Synthesis, ^{1}H- and ^{13}C-NMR Spectra, Crystal Structure and Ring Openings of 1-Methyl-6,9-epoxy-9-aryl-5,6,9,10-tetrahydro-1*H*-imidazo[3,2-*e*][2*H*-1,5]oxazocinium Methanesulfonate [1]

Subhash P. Upadhyaya, Frank S. Davis, Jae Jeong Lee, Kyaw Zaw and Ludwig Bauer*

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

Norman E. Heimer

Department of Chemistry, US Air Force Academy, USAFA CO 80840-1134

Received December 5, 1996

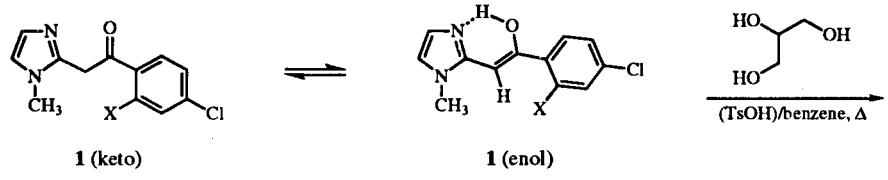
The methanesulfonic acid catalyzed reaction of 1-(4-chloro- and 2,4-dichlorophenyl)-2-(1-methyl-2-imidazolyl)ethanones **1a** and **1b** with glycerol produced *cis*- and *trans*-{2-haloaryl-2-[(1-methyl-2-imidazolyl)methyl]-4-hydroxymethyl}-1,3-dioxolanes **2a** and **2b** with a 2:1 *cis/trans* ratio. Besides these five-membered ketals, the reaction of **1a** with glycerol afforded a small amount of *trans*-{2-(4-chlorophenyl)-2-[(1-methyl-2-imidazolyl)methyl]-5-hydroxy}-1,3-dioxane (**3a**, 7%). The reaction of methanesulfonyl chloride with *cis*-**2** formed the corresponding methanesulfonates, *cis*-**4**, which rapidly cyclized to the title compounds **5**. Base-catalyzed ring opening of **5** furnished 1-methyl-5,6-dihydro-6-hydroxymethyl-8-(4-chloro- and 2,4-dichlorophenyl)-1*H*-imidazo[3,2-*d*][1,4]oxazepinium methanesulfonates **7**. Acid-catalyzed hydrolyses of **5** or **7** provided 1-methyl-2-[(4-chloro- and 2,4-dichloro)phenacyl]-3-[(2,3-dihydroxy)-1-propyl]imidazolium salts **12**. Structure proofs were based on extensive ^{1}H and ^{13}C chemical shifts and coupling constants and structures of **3a** and **5a** were confirmed by single crystal X-ray crystallography.

J. Heterocyclic Chem., **34**, 1607 (1997).

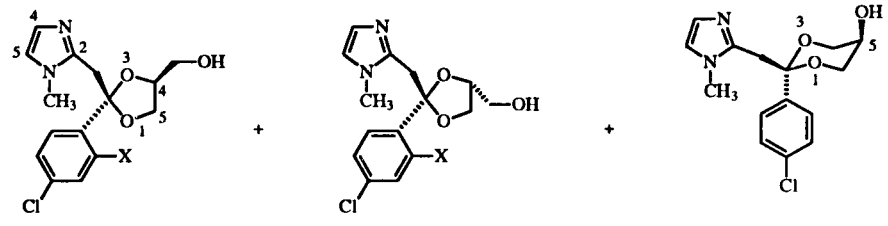
The acid-catalyzed condensations of ω-(imidazolyl)-alkyl ketones with glycerol produced mixtures of *cis*- and *trans*-1,3-dioxolanes in excellent yields [2-5]. This study reports some unique chemistry starting with *cis*-{2-(4-chloro- and 2,4-dichlorophenyl)-2-[(1-methyl-2-imidazolyl)methyl]-4-hydroxymethyl}-1,3-dioxolanes. Related prior work had reported some of the chemistry of *N*-unsubstituted imidazole analogs, while this work utilizes only the *N*-methylimidazole system [2].

The starting ketones for this project were made by literature methods [6-8]. Triethylamine-catalyzed substitution of the active methylene group of 1,2-dimethylimidazole by aroyl chlorides generated enol benzoates (whose stereochemistry was not elucidated) which were hydrolyzed by dilute hot hydrochloric acid to **1a** (X = H) and **1b** (X = Cl) [6-8]. These ketones exist to a large extent in the enol form as was evident from their ^{1}H and ^{13}C nuclear magnetic resonance (nmr) spectra (Tables 1 and 2). The ^{1}H and ^{13}C chemical shifts of the **1-keto** [CH_2-C(=O)] and **1-enol** [CH=C(OH)] forms were quite similar to those reported recently for a series of tautomeric (2-phenacyl)pyridines and related heterocycles [9]. The hydrogen-bonded enol structure, **1-enol,** is supported by nuclear Overhauser enhancements (nOe) between the *N*-methyl and alkene protons. Furthermore, such nOe effects also link the *N*-methyl with H-5 proton of imidazole, which then establishes the ^{1}H chemical shift of H-5 of **1**, unequivocally. Since H-5 is coupled to H-4 (narrow doublets), the chemical shift of H-4 becomes known. By means of HETCOR experiments, ^{13}C chemical shifts of C-4 and C-5 were established.

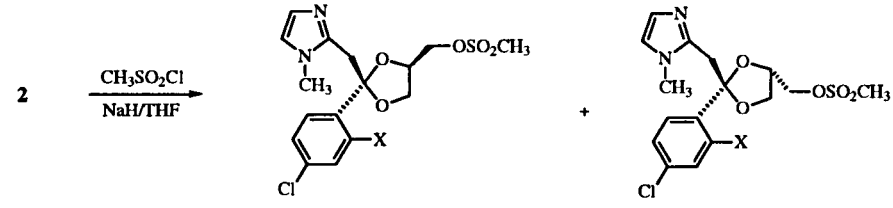
While non-basic ketones usually need just catalytic amounts of a sulfonic acid for ketalization with glycerol, these imidazolyl ketones require at least 1.2 equivalents of such an acid catalyst, since one equivalent is utilized in forming the imidazolium ion [10-12]. The rate of ketalization of **1** increases considerably if 10 equivalents of the sulfonic acid catalyst are used [2,3]. Thus, ketalization of **1a** or **1b** with glycerol in refluxing benzene containing methanesulfonic acid (and azeotropic removal of water) afforded an almost quantitative mixture of *cis*- and *trans*-{2-haloaryl-2-[(2-imidazolyl)methyl]-4-(hydroxymethyl)}-1,3-dioxolanes (**2**). The ratio of *cis* and *trans* isomers in such mixtures was estimated by integrating reasonably separated ^{1}H nmr signals in the crude mixture (*e.g.*, H-4 of imidazole, the methine (H-4) of the 1,3-dioxolane, or the *N*-methyl signal). The pair of racemic diastereomers was separated by column chromatography on silica gel. The predominant *cis*-isomer was eluted first while the isolation of pure *trans*-isomer proved considerably more tedious [2]. The stereochemistry of these ketal alcohols **2** was established relatively easily since *cis*-**2** cyclizes readily to **5**.



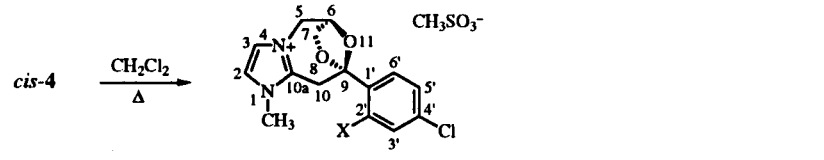
1 (keto) **1** (enol)



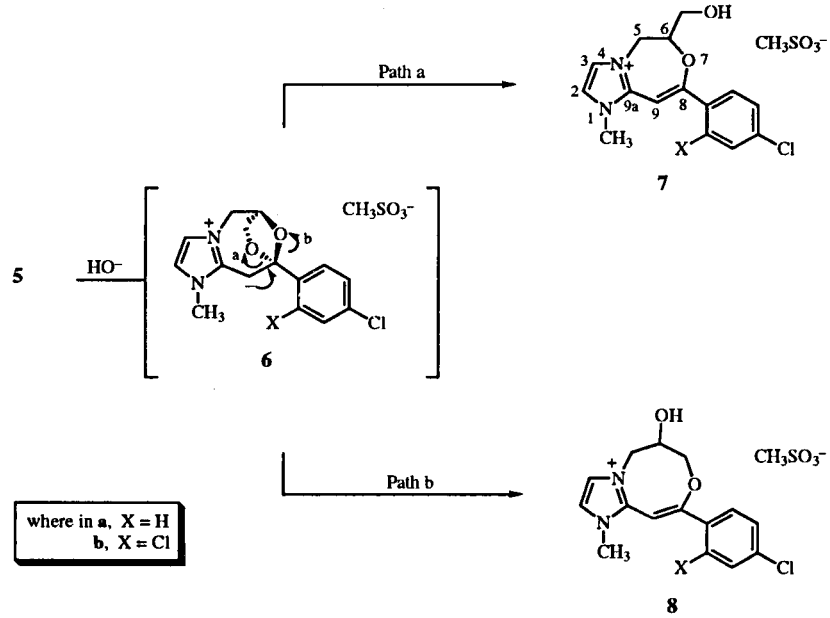
cis-**2** *trans*-**2** **3a**



cis-**4** *trans*-**4**



5



7 **6** **8**

Table 1

Selected Carbon-13 Chemical Shifts of **1**

Compound	Solvent	Imidazole				CH_2-C=O at C-2 of Imidazole		CH=C(OH) at C-2 of Imidazole			
		C-2	C-4 [a]	C-5 [a]	N-*Me*	*C*H_2	C=O	*C*H=	=*C*(OH)	–	–
1a-keto (53%)	$CDCl_3$	141.5	127.8	121.7	32.3	38.6	193.7	–	–	–	–
1a-enol	$CDCl_3$	148.5	123.5	118.7	33.1	–	–	81.8	160.9	–	–
1a-keto (23%)	DMSO-d_6	[b]	128.3	121.7	32.2	38.0	193.0	–	–	–	–
1a-enol [c]	DMSO-d_6	147.8	123.2	120.0	32.1	–	–	83.0	158.2	–	–
1b-enol (90%)	$CDCl_3$	148.4	121.3	118.4	32.3	–	–	85.0	163.1	–	–

Selected Carbon-13 Chemical Shifts of **2-4**

Compound	Solvent	Imidazole					1,3-Dioxolane [or 1,3-Dioxane]				
		C-2	C-4 [a]	C-5 [a]	N-*Me*	*C*H_2 at C-2	C-2	C-4	C-5	*C*H_2 at C-4	*Me*SO_3
cis-**2a**	$CDCl_3$	143.2	127.3	121.1	33.0	37.5	108.7	76.8	65.8	61.9	–
trans-**2a**	$CDCl_3$	142.6	126.8	121.0	32.8	38.5	109.7	77.9	67.3	61.9	–
cis-**2b** [c]	$CDCl_3$	143.1	127.3	121.4	33.3	34.6	108.5	76.5	65.7	61.7	–
cis-**2b**	DMSO-d_6	142.1	126.4	121.5	33.0	35.1	108.7	76.6	66.2	61.4	–
trans-**2b**	$CDCl_3$	142.6	127.3	121.1	33.2	35.7	108.9	77.9	67.1	61.9	–
3a [d]	$CDCl_3$	143.0	123.2	120.3	32.7	41.3	[99.8]	[63.4]	[66.8]	–	–
cis-**4a**	$CDCl_3$	142.1	127.2	121.1	33.0	37.8	109.9	73.3	68.5	65.7	37.2
trans-**4a**	$CDCl_3$	141.1	127.2	120.9	32.7	38.3	110.0	74.3	67.8	66.4	37.1

Selected Carbon-13 Chemical Shifts of **5**

Compound	Solvent	Imidazole				1,5-Oxazocine					
		C-10a	C-3[a]	C-2[a]	N-*Me*	C-10	C-9	C-6	C-7	C-5	*Me*SO_3 [e]
5a	$CDCl_3$	144.0	124.3	123.4	35.8	39.9	107.1	73.8	68.0	55.5	39.6
5a	D_2O	146.6	126.5	126.2	38.1	41.0	110.0	76.7	70.1	58.0	41.3
5a	DMSO-d_6	143.6	123.9	123.2	37.8	38.5	106.7	73.4	67.7	55.1	37.8
5b	$CDCl_3$	144.0	124.3	123.4	35.8	39.7	106.2	74.0	68.0	55.3	35.8
5b [c]	D_2O	146.3	126.0	126.5	38.0	40.0	109.0	76.7	70.2	57.9	41.2
5b	DMSO-d_6	143.7	123.8	123.0	35.1	37.2	105.8	73.5	67.2	54.8	39.7

Selected Carbon-13 Chemical Shifts of **7**

Compound	Solvent	Imidazole				1,5-Oxazepine					
		C-9a	C-3 [a]	C-2 [a]	N-*Me*	C-9	C-8	C-6	*C*H_2 at C-6	C-5	*Me*SO_3 [e]
7a	D_2O	143.6	125.6	124.3	37.3	86.3	163.6	82.7	64.2	54.9	41.3
7a	DMSO-d_6	140.9	123.0	122.0	34.8	84.3	159.6	80.4	60.9	51.9	39.7
7b [c]	D_2O	142.8	125.4	124.1	36.8	91.1	162.4	82.5	63.5	54.5	40.8
7b	DMSO-d_6	140.1	122.9	122.0	34.5	88.8	159.1	80.1	60.4	51.9	39.2

Selected Carbon-13 Chemical Shifts of **12**

Compound	Solvent	Imidazole						*N*-3 Side Chain			*Me*SO_3 [e]
		C-2	C-4 [a]	C-5 [a]	N-*Me*	*C*H_2 at C-2	C=O	*N*-*C*H_2	*C*H	*C*H_2OH	
12a [f]	D_2O	144.4	126.0	125.3	37.7	37.1 [g]	195.5	72.5	64.7	53.3	41.1
12b	D_2O	143.7	125.5	125.3	37.7	41.3 [g]	196.2	72.4	64.7	53.4	41.3

[a] Except when noted otherwise, these shifts are assigned by analogy and are interchangeable, since $\Delta\delta$'s are between 0 and 5 ppm. [b] This quaternary carbon signal was not found. [c] The chemical shifts reported for this compound have been verified by HETCOR experiments. [d] Is a 1,3-dioxane derivative. [e] To identify the *S*-methyl (*vs* the *N*-methyl) carbon signal, the solution is enriched with sodium methanesulfonate causing the relative intensity of the *S*-methyl carbon signal to (relatively) increase. Substantiated by COSY experiments. [f] Salt is the chloride. [g] This signal appeared as a quintet due to carbon-deuterium coupling.

Table 2
Selected Proton Chemical Shifts of **1**

Compound	Solvent	Imidazole	N-*Me*	Attached at *C*-2 of Imidazole				
		H-4, H-5 [a]		CH_2-C=O	C*H*=C(OH)	–	–	–
1a-keto (53%)	$CDCl_3$	6.86, 6.99	3.62	4.41	–	–	–	–
1a-enol	$CDCl_3$	6.74, 6.99	3.63	–	5.86	–	–	–
1a-keto (23%)	DMSO-d_6	6.80, 7.12	3.55	4.56	–	–	–	–
1a-enol	DMSO-d_6	7.03 (H-4), 7.15 (H-5) [b]	3.69	–	6.36	–	–	–
1b-keto	$CDCl_3$	6.89, 6.94	3.62	4.40	–	–	–	–
1b-enol (90%)	$CDCl_3$	6.71, 6.94	3.55	–	5.69	–	–	–

Selected Proton Chemical Shifts and Geminal Coupling Constants (J_{gem} in Hz) of **2-4**

Compound	Solvent	Imidazole				1,3-Dioxolane		
		H-4, H-5 [a]	N-*Me*	CH_2 at C-2 of imidazole	4-C*H*	5-CH_2	CH_2O at C-4	*Me*SO_3
cis-**2a**	$CDCl_3$	7.00, 6.81	3.46	3.25	4.15	3.79, 3.94 J = 7.8	3.26, 3.90 J = 12.4	–
trans-**2a**	$CDCl_3$	6.94 6.76	3.42	3.23, 3.28 J = 15.0	4.09	3.62, 3.98 J = 8.0	3.43, 3.58 J = 11.8	–
cis-**2b**	$CDCl_3$	6.99 (H-4), 6.83 (H-5) [b]	3.60	3.41, 3.61 J = 15.3	4.16	3.75, 3.84 J = 8.0	3.23, 3.86 J = 12.4	–
cis-**2b**	DMSO-d_6	7.00, 6.68	3.61	3.38, 3.44 J = 14.8	3.97	3.67	3.16, 3.27 J = 11.6	–
trans-**2b**	$CDCl_3$	6.88, 6.79	3.64	3.43	3.96	3.55, 3.92 J = 7.4	3.45-3.60 [c]	–
3a	$CDCl_3$	7.05, 6.79	3.42	3.02	3.78, 3.93	3.46	–	–
cis-**4a**	$CDCl_3$	6.97, 6.83	3.55	3.27, 3.32 J = 14.4	4.26	3.74, 3.81 J = 8.8	3.68, 3.86 J = 10.4	3.03
cis-**4a**•HCl	$CDCl_3$	7.33, 7.05	3.80	3.68, 3.83	4.28	3.82, 3.90	4.05, 4.19	3.07
cis-**4b**	$CDCl_3$	7.02, 6.90	3.73	3.50-3.90 [c]	4.29	3.50-3.90 [c]	3.50-3.90 [c]	3.04
cis-**4b**•HCl	$CDCl_3$	7.38, 7.10	3.90	3.95	4.32	3.81, 3.90	4.07, 4.22	3.10

Selected Chemical Shifts and Geminal Coupling Constants (J_{gem} in Hz) of **5**

Compound	Solvent	Imidazole H-3, H-2 [a,d]	N-*Me*	1,5-Oxazocine H-10	H-6	H-7	H-5	*Me*SO_3 [e]
5a	$CDCl_3$	7.46, 7.92	3.85	3.53, 3.98 J = 17.1	5.00	4.14, 4.16 J = 8.8	4.80, 5.09 J = 14.8	2.72
5a	D_2O	7.48 (H-3), 7.92 (H-2) [b]	3.83	3.86, 3.96 J = 17.2	5.17	4.16, 4.26 J = 8.0	4.65, 4.75 J = 15.2	2.82
5a	DMSO-d_6	7.74	3.83	3.80, 3.94 J = 17.2	5.13	4.03, 4.08 J = 8.0	4.61, 4.72 J = 14.8	2.31
5b	$CDCl_3$	7.52, 7.99	3.93	3.97	5.01	4.00, 4.10 J = 8.0	4.75, 5.20 J = 15.2	2.72
5b	D_2O	7.57 (H-3), 7.48 (H-2) [b]	3.84	3.94, 4.10 J = 17.1	5.22	4.15	4.66, 4.82 J = 15.2	2.84
5b	DMSO-d_6	7.75	3.81	3.92, 4.05 J = 17.1	5.16	3.98	4.62, 4.75 J =15.2	2.30

Selected Proton Chemical Shifts and Geminal Coupling Constants (J_{gem} in Hz) of **7**

Compound	Solvent Solvent	Imidazole H-3, H-2 [a,d]	N-*Me*	1,5-Oxazapine H-9	H-6	CH_2 at C-6	H-5	*Me*SO_3 [e]
7a	D_2O	7.36, 7.35	3.81	6.21	4.52	4.06, 4.11 J = 12.0	4.30, 4.75 J = 15.2	2.82
7a	DMSO-d_6	7.66, 7.64	3.88	6.48	4.49	3.74-3.93 [c]	4.31, 4.85 J = 15.2	2.30

Table 2 (continued)

Selected Proton Chemical Shifts and Geminal Coupling Constants (J_{gem} in Hz) of **7**

Compound	Solvent	Imidazole	N-*Me*	1,5-Oxazapine				
	Solvent	H-3, H-2 [a,d]		H-9	H-6	CH_2 at C-6	H-5	$MeSO_3$ [e]
7b	D_2O	7.46 (H-3), 7.44 (H-2)[b]	3.78	6.06	4.51	4.05, 4.35 J = 12.2	4.36, 4.86 J = 15.2	2.82
7b	DMSO-d_6	7.73	3.83	6.27	4.55	3.70-4.05 [c]	4.36, 4.96 J = 15.2	2.30

Selected Proton Chemical Shifts and Geminal Coupling Constants (J_{gem} in Hz) of **12**

Compound	Solvent	Imidazole		*N*-3 Side Chain				
		H-4, H-5 [a]	N-*Me*	CH_2-C=O	C*H*(OH)H	CH_2-OH	CH_2 at *N*-3	$MeSO_3$ [e]
12a	D_2O	7.58	3.82	[f]	3.98	3.53	4.21, 4.36 J = 14.9	2.81
12a	DMSO-d_6	7.82, 7.75	3.80	5.24	3.87	3.20, 3.37	4.19, 4.32	2.35
12b	D_2O	7.63	3.81	[f]	4.03	3.58	4.39, 4.25	2.82

[a] These shifts cannot be assigned to specific protons with certainty unless auxiliary data are available. [b] Chemical shifts verified by nOe. [c] Buried in sets of overlapping complex multiplets. [d] In these systems, H-3 and H-2 are equivalent to H-4 and H-5 in imidazole, respectively. [e] To distinguish between *S*- and *N*-methyl signals, some sodium methanesulfonate was added to the test solution which increases the intensity of the *methanesulfonate* ion signal. [f] Not visible due to H-D exchange.

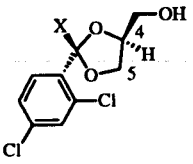
The nmr assignments in related systems, **2** and **4**, have been reported [1,13]. To assign ^1H and ^{13}C chemical shifts for the various compounds described now, a number of nmr correlation experiments were carried out. The arrangement of data in Tables 1 and 2 is such that chemical shifts of *corresponding* carbons and hydrogens are placed in the *same* column, irrespective of the numbering of a particular ring system. We resorted to various nmr correlation experiments (HETCOR, COSY, nOe) to distinguish between relatively close chemical shifts. In the structures to be discussed, there were three sets of diastereotopic methylene groups giving rise to complex overlapping ^1H resonances with relatively close ^{13}C chemical shifts. The chemical shifts of the methylene group of the relatively insulated CH_2 attached at C-2 of the imidazole ring (an A_2 or AB system) for all of the systems were established relatively quickly. The more challenging task involved sorting the ^1H and ^{13}C chemical shifts of the ring 5-CH_2 of the ketal and the CH_2 of the hydroxymethyl attached to the ketal at C-4 in **2**. The last two methylene groups are part of the highly coupled five proton spin system [-O-CH_2-C*H*(-O-)-CH_2OH].

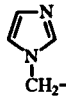
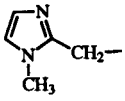
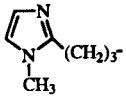
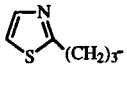
Homonuclear decoupling of the ketal methine (H-4) of **2** simplified ^1H signals associated with the neighboring ketal ring (5-CH_2) and exocyclic CH_2OH. A feature which distinguishes between the chemical shifts of the ring ketal and the exocyclic hydroxymethyl group is the relative sizes of their respective *geminal* coupling constants [11]. It had been reported, and substantiated in our laboratory, that the *geminal* coupling constants of the ring methylene (5-CH_2) protons is of the order of 8.0 Hz, while that of the exocyclic hydroxymethyl methylene protons (CH_2OH at C-4) is always larger, approaching 12.0 Hz [11,12]. These findings are best summarized by the data in Table 3. Furthermore, in knowing the size of these *geminal* coupling constants helps to locate the appropriate ^1H chemical shifts in overlapping multiplets arising from these two sets of diastereotopic protons. In any one of the systems reported here, it seems that the geminal coupling constants in freely rotating, *e.g.*, **2**, **4**, and less constrained ring system, *e.g.*, **5**, **7**, was much larger than those in a more confined (*e.g.* five-membered) ring system. In addition, HETCOR experiments were used to correlate ^1H and ^{13}C chemical shifts assignments associated with these methylene groups.

Interestingly, ketalization of 4-chlorophenyl ketone **1a** with glycerol consistently also produced a small amount of the isomeric 5-hydroxy-1,3-dioxane, **3a**. Such a six-membered ketal was quite unexpected since none had been detected in prior ketalizations of similar ketones with glycerol. Six-membered acetals (frequently up to 50% of the product) have been isolated many times from acetalizations of aldehydes with glycerol [2-5,10]. The ^1H and ^{13}C chemical shifts support structure **3a** with multiplets at δ 3.78 and 3.93 (representing four protons on carbons 4 and 6, *geminal* coupling constant around 11 Hz) and a narrow doublet of doublets for the methine proton at C-5, δ 3.46 (J's = 2.2 and 1.1 Hz). The inherent small coupling constants associated with the signal from H-5 points to an equatorial proton, with the alcohol being axial and *cis* to the 1-methyl-2-imidazolyl group. The stereochemistry of **3a** was confirmed by means of X-ray crystallography, as presented, below. A search for a cognate six-membered ketal from the condensation of **1b** with glycerol proved futile as no 1,3-dichlorophenyl analog of **3a** could be

Table 3

Selected ^1H, ^{13}C Chemical Shifts and Coupling Constants of Ring Methylenes at C-5 and Exocyclic Methylenes of Hydroxymethyl Group attached at C-4 of 1,3-Dioxolane in



X	^1H Chemical Shifts (δ)		^{13}C Chemical Shifts (δ)		Ref.
	5-CH_2 (J_{gem} in Hz)	CH_2-OH at C-4 (J_{gem} in Hz)	5-CH_2	CH_2-OH at C-4	
	3.65, 3.78 (J = 8.0)	3.27, 3.42 (J = 12.0)	66.9	61.7	11
	3.65, 3.81 (J = 8.0)	3.31, 3.40 (J = 11.7)	–	–	12
4-Phenyl instead of 2,4-dichlorophenyl	3.69, 3.83 (J = 8.0)	3.27, 3.43 (J = 11.8)	–	–	12
	3.72, 3.87 (J = 8.0)	3.26, 3.68 (J = 12.0)	66.3	61.5	13
	3.75, 3.84 (J = 7.9)	3.23, 3.85 (J = 12.5)	65.7	61.7	This work
	3.79, 3.96 (J = 8.0)	3.61, 3.83 (J = 12.4)	65.5	62.4	13
	3.79, 3.95 (J = 8.1)	3.66, 3.95 (J = 12.1)	65.9	63.1	13

detected. It is interesting to note that upon storing pure **3a** for several months at room temperature, some of it was converted to *cis*-**2a** (30%).

Cyclization of **2**.

It was anticipated that the reaction of *cis* and *trans* **2** with methanesulfonyl chloride, in the presence of a suitable base, would produce *cis* and *trans* sulfonates **4**. Although such sulfonates are formed initially (^1H and ^{13}C nmr spectra in deuteriochloroform), in a relatively short period of time their nmr spectra would change and soon thereafter a new crystalline substance separates from solution. An analysis of the situation revealed that *cis*-**4** reacts, while *trans*-**4** remains unchanged. The new product proved to be **5**. Apparently, *N*-3 of imidazole in *cis*-**4** is sufficiently proximal to the methanesulfonate to bring about a facile intramolecular alkylation [1a]. One of the best methods to carry out these steps more systematically is to treat *cis*-**2** with methanesulfonyl chloride in dichloromethane containing 1.1 equivalent of pyridine which produces pure and stable *cis*-**4** hydrochlorides. While this hydrochloride is stable for months, upon neutralization with sodium bicarbonate, the free base, *cis*-**4**, is released which cyclizes quickly to **5**.

The structure of the water-soluble salt **5** was deduced initially by an analysis of significant ^1H chemical shift differences between *cis*-**2**, *cis*-**4** and **5**. As expected, H-4, H-5 and the *N*-methyl protons became more deshielded as the imidazole ring was quaternized. The most pronounced ^1H nmr shift changes (in deuteriochloroform) are associated with the methylene protons which are originally part of the hydroxymethyl group (CH_2OH) at C-4 of *cis*-**2a** (δ 3.26, 3.90), with those of the corresponding sulfonate (CH_2OSO_2Me) of *cis*-**4a** (δ 3.68, 3.86), and finally those of the 5-methylene protons of **5a**, (CH_2-N^+, δ 4.80, 5.09). In their corresponding ^{13}C nmr spectra, the shifts are less dramatic, with differences of the order of 2-6 ppm, the most significant differences were when the CH_2-OH at *C*-4 in *cis*-**2a** (δ 61.9) and that of C-5 of **5a** (CH_2-N^+, δ 55.5).

The structure of salt **5a** was confirmed by means of single crystal X-ray crystallography. Since there was a considerable decrease of solubility of salt **5**, as well as subsequent salts, in deuteriochloroform, nmr parameters were measured in deuterium oxide and deuteriodimethyl sulfoxide, as these data have bearing upon subsequent transformations. In deuterium oxide, especially, reactions of some of these salts, **5**, **7**, with acids and bases could be followed initially in nmr tubes, before larger scale reactions were attempted.

Base-catalyzed Ring Opening of **5**.

Brief exposure of **5a** and **5b** to sodium deuteroxide in deuterium oxide (5 minutes), or potassium carbonate (1 hour) caused considerable changes in their ^1H nmr spectra. Most striking was the disappearance of the signal around δ 5.0 in **5** and the quick entrance of a new singlet around δ 6.0. In the ^{13}C nmr spectrum, concomitant changes were the replacement of signals around δ 40 and 108 by two new signals in the vicinity of δ 86 and 160. Two final structures can be proposed within the framework of these nmr signal changes. Neutralization of one of the active methylene protons, H-10 in **5**, generates anion **6** which collapses with ring opening of the ketal, *via* path a *or* b, to form either the seven or eight-membered enol ether alcohols, **7** or **8**, respectively. To distinguish between these isomers, the recently published method of Pearce and Sanders [15] was employed. Using extremely dry deuteriodimethyl sulfoxide, devoid of traces of hydrogen chloride (by drying the solvent over potassium carbonate for 24 hours), the ^1H nmr spectrum of the new salt exhibited a triplet at δ 5.57, with a coupling constant of 5.6 Hz, expected for vicinal coupling of the hydroxyl with the methylene protons. Addition of deuterium oxide caused

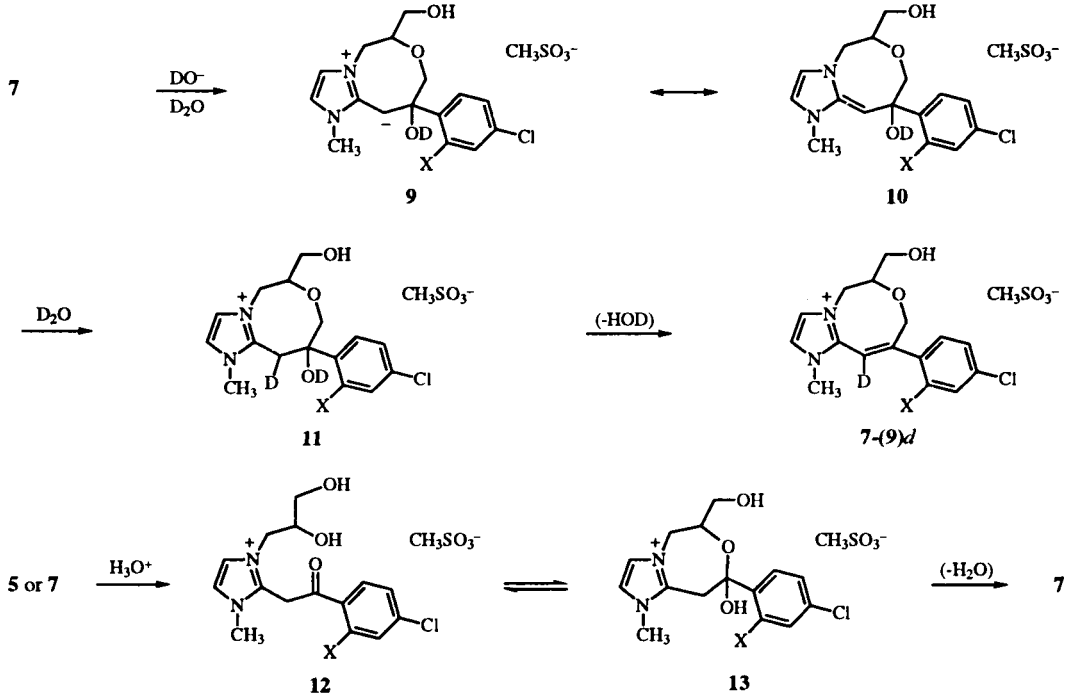
this triplet to first change to a singlet, and then disappear, simplifying the adjacent methylene signal pattern. The original triplet, indicative of *6-CH_2*, *OH* coupling distinguishes between isomers **7** and **8**, since for the latter, coupling of the hydroxyl to the methine group would give an exchangeable doublet.

There were other unexpected changes in the ^1H nmr spectra during these extremely fast base-catalyzed conversions of **5** to **7**. Initially, it was thought that there might be facile H-D exchange of the active methylene protons of **5** in deuterium oxide, namely the C-10 methylene protons. Yet, this did not take place in the facile conversion of **5** to **7**, since the new vinyl signal (around δ 6.00) appeared very quickly. But, as **7** remained in the alkaline deuterium oxide solution, this vinyl proton signal began to fade away (2 hours). This H-D exchange is explained as follows. The highly electrophilic vinyl carbon at C-8 in **7** is a β-vinyl carbon of the 2-vinyl-1,3-dialkylimidazolium ion system, and hence highly susceptible for nucleophilic attack. Addition of the deuteroxide ion generates the resonance-stabilized anion, **9**, **10**, in which the anionic site is neutralized by deuterium oxide to form the 9-deuterio derivative **11**. Elimination of HOD from **11** would lead to **7** which now bears one deuterium atom on C-9. The presence of deuterium was substantiated when the ^{13}C signal of C-9 in the deuterio derivative of **7a** appeared as a triplet.

Acid-catalyzed Reactions of **5** and **7**.

In exploratory experiments, upon heating deuterium oxide solutions of **5a** or **7a** and additional methanesulfonic acid in nmr tubes, relatively slow reactions were taking places, as reflected by changes in the ^1H and ^{13}C spectra. Spectral analysis supported the hydrolysis of the ketal of **5a** and the enol ether of **7a** to generate the keto alcohol **12a**. However, there always remained some of the enol ether **7a**, with H-9 exchanged by deuterium. The most telling evidence of change was the appearance of a ^1H nmr signal around δ 8.0 ppm which is attributed to an *ortho* proton of the phenyl ring (H-2', H-6'). This signal was deshielded due to anisotropic effect of the carbonyl group in **12a** on an *ortho* proton. In the ^{13}C spectra, signals appeared around δ 195 (typical of a C=O carbon). Attempted hydrolysis of **5b** and **7b** with methanesulfonic acid (nmr tubes, or preparatively) were so slow that in effect not useful. However, when these hydrolyses were repeated using hot dilute hydrochloric acid on a preparative scale for **5a**, **7a**, **5b** and **7b**, hydrolysis products **12**, along with (small amounts of) **7** were obtained. It is not unreasonable to assume that during the process of concentrating the acidic aqueous solution from the hydrolyses, as the mixture became more anhydrous, some **12** might recyclize to **7**. The formation of **7** from **12** is understood in term of an intermediate hemiketal, **13**, when the ketone reacts with the neighboring alcohol under these relatively anhydrous acidic conditions (near the end of the vacuum concentration). There were also distinct differences in experimental behavior between the 4-chloro and 2,4-dichlorophenyl derivatives, in the sense that compounds of the 4-chloro series were much easier to handle than their 2,4-dichloro counterpart.

Isolation of pure salts **12a** and **12b** proved to be difficult. Fractional crystallizations proved to be very tedious. Attempts to purify **12**, by column chromatography, eluting



with such polar solvent mixtures as dichloromethane and methanol, also had its limitations. When **5a** was boiled with 12% aqueous hydrochloric acid for several hours, the thick oil remaining after evaporation to dryness proved to be mainly **12a**, along with some **7a**. However, fractional crystallization provided some pure **12a**, which is the chloride and not the methanesulfonate. A similar hydrolysis of **5b** led to **12b** which was isolated as the methanesulfonate after chromatography. Attempts to isolate **13**, particularly by column chromatography, failed.

Structure Determinations of **3a** by Single Crystal X-Ray Diffraction.

Table 4

Crystal Data and Structure Refinement for **3a**

Empirical formula	$C_{15}H_{17}ClN_2O_3$
Formula weight	308.76
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbcn
Unit cell dimensions	a = 18.344(4) Å α = 90°.
	b = 12.242(2) Å β = 90°.
	c = 15.580(3) Å γ = 90°.
Volume	3498.8(12) Å^3
Z	8
Density (calculated)	1.319 Mg/m^3
Absorption coefficient	0.257 mm^{-1}
F(000)	1458
Crystal size	0.45 x 0.42 x 0.30 mm
Theta range for data collection	2.00 to 20.02°.
Index ranges	-1<=h<=17, -1<=k<=11, -1<=l<=15
Reflections collected	2157
Independent reflections	1632 [R(int) = 0.1823]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1622/0/217
Goodness-of-fit on F^2	1.099
Final R indices [I>2σ(I)]	R1 = 0.0698, wR2 = 0.1808
R indices (all data)	R1 = 0.0906, wR2 = 0.9352
Largest diff. peak and hole	0.611 and -0.327 e. Å^{-3}

The crystal used for the structure determination was prepared by crystallization from benzene and hexane. Unit cell dimensions were determined from 50 centered reflections with a 2θ range of 7 to 27°. Data, θ-2θ scans, was collected on two different crystals and that data was merged before refinement of the structure. The details of the data collection and refinement are given in Table 4. The structure was solved by a combination of direct, SHELXT PLUS (PC Version) [16], and Fourier methods since not all the atoms could be found in the E-map from the direct method solution. The benzene molecule was not expected, but appeared as a series of Difference Fourier peaks that had electron densities too large to be ignored. The asymmetric unit for the benzene molecule is half of a molecule with the remaining half being generated by a symmetry operation. The benzene molecules occupies holes in the unit cell not filled by the ketal structure. The refined structure clearly shows the hydroxyl group in an axial position *trans* to the 4-chlorophenyl group. The equatorial hydroxyl isomer was built and refinement was attempted to be sure the axial hydroxyl isomer was correct. This isomer did not refine satisfactorily. The refined structure with hydrogen atoms placed in calculated positions is shown in Figure 1. Atom positions and thermal factors are given in Tables 5 and 6. Bond lengths and bond angles are given in Table 7. Refinement was carried out on F^2 for all reflections except for 10 with very negative F^2. Weighted R-factors, wR, and all goodness of fit S are based on F^2. The observed criterion of $F^2 > 2\sigma(F^2)$ is used only for calculating (Those underline

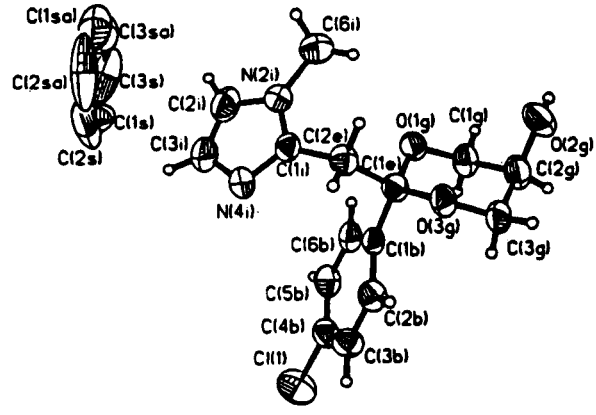


Figure 1. ORTEP plot of structure **3a**. Thermal ellipsoids are drawn as 50% level.

Table 5

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for **3a**

Atom	x	y	z	U(eq) [a]
O(1G)	1558(2)	1631(3)	7212(2)	44(1)
O(2G)	1550(2)	1386(3)	9099(3)	64(1)
O(3G)	1708(2)	-186(3)	7632(2)	45(1)
C(1G)	2105(3)	2000(5)	7806(4)	48(2)
C(2G)	2163(4)	1244(5)	8567(4)	56(2)
C(3G)	2253(3)	99(5)	8237(3)	50(2)
Cl(1)	4096(1)	40(2)	4364(1)	75(1)
C(1B)	2317(3)	448(4)	6335(3)	36(2)
C(2B)	2661(3)	-549(5)	6219(4)	43(2)
C(3B)	3209(3)	-677(5)	5620(4)	47(2)
C(4B)	3423(3)	205(5)	5136(4)	47(2)
C(5B)	3101(3)	1212(5)	5236(4)	46(2)
C(6B)	2546(3)	1322(5)	5835(3)	43(2)
C(1I)	803(3)	798(5)	5651(4)	40(2)
N(2I)	423(3)	1740(4)	5600(3)	49(1)
C(2I)	399(4)	2023(6)	4747(4)	63(2)
C(3I)	753(4)	1244(6)	4328(4)	61(2)
N(4I)	1006(3)	466(4)	4887(3)	53(1)
C(1S)	663(5)	3826(15)	2152(7)	119(5)
C(1E)	1656(3)	545(4)	6927(3)	40(2)
C(2E)	960(3)	201(5)	6462(4)	44(2)
C(6I)	78(4)	2334(6)	6305(4)	74(2)
C(3S)	310(6)	4668(10)	2341(8)	132(6)
C(2S)	376(8)	2811(9)	2306(6)	161(8)

[a] U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 6
Anisotropic Displacement Parameters (Å^2 x 10^3) for **3a**

Atom	U11	U22	U33	U23	U13	U12 [a]
O(1G)	56(3)	39(2)	36(2)	0(2)	-1(2)	5(2)
O(2G)	91(3)	55(3)	46(3)	-11(2)	13(3)	9(2)
O(3G)	58(3)	45(2)	30(2)	6(2)	0(2)	-1(2)
C(1G)	64(4)	43(4)	38(4)	-1(3)	-7(3)	-7(3)
C(2G)	71(5)	58(4)	38(4)	-4(3)	-6(4)	1(4)
C(3G)	67(4)	53(4)	31(3)	6(3)	-3(3)	10(3)
Cl(1)	69(1)	82(1)	74(1)	2(1)	31(1)	-7(1)
C(1B)	48(4)	35(4)	26(3)	4(3)	-5(3)	1(3)
C(2B)	53(4)	38(4)	39(3)	5(3)	2(3)	-2(3)
C(3B)	53(4)	39(4)	50(4)	2(3)	3(3)	2(3)
C(4B)	44(4)	59(5)	37(3)	-1(3)	7(3)	-2(3)
C(5B)	53(4)	50(4)	36(3)	9(3)	1(3)	-13(3)
C(6B)	57(4)	41(4)	31(3)	4(3)	-7(3)	-3(3)
C(1I)	36(3)	45(4)	38(4)	-4(3)	-7(3)	-5(3)
N(2I)	49(3)	54(3)	43(3)	-5(3)	-5(2)	10(3)
C(2I)	68(5)	69(5)	51(5)	11(4)	-16(4)	9(4)
C(3I)	67(5)	78(5)	38(4)	5(4)	-10(4)	5(4)
N(4I)	57(3)	66(3)	35(3)	-7(3)	-6(3)	6(3)
C(1S)	60(6)	232(15)	63(6)	-1(11)	6(5)	49(9)
C(1E)	50(4)	38(3)	33(3)	6(3)	2(3)	4(3)
C(2E)	42(4)	51(4)	38(3)	1(3)	3(3)	-8(3)
C(6I)	74(5)	80(5)	68(5)	-14(4)	-10(4)	34(4)
C(3S)	138(14)	156(9)	102(13)	59(11)	-66(13)	-65(8)
C(2S)	300(24)	119(7)	66(10)	-45(8)	-85(12)	125(11)

[a] The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 a*^{2} U11 + ... + 2 h k a* b* U12]

Table 7
Bond Lengths [Å] and Angles [deg] for **3a** [a]

O(1G)-C(1E)	1.413(6)
O(1G)-C(1G)	1.440(7)
O(2G)-C(2G)	1.409(7)
O(3G)-C(3G)	1.418(7)
O(3G)-C(1E)	1.421(6)
C(1G)-C(2G)	1.508(8)
C(2G)-C(3G)	1.502(8)
Cl(1)-C(4B)	1.736(6)
C(1B)-C(2B)	1.385(7)
C(1B)-C(6B)	1.388(7)
C(1B)-C(1E)	1.527(8)
C(2B)-C(3B)	1.381(8)
C(3B)-C(4B)	1.374(8)
C(4B)-C(5B)	1.376(8)
C(5B)-C(6B)	1.387(8)
C(1I)-N(4I)	1.313(7)
C(1I)-N(2I)	1.349(7)
C(1I)-C(2E)	1.487(8)
N(2I)-C(2I)	1.375(8)
N(2I)-C(6I)	1.461(8)
C(2I)-C(3I)	1.325(9)
C(3I)-N(4I)	1.371(8)
C(1S)-C(3S)	1.252(14)
C(1S)-C(2S)	1.37(2)
C(1E)-C(2E)	1.529(8)
C(3S)-C(3S)#1	1.24(3)
C(2S)-C(2S)#1	1.51(3)
C(1E)-O(1G)-C(1G)	114.1(4)
C(3G)-O(3G)-C(1E)	113.9(4)
O(1G)-C(1G)-C(2G)	111.3(5)
O(2G)-C(2G)-C(3G)	113.9(5)
O(2G)-C(2G)-C(1G)	109.3(5)
C(3G)-C(2G)-C(1G)	108.1(5)
O(3G)-C(3G)-C(2G)	112.3(5)
C(2B)-C(1B)-C(6B)	117.9(5)
C(2B)-C(1B)-C(1E)	120.5(5)
C(6B)-C(1B)-C(1E)	121.3(5)
C(3B)-C(2B)-C(1B)	121.3(5)
C(4B)-C(3B)-C(2B)	119.3(5)
C(3B)-C(4B)-C(5B)	121.3(5)
C(3B)-C(4B)-Cl(1)	119.5(5)
C(5B)-C(4B)-Cl(1)	119.2(5)
C(4B)-C(5B)-C(6B)	118.5(5)
C(5B)-C(6B)-C(1B)	121.6(5)
N(4I)-C(1I)-N(2I)	111.0(5)
N(4I)-C(1I)-C(2E)	124.3(5)
N(2I)-C(1I)-C(2E)	124.7(5)
C(1I)-N(2I)-C(2I)	106.8(5)
C(1I)-N(2I)-C(6I)	127.2(5)
C(2I)-N(2I)-C(6I)	125.9(6)
C(3I)-C(2I)-N(2I)	106.2(6)
C(2I)-C(3I)-N(4I)	110.7(6)
C(1I)-N(4I)-C(3I)	105.3(5)
C(3S)-C(1S)-C(2S)	120.5(11)
O(1G)-C(1E)-O(3G)	111.0(4)
O(1G)-C(1E)-C(1B)	111.4(4)
O(3G)-C(1E)-C(1B)	111.5(4)
O(1G)-C(1E)-C(2E)	107.5(4)
O(3G)-C(1E)-C(2E)	104.4(4)
C(1B)-C(1E)-C(2E)	110.8(4)
C(1I)-C(2E)-C(1E)	115.4(4)
C(3S)#1-C(3S)-C(1S)	124.6(9)
C(1S)-C(2S)-C(2S)#1	114.9(7)

[a] Symmetry transformations used to generate equivalent atoms: #1 -x,y,-z+1/2

Table 8
Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters (Å^2 x 10^3) for **3a**

Atom	x	y	z	U(eq)
H(2GA)	1529(2)	2045(3)	9269(3)	80
H(1GA)	1979(3)	2720(5)	8001(4)	80
H(1GB)	2564(3)	2046(5)	7512(4)	80
H(2GB)	2592(4)	1442(5)	8884(4)	80
H(3GA)	2721(3)	25(5)	7967(3)	80
H(3GB)	2233(3)	-405(5)	8708(3)	80
H(2BA)	2516(3)	-1167(5)	6558(4)	80
H(3BA)	3438(3)	-1374(5)	5538(4)	80
H(5BA)	3251(3)	1825(5)	4894(4)	80
H(6BA)	2317(3)	2021(5)	5911(3)	80
H(2IA)	165(4)	2656(6)	4508(4)	80
H(3IA)	824(4)	1227(6)	3718(4)	80
H(2EA)	563(3)	335(5)	6850(4)	80
H(2EB)	972(3)	-569(5)	6348(4)	80
H(6IA)	179(4)	1975(6)	6839(4)	80
H(6IB)	268(4)	3065(6)	6321(4)	80
H(6IC)	-440(4)	2359(6)	6214(4)	80

lines next to R, *etc*, are OK) R-factor-obs *etc*. and is not relevant to the choice of reflections for refinement. All esds are estimated using the full covariance matrix and take into account the cell esds. Correlations between esds in cell parameters are only used when they are defined by crystal symmetry.

The crystal for the structure determination was prepared by crystallization from ethyl acetate. The unit cell parameters were determined from 38 centered reflections in the 2θ range of 11 to 24°. Data was collected, θ-2θ scans, on three different crystals and merged into one data set before refinement. Details of the data collection and refinement are given in Table 9. The structure was solved by direct methods, SHELXT PLUS (PC Version), and refined, SHELXL-93 [16], on F^2 for all reflections except for 825 with very negative F^2. The refined structure with hydrogen atoms placed in calculated positions is shown in Figure 2.

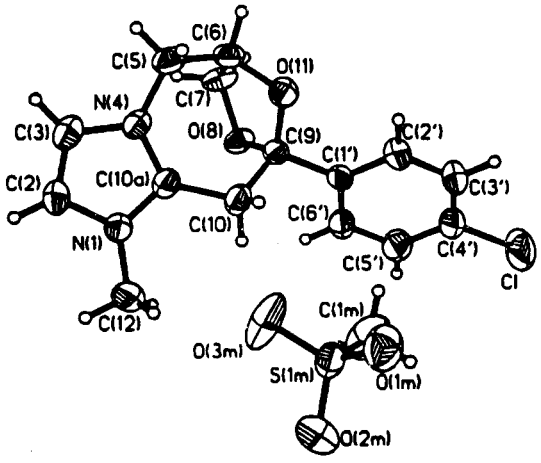


Figure 2. ORTEP drawing of **5a** drawn at the 50% level. Atoms with the suffix m are part of the methanesulfonate anion.

Atom positions and thermal factors are given in Tables 10 and 11. Bond lengths and bond angles are given in Table 12. Weighted R-factors, wR, and all goodness of fit, S, are based on F^2. Conventional R-factors, R, are based on F, with F set to zero for negative F^2. The observed criterion of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factor-obs and is not relevant to the choice of reflections for refinement. All esds are estimated using the full covariance matrix with the cell esds taken into account in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry.

Table 9
Crystal Data and Structure Refinement for **5a**

Empirical formula	$C_{16}H_{19}ClN_2O_5S$
Formula weight	386.84
Temperature	293(2)% K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Table 9 (continued)

Space group	$P2_1/c$	
Unit cell dimensions	a = 17.0120(10) Å	α = 90°
	b = 10.8170(10) Å	β = 91.450(10)°
	c = 10.0990(10) Å	γ = 90°
Volume	1857.8(3) $Å^3$	
Z	4	
Density (calculated)	1.383 Mg/m^3	
Absorption coefficient	0.346 mm^{-1}	
F(000)	808	
Crystal size	0.7 x 0.5 x 0.3 mm Triangular Prism	
Theta range for data collection	2.23 to 30.04°.	
Index ranges	-23<=h<=23, -15<=k<=1, -1<=l<=14	
Reflections collected	6827	
Independent reflections	5411 [R(int) = 0.0409]	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	4586/0/221	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2&(I)]	R1 = 0.0708, wR2 = 0.1564	
R indices (all data)	R1 = 0.1800, wR2 = 0.2204	
Extinction coefficient	0.0018(10)	
Largest diff. peak and hole	0.493 and -0.368 e. $Å^{-3}$	

Table 10
Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for **5a**

Atom	x	y	z	U(eq)[a]
Cl	-485(1)	2399(2)	2200(2)	128(1)
S(1M)	3291(1)	843(1)	758(1)	54(1)
O(1M)	3043(2)	184(3)	-416(3)	84(1)
O(2M)	3641(2)	-5(4)	1707(4)	102(1)
O(3M)	3768(2)	1894(3)	547(5)	107(2)
C(1M)	2439(3)	1344(6)	1502(7)	102(2)
N(1)	4418(2)	5366(3)	1577(3)	46(1)
C(2)	4970(2)	6253(4)	1305(4)	54(1)
C(3)	4643(3)	7018(4)	406(4)	57(1)
N(4)	3897(2)	6589(3)	116(3)	46(1)
C(5)	3382(3)	7139(4)	-924(4)	53(1)
C(6)	2520(2)	7159(4)	-597(4)	49(1)
C(7)	2329(3)	7640(4)	752(4)	54(1)
O(8)	2332(2)	6557(2)	1561(2)	46(1)
C(9)	2285(2)	5499(3)	719(3)	39(1)
C(10)	3058(2)	4784(4)	890(5)	54(1)
C(10A)	3774(2)	5570(3)	838(4)	44(1)
O(11)	2190(2)	5942(3)	-588(2)	52(1)
C(12)	4539(1)	4333(2)	2500(2)	61(1)
C(1')	1594(1)	4710(2)	1072(2)	41(1)
C(2')	1063(1)	4282(2)	123(2)	53(1)
C(3')	426(2)	3567(4)	476(5)	63(1)
C(4')	326(3)	3287(5)	1764(5)	68(1)
C(5')	840(3)	3702(5)	2732(5)	76(2)
C(6')	1479(2)	4406(4)	2376(4)	58(1)

[a] U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 11
Anisotropic Displacement Parameters ($Å^2$ x 10^3) for **5a** [a]

Name	U11	U22	U33	U23	U13	U12
Cl	79(1)	182(2)	120(1)	55(1)	-25(1)	-75(1)
S(1M)	44(1)	45(1)	72(1)	-5(1)	4(1)	-6(1)
O(1M)	95(3)	86(3)	70(2)	-11(2)	-5(2)	-23(2)
O(2M)	78(2)	104(3)	121(3)	27(3)	-30(2)	7(2)

Table 11 (continued)

Name	U11	U22	U33	U23	U13	U12
O(3M)	97(3)	63(2)	162(4)	-28(3)	54(3)	-35(2)
C(1M)	82(4)	71(4)	155(6)	3(4)	47(4)	7(3)
N(1)	41(2)	44(2)	52(2)	2(2)	1(2)	-2(2)
C(2)	45(2)	59(3)	57(3)	-7(2)	-2(2)	-14(2)
C(3)	61(3)	51(3)	58(3)	-2(2)	7(2)	-17(2)
N(4)	50(2)	40(2)	47(2)	2(2)	4(2)	-8(2)
C(5)	67(3)	52(2)	40(2)	11(2)	3(2)	-6(2)
C(6)	60(2)	48(2)	39(2)	9(2)	-4(2)	1(2)
C(7)	77(3)	36(2)	50(2)	9(2)	13(2)	7(2)
O(8)	72(2)	31(1)	35(1)	-2(1)	-1(1)	-5(1)
C(9)	45(2)	37(2)	34(2)	1(2)	-3(2)	-3(2)
C(10)	42(2)	36(2)	83(3)	3(2)	1(2)	-4(2)
C(10A)	43(2)	38(2)	52(2)	-2(2)	5(2)	-3(2)
O(11)	61(2)	60(2)	34(1)	-2(1)	-3(1)	-14(2)
C(12)	50(2)	65(3)	67(3)	13(2)	-1(2)	6(2)
C(1')	39(2)	36(2)	47(2)	-1(2)	-5(2)	3(2)
C(2')	49(2)	58(3)	52(2)	-5(2)	-7(2)	-5(2)
C(3')	47(2)	67(3)	74(3)	-2(3)	-14(2)	-12(2)
C(4')	47(2)	77(3)	79(3)	22(3)	-9(2)	-23(2)
C(5')	71(3)	93(4)	63(3)	22(3)	-5(2)	-29(3)
C(6')	53(2)	68(3)	53(3)	9(2)	-9(2)	-19(2)

[a] The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

Table 12
Bond Lengths [Å] and Angles [°] for **5a**

Bond	Length
Cl-C(4')	1.748(4)
S(1M)-O(3M)	1.416(3)
S(1M)-O(1M)	1.438(3)
S(1M)-O(2M)	1.444(4)
S(1M)-C(1M)	1.736(5)
N(1)-C(10A)	1.328(5)
N(1)-C(2)	1.376(5)
N(1)-C(12)	1.466(4)
C(2)-C(3)	1.340(6)
C(3)-N(4)	1.376(5)
N(4)-C(10A)	1.340(5)
N(4)-C(5)	1.476(5)
C(5)-C(6)	1.511(6)
C(6)-O(11)	1.431(5)
C(6)-C(7)	1.502(6)
C(7)-O(8)	1.429(4)
O(8)-C(9)	1.427(4)
C(9)-O(11)	1.409(4)
C(9)-C(1')	1.503(4)
C(9)-C(10)	1.532(5)
C(10)-C(10A)	1.489(5)
C(1')-C(6')	1.375(5)
C(1')-C(2')	1.380(5)
C(2')-C(3')	1.385(5)
C(3')-C(4')	1.350(7)
C(4')-C(5')	1.370(7)
C(5')-C(6')	1.383(6)
O(3M)-S(1M)-O(1M)	115.6(3)
O(3M)-S(1M)-O(2M)	112.5(3)
O(1M)-S(1M)-O(2M)	109.9(3)
O(3M)-S(1M)-C(1M)	107.6(3)
O(1M)-S(1M)-C(1M)	106.3(3)
O(2M)-S(1M)-C(1M)	104.2(3)

Table 12 (continued)

Bond	Length
C(10A)-N(1)-C(2)	109.2(3)
C(10A)-N(1)-C(12)	125.8(3)
C(2)-N(1)-C(12)	125.0(3)
C(3)-C(2)-N(1)	107.0(3)
C(2)-C(3)-N(4)	107.5(4)
C(10A)-N(4)-C(3)	108.5(3)
C(10A)-N(4)-C(5)	128.4(3)
C(3)-N(4)-C(5)	122.9(3)
N(4)-C(5)-C(6)	114.3(3)
O(11)-C(6)-C(7)	102.7(3)
O(11)-C(6)-C(5)	111.8(3)
C(7)-C(6)-C(5)	115.9(4)
O(8)-C(7)-C(6)	103.7(3)
C(9)-O(8)-C(7)	108.5(3)
O(11)-C(9)-O(8)	106.8(3)
O(11)-C(9)-C(1')	110.1(3)
O(8)-C(9)-C(1')	110.3(3)
O(11)-C(9)-C(10)	110.8(3)
O(8)-C(9)-C(10)	107.6(3)
C(1')-C(9)-C(10)	111.1(3)
C(10A)-C(10)-C(9)	114.1(3)
N(1)-C(10A)-N(4)	107.8(3)
N(1)-C(10A)-C(10)	123.3(4)
N(4)-C(10A)-C(10)	128.9(4)
C(9)-O(11)-C(6)	106.5(3)
C(6')-C(1')-C(2')	118.6(2)
C(6')-C(1')-C(9)	119.6(3)
C(2')-C(1')-C(9)	121.8(2)
C(1')-C(2')-C(3')	120.7(2)
C(4')-C(3')-C(2')	119.4(4)
C(3')-C(4')-C(5')	121.4(4)
C(3')-C(4')-Cl	119.0(4)
C(5')-C(4')-Cl	119.6(4)
C(4')-C(5')-C(6')	119.1(5)
C(1')-C(6')-C(5')	120.8(4)

Table 13
Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters (Å^2 x 10^3) for **5a**

Atom	x	y	z	U(eq)
H(1MC)	2104(3)	647(6)	1655(7)	80
H(1MB)	2172(3)	1919(6)	925(7)	80
H(1MA)	2568(3)	1740(6)	2330(7)	80
H(2A)	5474(2)	6314(4)	1680(4)	80
H(3A)	4879(3)	7708(4)	37(4)	80
H(5B)	3443(3)	6676(4)	-1738(4)	80
H(5A)	3554(3)	7980(4)	-1085(4)	80
H(6A)	2242(2)	7645(4)	-1252(4)	80
H(7B)	2722(3)	8227(4)	1068(4)	80
H(7A)	1817(3)	8036(4)	741(4)	80
H(10B)	3059(2)	4353(4)	1733(5)	80
H(10A)	3082(2)	4165(4)	197(5)	80
H(12C)	5055(1)	4396(2)	2902(2)	96
H(12B)	4492(1)	3562(2)	2034(2)	91
H(12A)	4152(1)	4369(2)	3175(2)	95
H(2')	1134(1)	4473(2)	-764(2)	80
H(3'A)	72(2)	3279(4)	-170(5)	80
H(5')	762(3)	3511(5)	3617(5)	80
H(6')	1835(2)	4681(4)	3025(4)	80

EXPERIMENTAL

All research chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI. Dichloromethane and pyridine were dried by storage over 4 Å molecular sieves. Anhydrous acidic solutions of ketals were worked up by pouring *into* ice-cold 1 *M* aqueous sodium carbonate or other basic solutions, (*p*H of 8 or higher). Extraction of organic products used either dichloromethane or ethyl acetate and the extracts were washed once or twice with brine and dried (sodium sulfate) before removing solvents, *in vacuo*. Evaporation of solvents, *in vacuo*, utilized a rotary flash evaporator at a water pump (20-30 Torr) between 30-40°. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. 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 by iodine vapor. Column or flash chromatography was carried on Aldrich grade 60 Å silica gel (70-230 or 200-400 mesh), the latter usually giving better separations. If the product was a gum, it was dried (50-70°) at 1Torr prior to microanalysis. Elemental analyses were obtained by Midwest Microlab, Indianapolis, IN.

The ^1H And ^{13}C nmr spectra were recorded on a Varian XL-300 spectrometer, at 299.9 and 75.4 MHz, respectively. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane for organic solvents, and from sodium 3-(trimethylsilyl)propanesulfonate in deuterium oxide. Additional APT, COSY, HETCOR, homonuclear decoupling nOe experiments were performed on the same instrument using standard pulse sequences. Centers of complex multiplets are reported as their chemical shifts. Selected chemical shifts and coupling constants are complied in Tables 1 and 2.

cis- And *trans*-{2-(4-Chlorophenyl)-2-[(1-methyl-2-imidazolyl)methyl]-4-hydroxymethyl}-1,3-dioxolane (**2a**) and *trans*-{2-(4-Chlorophenyl)-2-[(1-methyl-2-imidazolyl)methyl]-5-hydroxy}-1,3-dioxane (**3a**).

A mixture of **1a** [6] (3.49 g, 0.015 mole), glycerol (5.53 g, 0.06 mole), methanesulfonic acid (14.4 g, 0.15 mole) in benzene (20 ml) was refluxed (4 hours), with azeotropic removal of water. The mixture was concentrated, *in vacuo*, and the residue was poured into ice-cold sodium bicarbonate solution. The product was extracted into dichloromethane (2 x 50 ml), dried and solvents removed, *in vacuo*. The gummy residue showed three major spots on tlc (chloroform-methanol, 97:3): R_f = 0.44 (*cis*-**2a**), 0.38 (**3a**), 0.33 (*trans*-**2a**). Using the resonances at δ 7.00, 6.94 and 7.05 in the ^1H-nmr spectrum (deuteriochloroform), the ratio of *cis*-, *trans*-**2a** and *trans*-**3a** was estimated to be approximately 68:25:07. Since this oil tended to color after 2 days, it is best to chromatograph as soon as possible. Chromatography of the gum (4.5 g) on silica gel (100 g, 70-230 mesh) was carried out and 125 ml fractions were collected. Elution started with dichloromethane-methanol (49:1), the first 3 fractions containing highly colored compounds which were not investigated further. The next 8 fractions yielded *cis*-**2a** (2.67 g, 60%), first as a gum which crystallized upon trituration with ether, mp 112.5-113.5°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_3$: C, 58.35; H, 5.55; N, 9.07. Found: C, 58.07; H, 5.49; N, 8.95.

The next 3 fractions contained a mixture of mainly **3a** admixed with a small amount of *trans*-**2a**. Rechromatography on silica gel (200-400 mesh) and elution with chloroform-methanol (49:1) provided **3a** (0.12 g, 3%) as a gum which solidified upon trituration with ether, mp 179-181°.

Anal. Calcd. for $C_{15}H_{17}ClN_2O_3$: C, 58.35; H, 5.55; N, 9.07. Found: C, 58.25; H, 5.90; N, 8.99.

Further elution from the original column (above) with dichloromethane-methanol (97:3 and then 24:1) afforded *trans*-**2a** as a colorless gum (0.7 g, 16%).

Anal. Calcd. for $C_{15}H_{17}ClN_2O_3 \cdot 0.5H_2O$: C, 56.70; H, 5.71; N, 8.82. Found: C, 56.89; H, 5.70; N, 8.61.

cis- And *trans*-2-(2,4-Dichlorophenyl)-2-[(1-methyl-2-imidazolyl)methyl]-4-hydroxymethyl-1,3-dioxolane (**2b**).

Ketone **1b** [3] (4.04 g, 0.015 mole) was condensed with glycerol (5.53 g, 0.06 mole) in the presence of methanesulfonic acid (14.4 g, 0.15 mole) in boiling benzene (20 ml) with azeotropic removal of water (4 hours). After a similar work-up to that described for the isolation of **2a**, there was obtained after chromatography on silica gel, *cis*-**2b**, (dichloromethane-ethanol, 97:3) first as an oil which solidified under hexane:ether (1:1) to a colorless powder (1.4 g, 27%). Recrystallization from dichloromethane-hexane (1:9) afforded a solid, mp 118.5-120°; tlc, R_f = 0.5 (dichloromethane-ethanol, 9:1).

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O_3$: C, 52.49; H, 4.70; N, 8.16. Found: C, 52.29; H, 4.67; N, 8.04.

Further elution with the same solvent furnished *trans*-**2b** as a light orange syrup (0.2 g, 4%); tlc, R_f = 0.45 (dichloromethane-ethanol, 9:1).

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O_3 \cdot 0.6CHCl_3$: C, 45.17; H, 4.03; N, 6.75. Found: C, 45.28; H, 4.11; N, 6.61.

cis-{2-(4-Chlorophenyl)-2-[(1-methyl-2-imidazolyl)methyl]-4-methanesulfonyloxy}-1,3- dioxolane Hydrochloride (*cis*-**4a**•HCl).

Methanesulfonyl chloride (0.6 ml, 0.89 g, 7.75 mmoles) was added dropwise to a stirred solution of *cis*-**2a** (1.94 g, 6.28 mmoles) in dry dichloromethane (25 ml) containing dry pyridine (1 ml, 0.98 g, 12.4 mmoles) at 0°. After stirring the mixture at room temperature for 14 hours, colorless **4a** hydrochloride (1.54 g, 58%) was filtered, washed with small portions of dry dichloromethane and dried, mp 153°. The *salt* was stable in boiling dichloromethane (24 hours).

Anal. Calcd. for $C_{16}H_{19}ClN_2O_5S$•HCl: C, 45.36; H, 4.76; N, 6.61. Found: C, 45.32; H, 4.72; N, 6.67.

Some of this salt remained dissolved in the mother liqor and washings. When such a dichloromethane solution of **4a** *hydrochloride* was washed with aqueous sodium hydroxide solution (25 ml), the organic layer separated, washed with water, dried and concentrated, *in vacuo*, there was obtained **4a** (0.75 g, 30%) as an oil. The ^1H nmr spectrum indicated that some pyridine adhered to this product. Cyclization of **4a** to **5a** is best carried out on samples devoid of pyridine. Pure **4a** is made best by neutralizing the above *hydrochloride* with sodium bicarbonate and extracting the base with dichloromethane, as described in the next experiment.

1-Methyl-6,9-epoxy-9-(4-chlorophenyl)-5,6,9,10-tetrahydro-1*H*-imidazo[3,2-*e*][2*H*-1,5]oxazocinium Methanesulfonate (**5a**).

Method A.

A suspension of *cis*-**4a** *hydrochloride* (1.0 g) in dichloromethane (25 ml) was neutralized by aqueous saturated sodium

bicarbonate solution (25 ml). The aqueous layer was extracted once more with dichloromethane (25 ml). The combined organic extract was dried and evaporated, *in vacuo,* to provide *cis*-**4a** (0.94 g, 100%) as a colorless oil; tlc, R_f = 0.5 (chloroform-methanol, 49:1). This oil was redissolved in dichloromethane (10 ml) and heated under reflux (17 hours). Upon cooling, **5a** crystallized out (0.55 g, 60%). Upon evaporation, *in vacuo*, there was obtained another batch of **5a** (0.35 g, for a total of 0.90 g, 98%), mp 197-199°. The *salt* could be recrystallized from dichloromethane or ethyl acetate.

Anal. Calcd. for $C_{16}H_{19}ClN_2O_5S \cdot H_2O$: C, 47.47; H, 5.23; N, 6.92. Found: C, 47.64; H, 5.15; N, 6.92.

Method B.

To a suspension of sodium hydride (60% suspension in mineral oil, 0.014 g, 0.356 mmole) in ice-cold anhydrous tetrahydrofuran (2 ml) was added the *cis*-**2a** (0.10 g, 0.324 mmole) in anhydrous tetrahydrofuran (2 ml). After 5 minutes, methanesulfonyl chloride (0.03 ml, 0.36 mmole) was added and the mixture stirred at room temperature (2 hours). Solvents were removed at room temperature, *in vacuo*, and the residue was diluted with dichloromethane. The organic layer was extracted with ice-cold aqueous sodium bicarbonate solution (3 x 40 ml). The extract was dried (sodium sulfate) and was evaporated, *in vacuo,* at room temperature to yield a brownish crude oil of *cis*-**4a**. This product was refluxed in chloroform (10 ml, 4 hours) and solvents removed, *in vacuo*. To provide **5a** (0.08 g, 64%, based on *cis*-**2a**), identical to **5a** made in Method A.

cis-{2-(2,4-Dichlorophenyl)-2-[(1-methyl-2-imidazolyl)methyl]-4-methanesulfonyloxy}-1,3-dioxolane Hydrochloride (*cis*-**4b** •HCl).

A mixture of *cis*-**2b** (0.2 g, 0.58 mmole), dry pyridine (0.05 ml), methanesulfonyl chloride (0.1 ml, 0.15 g, 1.13 mmoles) was stirred at room temperature (18 hours). The mixture was filtered, washed with dichloromethane (2 x 2 ml) to yield *cis*-**4b** *hydrochloride* (0.061 g, 23%), mp 142-144°.

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O_5S \cdot HCl$: C, 41.98; H, 4.18; N, 6.12. Found: C, 41.98; H, 4.15; N, 6.01.

The mother liquor was not investigated for additional product.

cis-2-(2,4-Dichlorophenyl)-2-[(1-methyl-2-imidazolyl)methyl]-4-methanesulfonyloxy-1,3-dioxolane (**4b**) and 1-Methyl-6,9-epoxy-9-(2,4-dichlorophenyl)-5,6,9,10-tetrahydro-1*H*-imidazo[3,2-*e*][2*H*-1,5]oxazocinium Methanesulfonate (**5b**).

Method A.

Methanesulfonyl chloride (0.3 ml, 0.45 g, 3.38 mmoles) was added to a stirred solution of *cis*-**2b** (1.07 g, 3.14 mmoles) in dry dichloromethane (15 ml) containing dry pyridine (0.5 ml, 0.49 g., 6.2 mmoles) at room temperature. After 14 hours, the mixture was partitioned between dichloromethane and sodium hydroxide and *cis*-**4b** was obtained, from the organic extract as a thick oil (1.30 g). This product was dissolved in dichloromethane (20 ml), boiled 17 hours, cooled, and then diluted with water 25 ml). Upon evaporation of the aqueous layer, *in vacuo* (1 Torr), **5b** (1.25 g, 95%) was obtained, mp 219-220°.

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O_5S$: C, 45.62; H, 4.31; N, 6.65; S, 7.61. Found: C, 45.68; H, 4.25; N, 6.62; S, 7.46.

Method B.

When *cis*-**2b** (0.5 g, 1.46 mmoles) was reacted first with sodium hydride (0.064 g, 1.74 mmoles) in ice-cold anhydrous tetrahydrofuran (15 ml), and then (after 5 minutes) with methanesulfonyl chloride (0.12 ml, 1.60 mmoles) in anhydrous tetrahydrofuran (10 ml), as described for *cis*-**2a**, there was obtained crude *cis*-**4b** as a brown oil (0.71 g); tlc, R_f = 0.62 (chloroform-methanol, 99:1). Upon refluxing a solution of this oil in chloroform (10 ml, 20 hours), evaporation of solvents, *in vacuo*, there was obtained a colorless solid which was recrystallized from ethyl acetate to provide **5b** (0.538 g, 88%), which was identical to the *salt* made by Method A.

1-Methyl-5,6-dihydro-6-hydroxymethyl-8-(4-chlorophenyl)-1*H*-imidazo[3,2-*d*][1,4]oxazepinium Methanesulfonate (**7a**).

A solution of **5a** (0.570 g, 1.47 mmoles) in 6.0 ml of 0.5 *N* sodium hydroxide was stirred at room temperature (18 hours). The solution was cooled at 0° by the addition of crushed ice and neutralized (*p*H 7) with a solution of methanesulfonic acid (0.3 g) in water (0.3 ml). Water was evaporated, *in vacuo*, at room temperature to give a white solid. The solid was suspended in chloroform (50 ml) and was filtered from a colorless solid (0.526 g). The filtrate was evaporated, *in vacuo*, and residue was triturated with dichloromethane (5 ml) and the solid was filtered, washed with dichloromethane to give the title compound (0.206 g, 36%) as a colorless solid, mp 190-191°.

Anal. Calcd. for $C_{16}H_{19}ClN_2O_5S$: C, 49.68; H, 4.95; N, 7.24. Found: C, 49.40; H, 4.91; N, 7.12.

1-Methyl-6-hydroxymethyl-8-(2,4-dichlorophenyl)-5,6-dihydro-1*H*-imidazo[2,3-*d*][1,4]oxazepin-4-ium Methanesulfonate (**7b**).

A solution of **5b** (0.211 g, 0.5 mmole) in 2 ml of 0.5 *N* sodium hydroxide was stirred at room temperature for 17 hours. The solution was cooled (0°), neutralized by a solution of methanesulfonic acid (0.1 g) in water (2 ml) to achieve *p*H 7. Water was evaporated, *in vacuo*, and the semisolid remaining was suspended in chloroform (50 ml). After warming on a water bath for few seconds dissolve the product, the mixture was filtered to remove sodium methanesulfonate (0.110 g, ^{1}H nmr, δ 2.82 in deuterium oxide). The filtrate was evaporated, *in vacuo*, to give oily residue (0.200 g) which was dissolved again in chloroform (40 ml) and was filtered. The filtrate was evaporated, *in vacuo*, and residue (0.180 g) was triturated with dichloromethane (5 ml). The solid was filtered and washed with dichloromethane (5 ml) to give **7b** (0.120 g, 57%) as colorless solid, mp 194-196°.

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2O_5S$: C, 45.62; H, 4.31; N, 6.65. Found: C, 45.59; H, 4.26; N, 6.59.

1-Methyl-2-[4-chlorophenacyl]-3-[(2,3-dihydroxy)-1-propyl]imidazolium Chloride (**12a**).

A mixture of **5a** (0.194 g, 0.5 mmole) and 12% hydrochloric acid (3 ml) were refluxed (2 hours). Solvents were removed, *in vacuo*, first at 30 torr, then at 1 torr. The ^{1}H nmr spectrum indicated that the residue consisted mainly of **12a**, admixed with **7a** (approximately 5%). The oil (0.2 g) was dissolved in methanol (2 ml) and diluted with dichloromethane (20 ml). After 2 days, crystalline **12a** (0.020 g, 11%), separated as the chloride, since no nmr signal for the methyl group of the methanesulfonate was observed, mp 178-180°.

Anal. Calcd. for $C_{15}H_{18}Cl_2N_2O_3 \cdot 0.5H_2O$: C, 50.86; H, 5.41; N, 7.91. Found: C, 51.08; H, 5.18; N, 7.72.

1-Methyl-2-[2,4-dichlorophenacyl]-3-[(2,3-dihydroxy)-1-propyl]imidazolium Methanesulfonate (**12b**).

A mixture of **5b** (0.105 g, 0.25 mmole) and 6% hydrochloric acid (2 ml) was refluxed for 17 hours. Solvents were removed, *in*

vacuo, first at 30 torr, then at 1 torr. The ^1H nmr spectrum that the residue consisted mainly of **12b**, with some **7b** (approx 5%). The oil (0.11 g) was chromatographed on silica gel (3 g). Elution with dichloromethane-methanol (3:1 to 1:1) provided **12b** (0.08 g, 73%) as a gum.

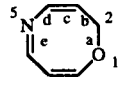
Anal. Calcd. for $C_{16}H_{20}Cl_2N_2O_6S \cdot H_2O$: C, 42.02; H, 4.85; N, 6.13. Found: C, 41.64; H, 4.99; N, 6.23.

Acknowledgments.

Support of this work by the National Institute Child Health and Human Development through Research Contract HHS N01-HD-3-3178 is gratefully acknowledged. We thank Dr. H. K. Kim for helpful suggestions.

REFERENCES AND NOTES

[1a] Presented in part, 206th American Chemical Society National Meeting, Chicago Illinois, August 23, 1993, Organic Abstract, No. 337; [b] Nomenclature of the ring system is based on 2*H*-1,5-oxazocine ring system:



2*H*-1,5-oxazocin

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