	122.3	32.9	27.4	42.8	22.9	97.8	34.1	85.0	—	62.7	—
cis-**26a**	147.5	127.2	120.4	32.3	20.6	37.8	—	110.4	73.5	66.4	64.7	—	166.3
cis-**27a**	147.9	126.9	120.3	32.5	26.6	39.9	21.7	110.9	73.4	66.3	64.7	—	166.2
trans-**27a**	148.0	127.0	120.3	32.6	26.6	40.7	21.7	110.0	75.3	66.6	63.7	—	166.2
cis-**28a**	147.4	126.8	120.4	32.4	22.2	41.5	—	97.9	35.7	80.0	—	64.5	166.1
cis-**29a**	147.8	127.0	120.4	32.5	26.6	43.9	23.4	98.6	35.6	79.9	—	64.7	166.1
cis-**31a**	142.0	121.6	121.6	—	39.6	—	—	109.3	73.8	66.2	64.3	—	166.2
cis-**32a**	147.9	121.0	121.0	—	22.5	38.3	—	110.7	73.6	66.2	64.7	—	166.0
cis-**33a**	148.1	121.3	121.3	—	28.2	39.6	22.4	111.1	73.5	66.2	64.8	—	166.5

[a] Spectra determined in deuteriochloroform and shifts are reported in ppm (δ) downfield from TMS. [b] Im is 2- imidazolyl and the ketal is either a 1,3-dioxolane or a 1,3-oxathiolane. [c] Values projected by A. Fürst and E. Pretch, Ref 12.

$(CH_2)_a$-$(CH_2)_c$-$(CH_2)_b$-$C(OCH_2)_2$-C_6H_4-Br(4), revealed shifts for ^1H, δ 2.63, 1.80 and 1.95 [8], and for ^{13}C, δ 26.7, 21.8 and 39.8, respectively. Once more, unlike the ketone, the protons of the $(CH_2)_b$ group are quite shielded, while the carbon is very deshielded.

Identification of the methine and methylene proton chemical shifts associated with the 1,3-oxathiolane system of *cis*-**25b** was arrived at as follows. Prior studies in related systems established that the methine ^1H nmr resonance (H-4 of 1,3-dioxolanes, H-5 of 1,3-oxathiolanes) usually appears as a narrow multiplet between δ 4.0 and 4.5 [3]. In general, two sets of multiplets, around δ 3.0 and 3.8 are associated with the protons of the ring CH_2-S and CH_2-O, respectively. Selective homonuclear ^1H-^1H decoupling experiments by irradiating the methine (H-5) at δ 4.13 in *cis*-**25b** causes the sets of multiplets at δ 3.95, 3.74, and 3.17, 2.94 (one proton, each) to simplify drastically, thereby establishing the chemical shifts of the methylene protons surrounding H-5. Carbon chemical shift assignments of corresponding carbons follow those published earlier [3,9]. Complete assignments are in Tables 1 and 2.

Definitive nOe experiments settled the stereochemistry of *cis*-**25b**. The ^{13}C chemical shifts of the 4-bromophenyl group are at δ 127.0 and 131.4 are assigned to C-2(6) and C-3(5), in agreement with literature values [9]. HETCOR experiments revealed that these two ^{13}C chemical shifts correlated with ^1H chemical shifts for H-2(6) and H-3(5) at δ 7.28 and 7.43, respectively. Irradiation of the protons associated with the δ 7.28 signal produced a definite nOe of the signal attributed to H-5 of the 1,3-oxathiolane (6%). In establishing that this methine proton (H-5 of the 1,3-oxathiolane ring) is on the same side as the 4-bromophenyl substituent completes the proof of the stereochemistry of *cis*-**25b**.

Having established the stereochemistry of *cis*-**25b**, we wanted to ensure that similar methodology would apply in establishing the *cis*-configuration in corresponding 1,3-dioxolanes. A full analysis was applied to prove the structure of **19a**, in which the 1-methyl-2-imidazolyl ring is separated from the ketal by two methylene groups, $(CH_2)_a$-$(CH_2)_b$. One of the salient points in the structure assignments was that nOe's upon irradiation the protons of the *N*-Me group enhanced the intensity of the δ 6.76 signal by 7.8%, thus establishing the chemical shift of H-5 of

Table 2
Selected Proton Chemical Shifts of 2-Im-$(CH_2)_a$-$(CH_2)_c$-$(CH_2)_b$-Ketal [a,b]

Compound	Imidazole H-4 [c]	Imidazole H-5 [c]	Imidazole *N*-Me	$(CH_2)_a$	$(CH_2)_b$	$(CH_2)_c$	1,3-Dioxolane *or* 1,3-Oxathiolane Ring CH *or* CH_2 at H-4	Ring CH *or* CH_2 at H-5	CH_2-OR at C-4	CH_2-OR at C-5	NH, OH [d]
cis-**16a**	6.97	6.97	—	3.34	—	—	4.12	3.79, 3.92	3.41, 3.89	—	8.09
trans-**16a**	6.95	6.95	—	3.35	—	—	4.23	3.65, 4.13	3.47, 3.60	—	6.25[e]
cis-**17a**	6.88	6.88	—	2.80, 3.02	2.17	—	4.01	3.73, 4.01	3.58, 3.80	—	—
trans-**17a**	6.92	6.92	—	2.82	2.28	—	4.38	3.61, 4.21	3.59, 3.61	—	5.95
cis-**17d**	6.83	6.83	—	2.90	2.39	—	4.02	3.71, 3.95	3.62, 3.85	—	8.65
cis-**18a**	6.89	6.89	—	2.71, 2.90	1.85	1.75	4.12	3.59-3.86	3.59-3.86	—	6.69
trans-**18a**	6.91	6.91	—	2.71	1.86	1.75	4.29	3.51, 4.12	3.46, 3.51	—	3.25
cis-**19a**	6.88	6.76	3.51	2.68, 3.14	2.10, 2.26	—	4.00	3.74, 4.13	3.53, 3.87	—	—
cis-**20a**	6.90	6.76	3.54	2.64, 2.98	1.95	1.78	4.14	3.71, 3.90	3.62, 3.81	—	5.20
cis-**20c**	6.90	6.76	3.54	2.63, 2.80	1.97	1.78	4.15	3.72, 3.88	3.63, 3.88	—	—
cis-**22a**	6.90	6.90	—	2.88	2.39	—	2.97, 3.30	4.24	—	3.70, 3.98	5.10
trans-**22a**	6.91	6.91	—	2.69	2.56	—	2.68, 2.93	4.52	—	3.14, 3.82	—
cis-**23a**	6.85	6.85	—	2.72	2.00	1.73	2.90, 3.06	4.23	—	3.73, 3.92	7.66
cis-**24a**	6.91	6.75	3.48	2.78, 2.98	2.37, 2.51	—	3.00, 3.44	4.28	—	3.77, 4.00	—
cis-**25a**	6.88	6.75	3.50	2.60, 2.71	2.10	1.74, 1.86	2.95, 3.14	4.28	—	3.75, 3.93	4.58
trans-**25a**	6.86	6.74	3.74	2.60, 2.71	2.18, 2.25	1.55, 1.72	2.89, 3.10	4.56	—	3.80	4.34
cis-**25b**	6.89	6.75	3.51	2.60, 2.81	2.11	1.72, 1.84	2.94, 3.17	4.13	—	3.74, 3.95	4.65
trans-**25b**	6.83	6.71	3.42	2.56, 2.70	2.18	1.51, 1.63	2.82, 3.04	4.52	—	3.77	—
cis-**26a**	6.87	6.73	3.40	2.77	2.38	2.38	4.35	3.89, 4.00	4.47	—	—
cis-**27a**	6.86	6.71	3.46	2.61	1.98	1.83	4.30	3.84, 3.93	4.43	—	—
trans-**27a**	6.89	6.75	3.52	2.63	1.95	1.83	4.54	3.68, 4.21	4.24, 4.35	—	—
cis-**27c**	6.89	6.72	3.48	2.63	1.98	1.82	4.29	3.85, 3.92	4.44	—	—
cis-**28a**	6.87	6.74	3.44	2.67, 2.91	2.53	—	3.14	4.47	—	4.57	—
cis-**29a**	6.87	6.72	3.45	2.61	2.15	1.79, 1.91	3.07	4.38	—	4.54	—
cis-**31a**	6.93	6.93	—	3.30	—	—	4.13	3.79	4.27	—	9.51
cis-**32a**	6.90	6.90	—	2.89	2.31	—	4.38	3.92, 3.98	4.49	—	9.15
cis-**33a**	6.88	6.88	—	2.70	1.90	1.81	4.31	3.82, 3.91	4.46	—	—

[a] Spectra determined in deuteriochloroform and shifts are reported in ppm (δ) downfield from TMS. [b] Im is 2-imidazolyl and the ketal is either a 1,3-dioxolane or 1,3-oxathiolane. [c] When observable, $J_{4,5}$ = 1.2 Hz (generally). [d] In deuteriochloroform, individual ^1H nmr signals for imidazole NH or alcoholic OH protons are rarely observed. [e] In deuteriochloroform, freed of acids by storing 24 hours over anhydrous potassium carbonate, a dilute solution showed two signals at δ 2.00 and 9.44.

Table 3
Experimental Data for Compounds **16-33**

Compound	Method	Ratio of *cis* & *trans* [a]	Yield (%) [b]	Elution solvent from column [c]	Mp, °C [d]	Formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
cis-**16a**	A	5:1	55	ethyl acetate-methanol (49:1)	185-188	$C_{14}H_{15}ClN_2O_3 \cdot 1.25H_2O$	53.00 52.89	5.56 5.11	8.83 8.48
trans-**16a**	A	—	11	ethyl acetate-methanol (49:1)	150-151	$C_{14}H_{15}ClN_2O_3 \cdot 0.2H_2O$	56.36 56.43	5.20 4.97	9.39 9.24
cis-**17a**	A	9:1	78	dichloromethane-methanol (9:1)	gum	$C_{15}H_{17}ClN_2O_3 \cdot 0.25H_2O$	57.51 57.68	5.63 5.89	8.94 8.62
trans-**17a**	A	—	1	dichloromethane-methanol (9:1)	gum	$C_{15}H_{17}ClN_2O_3 \cdot 0.5H_2O$	57.00 56.96	5.71 5.51	8.82 8.84
cis-**17d**	A	—	43	ethyl acetate-methanol (24:1), neutral alumina	gum	$C_{15}H_{16}Cl_2N_2O_3 \cdot 0.5CH_2Cl_2$	48.27 48.42	4.44 4.50	7.26 7.12
cis-**18a**	A	4:1	58	dichloromethane-methanol (7:1)	gum	$C_{16}H_{19}ClN_2O_3 \cdot 0.3H_2O$	58.56 58.47	6.02 6.12	8.54 8.42
cis- & *trans*-**18a**	A	—	84	dichloromethane-methanol (7:1)	gum	$C_{16}H_{19}ClN_2O_3$	59.54 59.57	5.93 6.02	8.68 8.55
cis-**19a**	B	—	95	dichloromethane-methanol (9:1)	gum	$C_{16}H_{19}ClN_2O_3$	59.54 59.38	5.93 5.88	8.68 8.54
cis- & *trans*-**20a**	A	2.8:1	86	ethyl acetate-methanol (8:1)	gum	$C_{17}H_{21}ClN_2O_3 \cdot 0.2H_2O$	59.98 59.95	6.34 6.40	8.23 8.17

Table 3 (continued)

Compound	Method	Ratio of *cis* & *trans* [a]	Yield (%) [b]	Elution solvent from column [c]	Mp, °C [d]	Formula	Microanalyses (%) C Calcd Found	H Calcd Found	N Calcd Found
cis -**20a**	B	—	94	dichloromethane-methanol (9:1)	97-97.5	$C_{17}H_{21}ClN_2O_3 \cdot 0.5H_2O$	59.04 59.15	6.41 6.52	8.10 7.98
cis-**20c**	A	2:1	30	dichloromethane-methanol (9:1)	102-103	$C_{17}H_{21}FN_2O_3$	63.73 63.68	6.61 6.57	8.75 8.66
cis- & *trans*-**22a**	A	11:1	59 [e]	dichloromethane-methanol (9:1)	gum	$C_{15}H_{17}ClN_2O_2S$	55.47 55.45	5.28 5.40	8.62 8.32
cis- & *trans*-**23a**	A	3:1	44 [e]	dichloromethane-methanol (8:1)	gum	$C_{16}H_{19}ClN_2O_2S$	56.71 56.47	5.65 5.76	8.27 7.90
cis-**24a**	B	—	73	ethyl acetate-methanol (8:1)	gum	$C_{16}H_{19}ClN_2O_2S$	56.71 56.80	5.65 5.66	8.27 8.13
cis-**25a**	B	—	88	ethyl acetate-methanol (8:1)	gum	$C_{17}H_{21}ClN_2O_2S \cdot 0.5H_2O$	56.42 56.40	6.13 5.91	7.74 7.61
	B-1		38						
trans-**25a**	B-1	—	30	ethyl acetate-methanol (8:1)	gum	$C_{17}H_{21}ClN_2O_2S \cdot 0.4H_2O$	56.70 56.85	6.10 6.16	7.78 7.62
cis-**25b**	A	2:1	32	chloroform-methanol (32:1)	gum	$C_{17}H_{21}BrN_2O_2S \cdot 0.5CHCl_3$	45.99 45.73	4.74 4.84	6.13 5.88
cis-**26a**	A	—	84	ethyl acetate-methanol (9:1)	gum	$C_{23}H_{23}ClN_2O_4$	64.71 64.72	5.43 5.41	6.56 6.44
cis-**27a**	C	—	88	ethyl acetate-methanol (9:1)	88-89	$C_{24}H_{25}ClN_2O_4$	65.38 65.48	5.72 5.80	6.35 6.25
	C-1		53						
trans-**27a**	C-1	—	10	ethyl acetate-methanol (10:1)	gum	$C_{24}H_{25}ClN_2O_4 \cdot 0.4H_2O$	64.33 64.25	5.80 5.70	6.25 6.27
cis-**27c**	C	—	50	dichloromethane-methanol (9:1)	81-82	$C_{24}H_{25}FN_2O_4$	67.91 67.79	5.94 5.90	6.60 6.77
cis-**28a**	C	—	83	ethyl acetate-methanol (9:1)	gum	$C_{23}H_{23}ClN_2O_3S$	62.37 62.42	5.23 5.21	6.32 5.99
cis-**29a**	C	—	90	ethyl acetate-methanol (9:1)	91-92	$C_{24}H_{25}ClN_2O_3S$	63.08 63.04	5.51 5.59	6.13 6.04
cis-**31a**	D	—	90	ethyl acetate	100-102	$C_{21}H_{19}ClN_2O_4 \cdot 0.25H_2O$	62.57 62.73	4.87 4.82	6.94 6.86
cis-**32a**	D	—	70	ethyl acetate	142-143	$C_{22}H_{21}ClN_2O_4$	64.00 64.11	5.13 5.20	6.78 6.68
cis-**33a**	D	—	73	ethyl acetate	gum	$C_{23}H_{23}ClN_2O_4$	64.71 64.44	5.43 5.44	6.56 6.39

[a] The ratio of *cis* and *trans* isomers is the one estimated (^1H nmr) in the product, prior to chromatography. [b] Yields of isolated pure product, after chromatography. [c] The ratios of mixed solvents can vary somewhat. Elution is begun with a minimum percentage of the more polar solvent; the percentage of polar solvent is increased, as seen fit. [d] Certain gums solidified after column chromatography and the solids were isolated after trituration with ethyl acetate-petroleum ether, usually, about 1:4 or 1:5, or with a 1:1 mixture of dichloromethane-petroleum ether. [e] Yields are those of the pure *cis*-isomer, after column chromatography.

the imidazole. The nOe upon irradiating the protons at δ 7.28 [H-2(6) of 4-chlorophenyl group] increased the intensity of the proton resonance of H-4 (of the ketal) at δ 4.00 by 2.5%. During this nOe experiment, the relative intensity of the magnetically nonequivalent proton resonances at δ 2.10 and 2.26 were enhanced by 2.4 and 2.5%, respectively. By HETCOR experiments, the two ^1H chemical shifts were linked to the ^{13}C resonance at δ 37.1, thus establishing these nmr parameters for $(CH_2)_b$. Other pertinent data for these *cis*- and *trans*-1,3-dioxolanes and 1,3-oxathiolanes, **16**, **17**, **18**, **20**, **22**, **23** and **24** are compiled in Tables 1 and 2.

Finally, to complete these assignments, the ^{13}C chemical shifts of several closely related methylene groups are discussed. These are the methylene groups which are a part of the side chain hydroxymethyl (CH_2-**OH**), that of the corresponding ester, benzoyloxymethyl (CH_2-**O-COC$_6$H$_5$**), and that of the ketal ring (Table 1). These relatively close chemical shifts are in the vicinity of δ 64-66 and the assignment are based on two sets of data: literature values from related systems [2,3,9] and comparisons between the hydroxymethyl and (benzoyloxy)methyl ^{13}C chemical shifts in the 1,3-oxathiolane system.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform on a

Varian XL-300 spectrometer, at 300 and 75.4 MHZ, respectively. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane. No attempt was made to obtain coupling constants from these complex ^1H-^1H spin systems. Centers of complex multiplets are reported as their chemical shifts. Benzenoid ^1H and ^{13}C chemical shifts are not reported. The majority of the chemical shifts are listed in Tables 1 and 2.

All research chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI. Dichloromethane and pyridine were dried by storage over 4Å molecular sieves. Petroleum ether refers to that fraction bp 30-60°. Thin layer chromatograms (tlc) were developed on Aldrich silica gel coated polyester, or aluminum, or glass plates, containing a 254 nm fluorescent indicator. Spots were detected by uv light and/or exposure to iodine vapor. Whenever tlc indicated sufficient separation between spots, flash chromatography was used. Unless mentioned otherwise, column or flash chromatography was carried out using Aldrich grade 60 Å silica gel (70-230 or 200-400 mesh), the latter usually giving better separations. Occasionally, some column chromatographic separations were more successful on neutral or basic alumina (Brockman I, 150 mesh). Most of the data are in Table 3.

General Work-up Procedures.

Since most of the compounds described below are ketals, precautions were taken to prevent undue hydrolyses. While stable in anhydrous acidic media, it is suggested that reaction mixtures are quenched by always pouring *into* ice-cold 1 *M* aqueous sodium carbonate solution, *p*H of 8, or higher. The "usual" workup procedure consisted of extracting the organic product into dichloromethane or ethyl acetate. The organic extract was washed once or twice with brine, dried (sodium sulfate) and solvents removed, *in vacuo*. Evaporation, or distillation of solvents, *in vacuo*, implies their removal by means of a rotary flash evaporator at the water pump (20-30 Torr) between 30-40°. Since many of the products were gums, they were dried at 1 Torr prior to microanalysis. Elemental analyses were obtained by Midwest Microlab, Indianapolis, IN. The results are incorporated in Table 3.

1-(4-Chlorophenyl)-2-(2-imidazolyl)-1-ethanone (**13a**).

To a cold solution (0 to -10°) of 2-methylimidazole **11** (12.0 g, 0.15 mole) and triethylamine (50.5 g, 0.5 mole) in acetonitrile (500 ml) was added 4-chlorobenzoyl chloride (63.5 ml, 0.50 mole), dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hours. Water (1500 ml) and ether (500 ml) were added and the product which precipitated was filtered and dried. Crystallization from ethanol afforded **12a** (65.0 g, 89%), mp 150°, which was used immediately in the next step; ^1H nmr: δ 6.91 (d, H-5, J = 1.5 Hz), 7.04 (d, H-4, J = 1.5 Hz), 7.32-8.19 (m, olefinic and Ar*H*); ms: (determined on a MAT 90 spectrometer), CI (methane) m/z (relative intensity) 501 (32), 500 (26), 499 (100, M+1), 498 (48), 497 (97), 496 (11), 361 (16), 359 (19), 157 (10), 139 (29).

The enol ester **12a** (5.0 g, 0.01 mole) was refluxed in a mixture of acetic acid (50 ml) and concentrated hydrochloric acid (25 ml) for 1 hour. After cooling to room temperature, 4-chlorobenzoic acid was filtered, mp 239-240°, (mp 241°, authentic sample). The filtrate was evaporated, *in vacuo*, and the residue was triturated with saturated aqueous sodium bicarbonate (50-100 ml) to liberate **13a**, which was filtered, washed with water and dried. It weighed 1.60 g (73%), mp 138-140°; R_f = 0.90 (alumina, ethyl acetate-methanol, 24:1); ^1H nmr: in deuteriochloroform only the ketone was observed, δ 4.51 (s, CH_2), 7.03 [s, Im H-4(5)], 7.43-7.98 (m, AA'BB', Ar*H*); in deuteriodimethyl sulfoxide, where the ketone and enol are present (2:1); δ 4.41 (s, ketone CH_2), 6.10 (s, enolic CH=), 6.93 (enolic imidazole H's), 7.05 (s, ketonic imidazole H's), 7.43-8.04 (m, Ar*H*).

Anal. Calcd. for $C_{11}H_9ClN_2O{\cdot}0.5H_2O$: C, 57.53; H, 4.38; N, 12.19. Found: C, 57.76; H, 3.97; N, 11.77.

General Method A: Ketalization of **13**, **14**, **15**, and **21** by Glycerol (**2**) *or* 3-Mercapto-1,2- propanediol (**3**).

A stirred mixture of the ketone (10 mmoles), glycerol (40 mmoles), *or* 3-mercapto-1,2- propanediol (20 mmoles) and 4-toluenesulfonic acid monohydrate (15 mmoles) was refluxed in benzene (150 ml) interposing a Dean-Stark adaptor for the azeotropic removal of water. Since the amount of water is relatively small, it was hard to judge the endpoint of the reaction. For most of these condensations, the reaction mixture consisted of two phases, the lower one being the more polar one, containing a mixture of imidazolium salts and glycerol. Reaction times varied a great deal, ranging typically between 3-5 hours, but can be reduced or extended depending if tlc and/or nmr data suggest incomplete reactions.

Reactions were monitored by tlc. Stirring of the reaction mixture was temporarily stopped at suitable intervals, a small sample was withdrawn from the polar (lower) benzene-insoluble layer and distributed between dichloromethane and aqueous sodium carbonate. A sample taken from the dichloromethane layer was analyzed by tlc. Solvent systems which provided fairly good separations are dichloromethane:methanol (8:1). The progress of the reaction can be judged by the disappearance of the ketone which is highly fluorescent (uv). If critical, a larger sample can be withdrawn and the mixture analyzed by its ^1H nmr spectrum. Usually, there are sufficient differences between starting ketone and product to judge the progress of the reaction. When most of the ketone has reacted, the reaction is quenched by pouring *into* aqueous sodium carbonate (1 *M*, 150 ml) and is worked up as "usual", as described above. Attempts were made to estimate the ratio of *cis* to *trans* isomers from the ^1H nmr spectra of products prior to extensive chromatography.

To separate *cis* and *trans*-isomers usually required one or two chromatographic columns, primarily on silica gel. Depending upon the degree of separation on tlc plates, the ratio of silica gel to crude product varied between 25 and 50 (or even more) to 1. For the *N*-H type of compounds, dichloromethane containing small quantities of methanol proved to be quite satisfactory. For the *N*-methyl series, ethyl acetate with very small quantities of methanol are a good start (Table 3). Usually, pure *cis*-isomers are eluted first, followed by a mixture of *cis* and *trans* isomers, and then some times, by pure *trans*-isomers. Unless both isomers are isolated pure, a mixture of pure *cis*- and *trans*- isomers was submitted for microanalysis.

General Method B: *N*-Methylation of **17**, **18**, **22**, and **23**.

To a stirred solution of the *N*-unsubstituted imidazolyl alcohol (10.0 mmoles) in dry tetrahydrofuran (140 ml) at room temperature was added sodium hydride (60% suspension in mineral oil, 420 mg, 10.5 mmoles). After 10-15 minutes, methyl iodide (0.68 ml, 1.56 g, 11 mmoles) was added and the mixture stirred at room temperature for 1 hour. Solvents were evaporated, *in vacuo*. The product was dissolved in dichloromethane (500 ml) and washed with water (100 ml), then with brine (2 x 100 ml).

The solvent was evaporated, *in vacuo,* and the residue purified by means of column chromatography.

Method B-1: *N*-Methylation and Separation of a Mixture of *cis*- and *trans*-Isomers. *cis*- and *trans*-{2-(4-Chlorophenyl)-2-[3-(1-methyl-2-imidazolyl)propyl]-5-hydroxymethyl}-1,3-oxathiolane (**25a**).

Sodium hydride (60% suspension in mineral oil, 0.084 g, 2.1 mmoles) was added to a stirred solution of *cis*- and *trans*-**23a** (1:1, 0.678 g, 2.0 mmoles) in dry tetrahydrofuran (25 ml). After 5 minutes, there was added methyl iodide (0.14 ml, 2.2 mmoles). After stirring at room temperature for 1 hour, solvents were evaporated, *in vacuo*. The residue was diluted with water (25 ml) and extracted with dichloromethane (120 ml). After the usual workup, the gum was chromatographed on silica gel (80 g). Elution with ethyl acetate-methanol (8:1) furnished, first *cis*-**25a** (0.268 g, 38%), as a colorless gum, then a gummy mixture of *cis*- and *trans*-**25a** (0.094 g, 13%), and finally, pure *trans*-**25a** (0.211 g, 30%) as a gum. Other data are in Table 3.

General Method C: Benzoylation of *N*-Methyl Imidazolyl Alcohols, **19**, **20**, **24**, and **25**.

To a stirred cold (0 to 5°) solution of the alcohol (10.0 mmoles) in dry dichloromethane (150 ml) containing dry pyridine (4.0 ml, 50 mmoles) was added benzoyl chloride (2.32 ml, 2.81 g, 20 mmoles). The reaction was monitored by tlc for the disappearance of the starting alcohol. Usually, after stirring for 1 hour, the mixture was deemed complete and was added to an ice-cold aqueous saturated solution of sodium bicarbonate (200 ml). The product was extracted into ethyl acetate (2 x 250 ml) and worked up, as usual, and then chromatographed.

Method C-1: Benzoylation and Separation of a Mixture of *cis*- and *trans*-Isomers. *cis*- and *trans*-{2-(4-Chlorophenyl)-2-[3-(1-methyl-2-imidazolyl)propyl]-4-benzoyloxy}-1,3-dioxolane (**27a**).

To a stirred cold solution (0 to 5°) of *cis*- and *trans*-**20a** (2.8:1, 1.68 g, 5.0 mmoles) in dry dichloromethane (60 ml) containing dry pyridine (4.0 ml, 50 mmoles) was added benzoyl chloride (1.16 ml, 10.0 mmoles), dropwise. After stirring for 1 hour at 0-5°, the reaction was judged to be complete (tlc) and the mixture was added to a saturated solution of sodium bicarbonate (150 ml) and the product extracted into ethyl acetate (2 x 150 ml). After the usual workup, there was obtained an oil which was chromatographed on silica gel (170 g). Elution with ethyl acetate-methanol (10:1) furnished *cis*-**27a** (1.12 g), followed by a mixture of *cis*- and *trans*-**27a**, (1:3, 0.698 g). The latter fraction was rechromatographed (silica gel, 90 g) to provide additional *cis*-**27a** (0.048 g) and pure *trans*-**27a** (0.208 g). This represents a 53% yield of *cis*-**27a**, which solidified as a colorless solid, mp 88-89°; tlc, R_f = 0.62 (ethyl acetate-methanol, 10:1). The *trans*-isomer of **27a** (10%) is a colorless gum, tlc, R_f = 0.60 (same solvent system). Other data are in Table 3.

General Method D: Monobenzoylation of *N*-Unsubstituted Imidazolyl Alcohols, **16**, **17**, and **18**.

To a stirred cold solution (0 to 5°) of the alcohol (10 mmoles) in dry dichloromethane (150 ml) containing dry pyridine (5.6 ml, 70 mmoles) was added benzoyl chloride (3.5 ml, 30 mmoles) dropwise. The reaction was stirred at room temperature for 2-3 hours, subject to the disappearance of the starting alcohol (tlc). The product appears to be primarily the dibenzoyl derivative, admixed with some *O*- benzoylated product (tlc, ^{1}H nmr). The mixture was poured into ice-cold sodium bicarbonate solution (200 ml). Extraction with dichloromethane (2 x 250 ml) and evaporation of the solvent, *in vacuo*, produced an oil which was analyzed by its ^{1}H nmr spectrum. Due to the inherent instability of the *N*-benzoyl part of the molecule, particularly in aqueous or alcohol media, the following procedure was followed to obtain good yields of stable products.

The crude mixture was dissolved in ethanol (100 ml) containing aqueous ammonium hydroxide solution (30%, 10 ml) and this mixture was stirred at room temperature for 10 min (judged to be complete when tlc indicated the absence of the dibenzoyl derivative). Solvents were evaporated, *in vacuo*, at 40°. The residue was added to saturated aqueous sodium bicarbonate solution (200 ml), extracted with dichloromethane (2 x 250 ml) and worked up as usual, followed by chromatography in order to obtain the pure product.

Hydrolysis of a Benzoate. *cis*-{2-(4-Chlorophenyl)-2-[3-(1-methyl-2-imidazolyl)propyl-4-(hydroxymethyl)}-1,3-dioxolane (**20a**).

A mixture of *cis*-**27a** (441 mg, 1.0 mmole), sodium carbonate (212 mg, 2.0 mmoles), water (1 ml) and methanol (20 ml) was refluxed for 1 hour. Tlc showed that the starting material disappeared completely. Solvents were removed, *in vacuo*. Workup (ethyl acetate) gave an oil (346 mg) which was chromatographed on silica gel (20 g). Elution by ethyl acetate-methanol (8:1) provided *cis*-**20a** (306 mg, 91%), as a colorless gum, which solidified to a colorless solid, mp 97-97.5°, identical to the product from Method B (*cis*-**18a** → *cis*-**20a**).

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