Reactions of Aromatic Ketones with 3-Mercapto-1,2-propanediol. Synthesis of *cis*- and *trans*-2-Alkyl-2-aryl-(1,3-oxathiolane-5-methanols and 1,3-dioxolane-4-methanethiols)

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Dedicated to Professor Charles D. Hurd on the occasion of his 95th birthday

Aromatic ketones react with 3-mercapto-1,2-propanediol (**1**) in refluxing benzene under the catalytic influence of a sulfonic acid and with azeotropic removal of water to yield a mixture comprised predominantly of *cis*- and *trans*-2-alkyl-2-aryl-1,3-oxathiolane-5-methanols **7**, accompanied by lesser amounts of *cis*- and *trans*-2-alkyl-2-aryl-1,3-dioxolane-4-methanethiols **8** (up to 30%). It was discovered that **8** is the kinetic product and is isomerized by 4-toluenesulfonic acid in hot benzene to the thermodynamically more stable **7**. Under these conditions, *ortho*- and α-substituted aromatic ketones tend to produce more of **8**, which can be attributed to steric hindrance encountered by the thiol as it attacks the ketone. Ketalizations of 1-aryl-2-(1*H*-imidazol-1-yl)-1- as well as 1-aryl-2-(1*H*-1,2,4-triazol-1-yl)-1-ethanones by **1** fail under these conditions, even after 24 hours of reflux in toluene. However, 1-(4-chlorophenyl)-3-(1*H*-imidazol-1-yl)-1-propanone and 1-(4-bromophenyl)-4-(1*H*-imidazol-1-yl)-1-butanone are ketalized by **1** as expected. Interestingly, the reaction of 2-bromo-4'-chloroacetophenone with **1** produces 1-(4-chlorophenyl)-2,8-dioxa-6-thiabicyclo[3.2.1]octane. Characterization of all isomers and separation of some diastereomers is described. Nuclear Overhauser enhancement experiments are utilized to establish the stereochemistry of 1,3-oxathiolanes.

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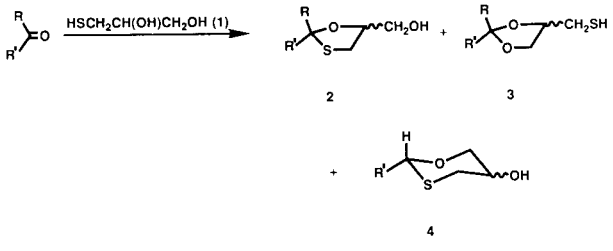
Introduction.

1,3-Oxathiolanes are synthesized readily through acid-catalyzed condensations of aldehydes and ketones with *vicinal* mercapto alcohols [1-11]. These reactions tend to become more complicated when additional groups are in close proximity to either the mercapto alcohol system or the carbonyl group of the aldehyde or ketone. For example, reactions of 3-mercapto-1,2-propanediol (**1**), which had been synthesized unequivocally by Sjöberg in 1942 [12], condenses with aldehydes and ketones. With aldehydes there is formed a mixture of *cis*- and *trans*-1,3-oxathiolanes **2**, *cis*- and *trans*-1,3-dioxolanes **3** and *cis*- and *trans*-1,3-oxathianes **4**. In contrast, with ketones only **2** and **3** are formed [3,7-11].



2 3 4

where R, R' can be H, alkyl or aryl

Sjöberg reported that acetone reacts with **1**, in the presence of phosphorus pentoxide, to produce 2,2-dimethyl-1,3-oxathiolane-5-methanol (**2**, R = R' = CH_3) and 2,2-dimethyl-1,3-dioxolane-4-methanethiol (**3**, R = R' = CH_3) in 78% yield, in the ratio of 65:35. He isolated his products by vacuum distillation and then separated **3** from **2** by sodium hydroxide extraction. However, Sjöberg also noted that upon standing about a month, **3** tended to rearrange to **2** [12].

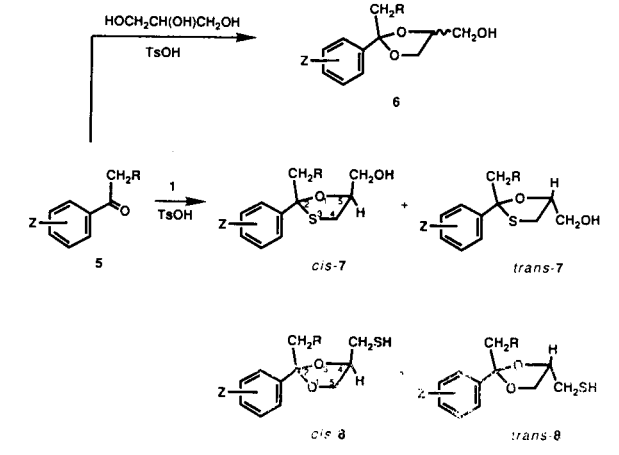
Ketalizations of Aromatic Ketones.

Since ketalizations of alkyl aryl ketones **5** with glycerol yield only *cis*- and *trans*-2-alkyl-2-aryl-1,3-dioxolane-4-methanols **6** (and no 1,3-dioxanes) [13,14], it is not surprising that similar reactions of **5** with **1** provide five-membered heterocycles only, the major product being *cis*- and *trans*-2-alkyl-2-aryl-1,3-oxathiolane-5-methanols **7**, accompanied usually by *cis*- and *trans*-2-alkyl-2-aryl-1,3-dioxolane-4-methanethiols **8** (as much as 30%). The stereo-nomenclature adopted in this paper parallels the one used for structurally related *cis*- and *trans*-2-alkyl-2-aryl-4-alkyl-1,3-dioxolanes **6** [13,14]. Thus, the alkyl chains at C-2 and C-5 (or C-4) are on the *same* side of the heterocyclic ring for the *cis*-isomers and on opposite sides for the *trans*-isomers.

Ketalization of **5** by **1** takes place relatively fast (2-8 hours) and on a preparative scale is deemed complete when benzene (or toluene) distillates indicate that azeotropic distillation of water has ceased. These reactions can be monitored by thin layer chromatography (tlc) based on the (virtual) disappearance of the starting ketone. However, a better understanding is gleaned by following the

progress of these reactions by means of ^1H and ^{13}C nuclear magnetic resonance (nmr) spectra. Such time-study experiments shed considerable light on the course of these reactions.

Böhm has investigated extensively acid-catalyzed condensations of aldehydes and ketones with a slight excess of **1** in boiling benzene (or toluene) with azeotropic removal of water (2-5 hours) [3]. For example, he reports that the reaction of 4-chloroacetophenone (**5a**) with **1**, in the presence of a catalytic amount of 4-toluenesulfonic acid (TsOH, 0.0026 molar equivalents of **5a**) yields only **7a** (70%) [3]. Böhm was aware of the potential presence of **8a** but suggests that such thiols are removed during an aqueous basic workup. We find thiols **8** in our series to be insoluble in aqueous sodium hydroxide solution. Böhm reports no attempts to separate *cis*- and *trans*-**7a**, but treated them with phosgene, and then ammonia, to obtain crystalline products consisting of mixtures of *cis*- and *trans*-carbamates of **7a** [3].



where a, R = H, Z = 4-Cl; b, R = H, Z = 2-Cl; c, R = H, Z = 2,4-Cl_2; d, R = C_6H_5, Z = H; e, R = 1-imidazolyl, Z = 2,4-Cl_2; f, R = 1,2,4-triazolyl, Z = 4-Cl; g, R = CH_2-1-imidazolyl, Z = 4-Cl; h, R = $(CH_2)_2$-1-imidazolyl, Z = 4-Br

In repeating the condensation of **5a** with **1**, it is expeditious to use a somewhat larger quantity of TsOH (0.02 molar equivalent of **5a**, 7.7 times as much as used by Böhm) since this permitted faster completion of the reactions. Ketalization of a 1 molar solution of **5a** by **1** in boiling benzene is virtually complete after 1.5 hours to give *cis*- and *trans*-**7a** and *cis*- and *trans*-**8a** (97:3) in 89% overall yield. The course of this reaction is best followed by nmr. In such a study, the ketone is added to a boiling mixture of the other (already azeotropically-dried) ingredients and aliquots are withdrawn at suitable intervals. Samples are quenched by aqueous base, worked up as usual, and their ^1H and ^{13}C nmr spectra analyzed. Integration of areas under the methyl signals provided an estimate of the ratio of starting ketone **5a** to that of expected products, **7a** and **8a**. Integration of as many pertinent and relatively well-separated ^1H nmr signals provided estimates of *cis*- and *trans*-isomer distributions of **7a** and **8a**. The data are listed in Table 1.

Table 1

Product Ratios from Reactions of 1 with 5a, 5b and 5c

Ketone	Concentration of 5 [a]	Time Min [b]	Yield % [c]	Ratios [d]		
			7 and 8	7:8	*cis*: *trans* 7	*cis*: *trans* 8
5a	0.6	1	15	47:53	26:74	61:39
		5	43	56:44	34:66	64:36
		10	68	62:38	46:54	65:35
		30	92	69:31	64:36	64:36
		60	93	72:28	65:35	69:31
	1.0	10	80	79:21	60:40	70:30
		90	89	97:3	70:30	70:30
5b	0.6	6	15	32:68	13:87	62:38
		15	35	46:54	15:85	68:32
		60	70	60:40	26:74	66:34
		90	90	70:30	40:60	65:35
		135	95	82:18	55:45	73:27
5c	0.6	6	8	23:77	12:88	54:46
		15	24	34:66	16:84	60:40
		30	46	42:58	15:85	64:36
		60	76	53:47	17:83	68:32
		130	84	59:41	22:78	75:25
		240	89	62:38	33:67	70:30
	2.0	5	30	28:72	15:85	70:30
		10	52	43:57	15:85	67:33
		20	60	55:45	18:82	71:29
		30	68	64:36	19:81	67:33
		40	86	68:32	21:79	69:31
		55	90	69:31	27:73	65:35
		90	95	74:26	30:70	75:25
		480	95	78:22	60:40	70:30

[a] Molar concentration of ketone in benzene; concentration of **1** was 1.2 equivalents and that of TsOH, 0.02 equivalent of ketone. [b] Time intervals between addition of ketone to boiling benzene solution and withdrawal of aliquots for nmr analysis. [c] Percent conversion of **5** to **7** and **8**, from integration of proton nmr spectra. [d] Ratio of *cis*/*trans* isomers determined from various proton nmr signals.

In the early stages of the reaction of **5a** with **1**, *cis*- and *trans*-1,3-dioxolanes **8a** are formed faster than *cis*- and *trans*-1,3-oxathiolanes **7a**, but this ratio changes dramatically with time (Table 1). Furthermore, the ratio of *cis*- and *trans*-isomers of **8a** remains virtually constant from begin-

ning to end (about 60-70%, *cis*-) the ratio of *cis*- and *trans*-isomers of **7a** alters drastically. We conclude that overall, *cis*- and *trans*-**8a** (as well as *trans*-**7a**) are the kinetic, and **7a** (particularly *cis*-**7a**) the thermodynamic products.

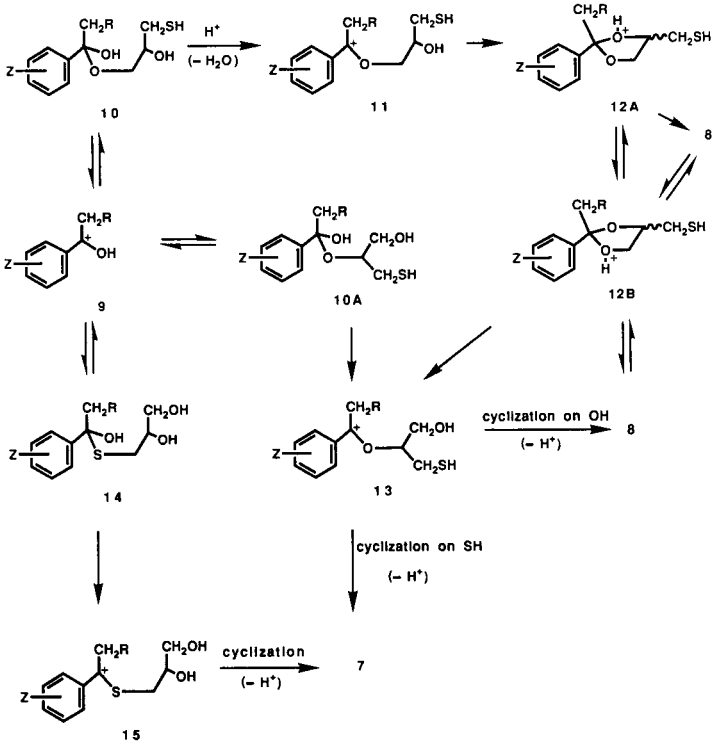
In light of these experiments with **5a**, and in an effort to establish the universality of these condensations of **5** with **1**, we explored cognate reactions of 2,4-dichloroacetophenone (**5c**). The progress of two reactions (starting with 0.6 and 2.0 *M* of **5c**, 1.125 equivalents of **1**, 0.02 equivalents of TsOH, in benzene) was followed by nmr and constituents estimated at certain time intervals to develop a reaction profile (Table 1). Early on, (6 minutes after benzene commences to boil) **8c** is formed predominantly in a mixture of **7c** and **8c** (28:72). This ratio is reversed to 74:26, after 1.5 hours of reflux.

The product of ketalization of a fairly concentrated solution of **5a** with **1** in benzene consists primarily of **7a** and is virtually devoid of **8a**, (after 90 minutes). But, a similar reaction of **5c** furnishes **7c** admixed with a considerable amount of **8c** (26%). This raises the question of whether an *ortho*-substituent, like the *o*-chloro substituent, exerts a steric effect. Heeres and Cutsem, in studying the ketalization of a number of aromatic ketones with glycerol, already noted that the presence of an *ortho*-substituent in such ketones "required larger amounts of TsOH and longer reaction times, while yields were significantly lower" [15].

It is apparent that a number of isomerizations occur during these reactions. In an effort to examine some of these transformations independently, the following experiments were carried out. The first one examines the rearrangement of **8** to **7**. Upon boiling a mixture of *cis*- and *trans*-**8c** (70:30, isolated by chromatography) in benzene with anhydrous TsOH for 1.5 hours, there is formed *cis*- and *trans*-**7c** (40:60, 65%) with *cis*- and *trans*-**8c** (70:30, 35%) remaining. The next experiments examines the isomerization of *cis*-**7c** to *trans*-**7c**. Under the same experimental conditions, but for 4 hours, a pure mixture of *cis*- and *trans*-**7c** (30:70, isolated from a "short period" experiment of **5c**) produces 88% of *cis*- and *trans*-**7c**, with *cis*-**7c** now predominating (70:30), and 12% of *cis*- and *trans*-**8c** (70:30). To follow up Sjöberg's observation that **3** rearranges to **2** (R = R′ = CH_3) after 1 month, a sample of *cis*- and *trans*-**8c** (70:30) which had stood at room temperature for 6 months was rechromatographed. There is isolated pure (by nmr) *trans*-**7c** (7%) whose stereochemistry is confirmed by a nuclear Overhauser enhancement (noe) experiment.

To test if an *ortho*-chloro group influences the ratio of **7** to **8**, ketalization of 2-chloroacetophenone (**5b**) with **1** was examined in some detail. After 1 hour, there is formed *cis*- and *trans*-**7b** and *cis*- and *trans*-**8b** in 70% yield, compared to a 93% yield of **7a** and **8a** from **5a**. Even after a much longer reaction period, the percentage of **8b** in the mixture of **7b** and **8b** tended to be larger. The only other reaction mixture which tended to produce a larger percentage of **8** (30%) is the one from deoxybenzoin (**5d**). These observations suggest that an *ortho*-substituent (*e.g.*

Chart I



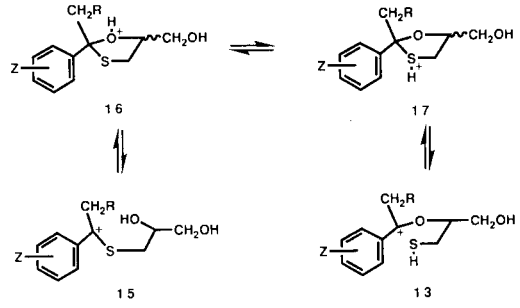
an *o*-chloro group in **5b**) or a relatively large α-substituent (*e.g.* a phenyl group in **5d**) offer some steric hindrance to 1,3-oxathiolane formation.

Mechanisms.

Standard mechanisms of acid-catalyzed ketalizations (Chart I) commence with protonation of ketone **5** to generate conjugate acid **9** which then reacts with one of the nucleophilic groups of **1**. Since **8** appears to be formed quickly, it is reasonable to speculate that one of the two alcohols, in preference to the thiol of **1**, attacks **9**. One might surmise that the more accessible primary alcohol preferentially forms the hemiketal **10**. To proceed from **10** to the five-membered ketal **8**, the hemiketal hydroxyl is protonated, water is eliminated to create the favorable α-alkoxycarbonium ion **11**, which cyclizes with the secondary alcohol to produce **8**, *via* oxonium ion **12A**. It must be stressed that the absence of the six-membered 1,3-oxathiane in the product precludes that **11** is cyclized by the thiol.

Although logical for the primary, rather than the secondary alcohol of **1** to attack **9** initially, one cannot dismiss the possibility that the ketalization commences with attack of the secondary alcohol to form the isomeric hemiketal **10A**. It is important to consider this alternate route because **10A** is the precursor to carbonium ion **13**. This particular carbonium ion, which is considered the pivotal intermediate, can explain rearrangements of **8** → **7**, as well as that of *cis*- and *trans*-isomers. Carbonium ion **13** can be formed if **8** is protonated on the seemingly more exposed ring oxygen to generate oxonium ion **12B**, (in equilibrium with **12A**, by proton transfer) which opens to **13**. Cyclization of **13** can lead to either *cis*- and *trans*-**7** or *cis*- and *trans*-**8**.

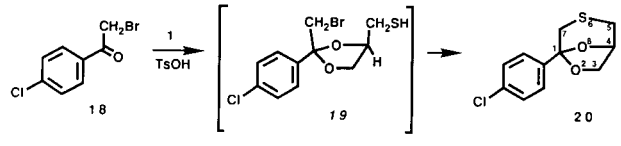
Although the above paths suggest that the alcohols of **1** really start the sequence of events (**5** → **7** and **8**), one can not rule out competing attack by the thiol on **9** to generate **14**. Cyclization of **14** through carbonium ion **15** would also lead to **7**. However, the initial high ratio of **8** in the product tends to argue against this route being a major beginning one. Unfortunately, it is rather difficult to ascertain how much of *cis*- and *trans*-**7** are formed by this direct route, *via* **14**, or by the rearrangement of *cis*- and *trans*-**8**. All isomerizations involve a considerable amount of ring openings-closings. While ring opening of **8** is activated through oxonium-carbonium (particularly as stable α-alkoxycarbonium) ions, those of **7** are more complex. One has to consider protonation on the ring oxygen or sulfur of **7** to generate **16** or **17**. What are the relative propensities of these cations to break the C-O or C-S bond to form **15** or **13**, respectively, and what are the relative stabilities of the corresponding resonance-stabilized α-alkoxycarbonium ions **13** and α-thioether-carbonium ions **15** [16,17]? There is precedent in the literature when it is reported that unsymmetical 2,2-(4-*t*-butylcyclohexylidene)-1,3-oxathiolane undergoes *cis-trans* isomerization catalyzed by Lewis acids [18].



Similar reactions of **1** with 2-chloroacetophenone (**5b**), 2,4-dichloroacetophenone (**5c**) and deoxybenzoin (**5d**) produce mixtures of *cis*- and *trans*-**7b-d** and *cis*- and *trans*-**8b-d**, with a relative large percentage of **8** (25-30%, compared to products from **5a**). One can surmise that some steric effects are operating during ring closure of carbonium ions as **11** and **13**. It is plausible that the bulkier thiol (compared to the alcohol) may encounter some steric hindrance offered by the *o-chloro substituent or by the relatively large phenyl group* α to the carbonium ion, thereby favoring faster ring closure by the alcohol of **11** or **13** to form **8**. One can extrapolate this hypothesis to some literature results also: as the size of the CH_2R gorup in **5** increases from methyl to propyl (acetophenone to butyrophenone), the yield of **7** from ketalizations of with **1** diminishes from 75 to 48% [3]. To test such a hypothesis further, a series of experiments would have to be designed utilizing suitable, large *o*- or α-substituents in **5**.

Ketalizations of Phenacyl Halides by **1**.

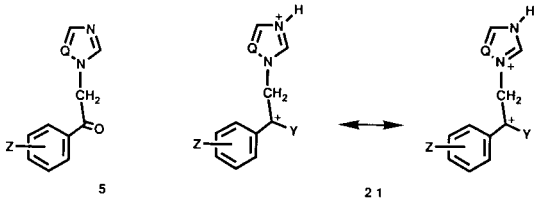
Ketalizations of some substituted acetophenones with **1** provide some interesting results. The reaction of 2-bromo-4'-chloroacetophenone (**18**) with **1** furnishes a solid which is identified as 1-(4-chlorophenyl)-2,8-dioxa-6-thiabicyclo-[3.2.1]octane (**20**). The *des*-chloro analog had been synthesized previously [10]. The structure of **20** is substantiated by comparison of its ^1H nmr parameters to those reported for the phenyl analog [10]. Furthermore, nmr spectra support the presence of two CH_2-S and one CH_2-O groups. This experiment corroborates the notion that the ketal **19** is the kinetic product which is forthwith frozen into the tricyclic system by virture of the formation of the fixed sulfide bridge in **20**. It is of interest to compare the results of the acid-catalyzed condensations of some phenacyl halides (including **18**) with glycerol to furnish the corresponding *cis*- and *trans*-2-aryl-2-halomethyl-4-hydroxymethyl-1,3-dioxolanes (in excellent yields) with no sign of the formation of an analogous tricyclic oxygen system [13].



Ketalizations of [ω-(1*H*-Imidazolyl- and (1*H*-1,2,4-Triazolyl)]alkyl Aryl Ketones with **1**.

A vexing problem is encountered as 1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (**5e**) and 1-(4-chlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (**5f**) fail to ketalize with **1**, even in boiling toluene (24 hours) and using an excess of anhydrous TsOH (1.2 equivalents of ketone). Starting ketones are recovered in good yields. This is surprising since glycerol reacts with these ketones, although at a slower rate and in the presence of excess sulfonic acid which is needed to neutralize first the azole and also be available as catalyst. For example, the reaction of **5e** with glycerol in the presence of 1.09 molar equivalent of TsOH, (24 hours, boiling toluene) gives *cis*- and *trans*-**6e** in 88% yield [13]. Similarly, 1-(4-fluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone is ketalized by glycerol in the presence of *26 equivalents* of methanesulfonic acid in boiling benzene (2 hours) to afford *cis*- and *trans*-2-(4-fluorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolane-4-methanol (97%) [19]. The 2,4-difluoro analog of the last ketone needed 3 hours of reflux to produce 67% of the corresponding 1,3-dioxolane analogs [19].

The failure of **5e** and **5f** to react with **1** presents an enigma since these ketones are ketalized by glycerol to form 1,3-dioxolanes **6** [13,19]. One can speculate that protonation of the imidazole or triazole creates an azolium cation *alpha* to the ketone which would discourage the first step (**5** → **9**), as well as formation of subsequent carbonium ion intermediates, such as **11**, **13** and **15**, generalized by structure **21**.

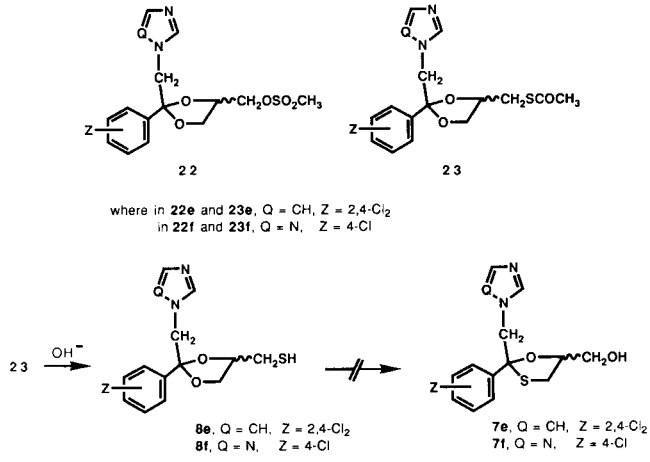


5 21

Yet, **5e** reacts with glycerol under these acidic conditions. Could it be that the thiol is less nucleophilic than oxygen in these acidic media, or encounters some steric hindrance as it approaches the carbonium ion center to form a C-S bond? Or it is, perhaps, that under these stringent acid conditions, **1**, unlike glycerol, loses water during the ketalizations easier and then polymerizes to a syrupy gum which is insoluble in hot toluene (also insoluble in methylene chloride).

There are several reports in the patent literature indicating that 2-mercaptoethanol reacts with *N*-phenacylazoles (like, **5e, 5f**), but only in the presence of 1-butanol and with exceptionally **long reaction times** to provide 1,3-oxathiolanes in realatively poor yield. For example, the reaction of 1-(1,1-biphenyl-4-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone in boiling toluene (also containing 1-butanol) for 72 hours produces the corresponding 1,3-oxathiolane in 42% yield [20]. Similarly, 1-(4-bromophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone condenses with 2-mercaptoethanol in boiling toluene (50 hours) to furnish the expected oxathiolane in 16% yield [21]. Careful scrutiny of the nmr spectra of products from our attempted reactions of **5e** and **5f** with **1** (up to 24 hours, and in the absence of 1-butanol) did not reveal characteristic signals of **7e** or **8e**, or **7f** or **8f**.

The discovery that anhydrous acids catalyze rearrangements of 4-mercaptomethyl 1,3-dioxolanes to 5-hydroxymethyl 1,3-oxathiolanes (**8** → **7**) suggests an alternate strategy for the synthesis of **7e** or **7f**. The ready availability of a number of 4-hydroxymethyl 1,3-dioxolane precursors prompted us to synthesize some of the prerequisite thiols, **8e** and **8f**, independently. Application of a time-honored thiol synthesis (**6e** → **8e**) proved unsuccessful. Thiourea failed to convert the *cis*-{2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl} methanesulfonate (**22e**) [22] to the corresponding *S*-isothiuronium salt, which was to be decomposed by base to the thiol, **8e**. This displacement by thiourea is unsuccessful even in boiling *N,N*-dimethylformamide (DMF), starting material **22e** being recovered in good yield. However, **22e** reacts smoothly with potassium thioacetate in DMF at 50 to 60° (1 hour) to afford the thioacetate **23e** in 83% yield. Mild basic hydrolysis of **23e** provides the corresponding thiol (**8e**) in 76% yield. However, all attempts to isomerize **8e** to the corresponding 1,3-oxathiolane alcohol **7e** under ketal forming conditions failed, the starting thiol being recovered in excellent yield.



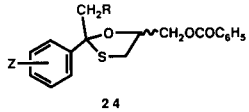
Analogous *cis*- and *trans*-1,2,4-triazolyl methanesulfonates (**22f**) react to furnish first **23f**, then *cis*- and *trans*-**8f**. Attempts to isomerize these *cis*- and *trans*-thiols **8f** to the corresponding 1,3-oxathiolane alcohols **7f** also failed (using 1.2 equivalents TsOH in boiling benzne). Under drastic conditions (20 equivalents of prior dried methanesulfonic acid) in boiling benzene (1 hour) gave only starting ketone **5f** in good yield. From these experiments we are

forced to conclude that when the starting ketone **5** fails to react with **1** in benzene (or toluene) in the presence of a sulfonic acids under azeotropic conditions, then the cognate isomerizations of thiols of type **8e** and **8f** to **7e** and **7f** also fail.

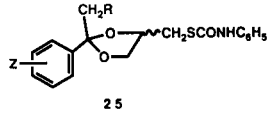
Assuming that the "proximity effect" of the azolium cation *alpha* to the ketone, or carbocationic intermediates is correct, then one could test this hypothesis by inserting methylene groups between two such potentially positively-charged centers. We set out to prepare *N*-(β- or γ)azolyl ketones by alkylating imidazole or 1,2,4-triazole with the requisite β- or γ-halo aromatic ketone to obtain **5g** and **5h**. The question is answered since **5g** and **5h** react with **1** as expected to yield *cis*- and *trans*-isomers of **7g**, **7h**, accompanied by very small amounts of *cis*- and *trans*-**8g** and **8h**. In the absence of *ortho*-substituents in **5g** or **5h**, the major product would be expected to be predominantly *cis*- and *trans*-1,3-oxathiolane alcohols **7g** and **7h**. These experiments establish that separation of an imidazole or 1,2,4-triazole ring sufficiently far from the ketone (and related potential carbocationic centers, Chart 1), permits normal ketalization by **1**.

Separation and Identification of Isomers.

Separation of *cis*- and *trans*-**7** from *cis*- and *trans*-**8** is achieved readily by means of column chromatography on silica gel. The less polar thiols **8** are eluted first, but are frequently accompanied by starting ketone **5**. However, to separate the diastereomers of **7** and **8** is more challenging. Limited success is reported for some members of **7**. Benzoylation of a mixture of *cis*- and *trans*-**7** produces *cis*- and *trans*-benzoates **24**, which in several instances can be fractionally crystallized to procure at least one pure isomer, which turns out to be *cis*-isomer of **24**. Subsequent hydrolysis of *cis*-**24** provides pure *cis*-**7**. Although mother liquors from *cis*-**24** are now enriched in *trans*-**24**, the *trans*-isomers have eluded isolation, except for some which had imidazole as part of their structure. It is possible to crystallize *trans*-**24g**, as the 4-toluenesulfonate. Details of all separations are elaborated in the Experimental section.



24



25

Unfortunately, separation of *cis*- and *trans*-thiols **8**, the minor products, are fraught with numerous problems. One of these stems from partial oxidation of **8** to disulfides during isolation. Three disulfides are possible, *cis-cis, trans-trans,* and *cis-trans*. Oxidation of **8** to disulfides with alkaline peroxide is successful but still produces an inseparable mixture. Nor is **8** amenable to form crystalline benzoates, or salts, when imidazole is part of the structure. But phenyl isocyanate converts mixtures of *cis*- and *trans*-**8** into crystalline mixtures of *cis*- and *trans*-*N*-phenylthiourethanes **25**, which, unfortunately have defied separation by fractional crystallization. During the conversion of **8** to **25**, such impurities as starting **5** are removed to give clean analyzable products. Nmr data are listed for both **8** nd **25**, but microanalytical data usually only for **25**.

The presence of frequently overlapping signals in the many complex spin-spin systems of *cis*- and *trans*-**7** and *cis*- and *trans*-**8** makes assignments of all ^{1}H nmr parameters a tedious task. The ^{13}C nmr signals were particularly useful in establishing the structure of the isomers. Differences in chemical shifts of methylene and methines attached to either oxygen and sulfur permit assignment of ^{1}H and ^{13}C signals associated with either **7** or **8**. Important and relevant ^{13}C and ^{1}H nmr signals are compiled in Table 2. Fortunately, there is sufficient room among the many complex multiplets in their ^{1}H nmr spectra to interpret and integrate signals critical for structure assignments and determination of isomer distributions. The ^{13}C chemical shifts of aryl and azole groups are omitted since these are virtually identical for those reported for 1,3-dioxolane analogs [13,14].

Identification of isomeric *cis*- and *trans*-1,3-dioxolane-4-methanethiols **8** is based largely on data established for analogous *cis*- and *trans*-1,3-dioxolane-4-methanols **6** [13,14,26]. More important is the correlation between chemical shifts of C-4 in *cis*- and *trans*-isomers **6**. It is found that the ^{13}C chemical shift of C-4 in the *trans*-isomer is on the average 1.6 ppm further downfield to that of the *cis*-isomer [13]. For *cis*- and *trans*-isomeric thiols **8**, and corresponding thiourethanes **25**, the same relationship held with carbon chemical shifts of C-4 in *trans*-isomers downfield from those of *cis*-isomers (between 1.2-1.7 ppm, Table 2). In view of limited published ^{1}H and ^{13}C nmr data on a few 2-alkyl-2-aryl-4-hydroxymethyl-1,3-dioxolanes [13,26] we thought perhaps we could have supporting data for stereo-assignments. In several 2-(halomethyl)-2-aryl-4-hydroxymethyl-1,3-dioxolanes **6** (R = Cl or Br), it would appear that in pairs of those *cis*- and *trans*-isomers, the *trans*-H-4 methine proton is more deshielded than the corresponding *cis*-H-4. When we re-examined the (unpublished) ^{1}H nmr spectra of many 1,3-dioxolanes [13,14] we came to the following conclusions: when the 2-alkyl substitutent was either a methyl or 2-halomethyl group (in **6**), the *trans*-H-4 proton nmr signal is downfield to that of the *cis*-isomer. **But**, when the 2-substituent of **6** changes to a 1-(1*H*-imidazolyl)methyl group (all other group remaining the same), there is an apparent reversal of the proton chemical shifts of *cis*-and *trans*-H-4 in the sense that now *cis*-H-4 is further downfield than *trans*-H-4. This implies that the 2-aryl group in that 2-aralkyl substituent exerts an anisotropic effect on the chemical shifts of H-4. This thesis is substantiated by the fact that 2-[1-(1*H*-1,2,4-triazolyl)-

Table 2

Selected Carbon-13 and Proton Chemical Shifts of Major Products in Deuteriochloroform, (in ppm Downfield from Internal Tetramethylsilane)

Compound	Carbon-13 NMR Signals											Proton NMR Signals					
	1,3-Dioxolane or 1,3-oxathiolane			Δδ [a]		CH_3's and CH_2's directly on ring									Δδ [a]		NOE [c]
	C-2	C-4	C-5	C-4	C-5	2-CH_3	2-CH_2	4-CH_2	5-CH_2	C=O	others	2-CH_3	H-4	H-5	H-4	H-5	%
7a-*cis*	95.5	34.8	82.6	–	–	32.4	–	–	63.5	–	–	1.86	–	4.17	–	–	2.7
7a-*trans*	94.5	35.1	83.3	–	0.7	31.5	–	–	63.6	–	–	1.91	–	4.55	–	0.38	10.0
24a-*cis*	95.7	36.0	80.0	–	–	32.6	–	–	64.9	166.1	–	1.88	–	4.42	–	–	–
24a-*trans*	94.4	35.8	80.9	–	0.9	31.7	–	–	64.6	166.1	–	1.91	–	4.77	–	0.35	–
7b-*cis*	93.8	34.5	83.0	–	–	30.5	–	–	63.5	–	–	2.02	–	4.30	–	–	0.8
7b-*trans*	93.2	34.4	82.2	–	–0.8	30.4	–	–	63.7	–	–	2.01	–	4.56	–	0.26	7.8
7c-*cis*	93.4	34.5	83.1	–	–	30.3	–	–	63.3	–	–	1.99	–	4.25	–	–	3.1
7c-*trans*	92.8	34.4	82.3	–	–0.8	30.3	–	–	63.5	–	–	1.99	–	4.53	–	0.28	12.2
24c-*cis*	93.5	35.8	80.3	–	–	30.3	–	–	64.7	166.1	–	2.01	–	4.45	–	–	–
24c-*trans*	92.8	35.1	79.9	–	–0.4	30.4	–	–	64.3	166.1	–	2.02	–	4.77	–	0.32	–
7d-*cis*	98.7	34.4	82.6	–	–	–	50.5	–	63.6	–	–	–	–	4.20	–	–	–
7d-*trans*	98.6	34.5	84.1	–	1.5	–	50.8	–	63.9	–	–	–	–	4.51	–	0.31	–
24d-*cis*	99.1	35.6	79.8	–	–	–	50.6	–	64.8	–	–	–	–	4.39 [b]	–	–	–
24d-*trans*	98.5	35.3	81.4	–	1.6	–	50.8	–	64.9	–	–	–	–	4.64	–	0.25	–
7g-*cis*	95.8	35.3	83.9	–	–	–	43.2	–	62.3	–	44.9 (CH_2N)	–	–	4.19	–	–	–
7g-*trans*	94.9	35.2	85.0	–	1.1	–	43.2	–	62.8	–	44.6 (CH_2N)	–	–	4.46	–	0.27	–
24g-*cis*	96.4	35.7	80.3	–	–	–	43.1	–	64.2	166.0	45.1 (CH_2N)	–	–	4.44	–	–	–
24g-*trans*	95.5	35.1	82.0	–	1.7	–	43.2	–	64.1	166.0	45.0 (CH_2N)	–	–	4.77	–	0.33	–
7h-*cis*	97.9	35.2	83.4	–	–	–	41.0	–	62.9	–	26.8 (C-CH_2-C) 46.7 (CH_2N)	–	–	4.18	–	–	–
7h-*trans*	96.8	35.1	84.7	–	1.3	–	40.5	–	63.3	–	26.7 (C-CH_2-C) 46.6 (CH_2N)	–	–	4.44	–	0.26	–
24h-*cis*	97.9	35.5	80.1	–	–	–	40.8	–	64.3	166.0	26.7(C-CH_2-C) 46.5 (CH_2N)	–	–	4.40	–	–	–
24h-*trans*	97.1	35.1	81.7	–	1.6	–	40.8	–	63.3	166.0	26.8 (C-CH_2-C) 46.4 (CH_2N)	–	–	4.69	–	0.29	–
8a-*cis*	109.3	76.8	68.0	–	–	28.0	–	27.7	–	–	–	1.64	4.06	–	–	–	–
8a-*trans*	109.3	78.3	69.2	1.5	–	28.0	–	27.2	–	–	–	1.59	4.30	–	0.24	–	–
25a-*cis*	109.5	75.0	68.2	–	–	28.2	–	33.5	–	164.9	–	1.66	4.22	–	–	–	–
25a-*trans*	109.5	76.2	69.1	1.2	–	28.1	–	32.8	–	164.9	–	1.60	4.48	–	0.26	–	–
8b-*cis*	109.4	76.8	68.1	–	–	27.8	–	25.8	–	–	–	1.80	4.08	–	–	–	–
8b-*trans*	109.3	78.3	69.0	1.5	–	27.4	–	25.9	–	–	–	1.75	4.36	–	0.28	–	–
25b-*cis*	109.5	74.8	68.1	–	–	25.7	–	33.5	–	165.0	–	1.84	4.24	–	–	–	–
25b-*trans*	109.4	76.1	68.9	1.3	–	25.9	–	32.7	–	165.0	–	1.77	4.47	–	0.23	–	–
8c-*cis*	109.1	76.9	68.0	–	–	27.7	–	25.7	–	–	–	1.79	4.08	–	–	–	–
8c-*trans*	109.1	78.3	68.8	1.4	–	27.2	–	25.9	–	–	–	1.73	4.33	–	0.25	–	–
25c-*cis*	109.1	74.9	68.1	–	–	25.7	–	33.3	–	165.0	–	1.84	4.23	–	–	–	–
25c-*trans*	109.1	76.1	68.9	1.2	–	25.8	–	32.5	–	165.0	–	1.77	4.48	–	0.25	–	–
8d-*cis*	110.7	76.9	68.1	–	–	–	47.0	27.5	–	–	–	–	4.00	–	–	–	–
8d-*trans*	111.0	78.6	69.3	1.7	–	–	47.7	27.3	–	–	–	–	4.00	–	0.00	–	–
25d-*cis*	110.2	75.0	67.9	–	–	–	46.4	31.9	–	–	–	–	4.09	–	–	–	–
25d-*trans*	110.3	75.9	68.5	0.9	–	–	46.3	31.5	–	–	–	–	4.18	–	0.09	–	–
8e-*cis*	108.0	77.9	68.9	–	–	–	51.4	26.5	–	–	–	–	4.06	–	–	–	–
8f-*cis*	107.8	77.5	68.7	–	–	–	55.8	26.7	–	–	–	–	4.09	–	–	–	–
8f-*trans*	107.9	79.2	69.6	1.7	–	–	56.6	26.7	–	–	–	–	3.93	–	–0.16	–	–

Table 2 (continued)

Compound	Carbon-13 NMR Signals											Proton NMR Signals						
	1,3-Dioxolane or 1,3-oxathiolane			Δδ [a]		CH_2's and CH_2's directly on ring										Δδ [a]		NOE [c]
	C-2	C-4	C-5	C-4	C-5	2-CH_3	2-CH_2	4-CH_2	5-CH_2	C=O	others	2-CH_3	H-4	H-5	H-4	H-5	%
8g-*cis*	109.1	76.6	68.2	–	–	–	[d]	27.4	–	–	[d] (CH_2N)	–	4.31	–	–	–	–
8g-*trans*	109.1	79.0	69.5	2.4	–	–	[d]	27.3	–	–	[d] (CH_2N)	–	4.42	–	0.11	–	–
22e-*cis* [f]	108.4	73.9	67.6	–	–	–	51.0	66.4	–	–	37.5 (OMs) [e]	–	4.30	–	–	–	–
22e-*trans* [f]	108.5	75.0	67.0	1.1	–	–	52.0	66.6	–	–	37.3 (OMs) [e]	–	4.02	–	–0.28	–	–
22f-*cis*	108.1	73.7	67.5	–	–	–	55.4	66.0	–	–	37.5 (OMs) [e]	–	4.24	–	–	–	–
22f-*trans*	108.3	75.0	67.1	1.3	–	–	56.3	66.8	–	–	37.3 (OMs) [e]	–	4.11	–	–0.13	–	–
23e-*cis*	107.9	75.3	68.9	–	–	–	51.2	30.9	–	194.8	30.3 (S-Ac) [e]	–	4.09	–	–	–	–
23f-*cis*	107.6	75.0	68.6	–	–	–	55.6	31.0	–	194.0	30.3 (S-Ac) [e]	–	4.13	–	–	–	–
23f-*trans*	107.7	76.6	69.3	1.6	–	–	56.5	30.8	–	193.8	30.2 (S-Ac) [e]	–	3.95	–	–0.18	–	–
6e-*cis* [f]	108.9	76.1	65.7	–	–	25.5	–	63.1	–	–	–	1.80	4.25	–	–	–	–
6e-*trans* [f]	108.9	77.5	66.1	1.4	–	25.9	–	62.8	–	–	–	1.75	4.53	–	0.28	–	–
6e-*cis*	107.6	77.1	66.9	–	–	–	51.4	61.9	–	–	–	–	4.10	–	–	–	–
6e-*trans*	107.8	78.6	67.1	1.5	–	–	52.3	61.7	–	–	–	–	3.82	–	–0.28	–	–
6e-*cis* benzoate [f]	108.1	74.3	67.1	–	–	–	51.5	63.9	–	166.1	–	–	4.34	–	–	–	–
6e-*trans* benzoate [f]	108.2	75.9	66.9	1.6	–	–	52.3	62.6	–	166.1	–	–	4.12	–	–0.22	–	–

[a] Represents chemical shift differences between *trans* and *cis* isomers (δ*trans*-δ*cis*). [b] Buried among overlapping signals. [c] These noe's indicate the percent enhancement of *trans*-H-5 signal, when 2-methyl is irradiated. [d] The three signals at 41.4, 41.8, 42.0 ppm cannot be assigned with certainty to any one of the two methylenes in *cis* and *trans* isomers. [e] Ac stands for acetyl, OMs for methanesulfonate. [f] Carbon nmr data from ref [13].

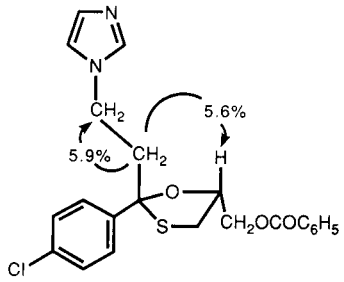
methyl] substituents (or a 2-benzyl group) in examples of **6**, **8**, **22**, **23** and **25** bring about such differences in the chemical shifts of H-4 (Table 2).

1,3-Dioxolane-4-methanethiols **8** are easily identified by the presence of SH signals in their ^{1}H nmr spectra. Furthermore, exocyclic CH_2 proton signals of **8** are found as complex multiplets in the neighborhood of 2.4-2.6 ppm and usually show strong coupling with the SH proton. In turn, the SH proton signals for *cis*- and *trans*-**8** are seen as triplets (or doublet of doublets - if CH_2 protons are magnetically not equivalent) around 1.25-1.65 ppm. Facile proton-deuterium exchange of these SH signals (deuterium oxide containing a trace of ammonia) identifies these multiplets. Unfortunately, ^{1}H nmr signals associated with methylene protons, such as those from the exocyclic CH_2SH, endocyclic CH_2S and any CH_2S-S groups appear between 2.2 and 3.2 ppm. However, the corresponding ^{13}C signals are relatively far apart: CH_2SH around 26, endocyclic CH_2S around 35, and CH_2S-S in the vicinity of 40 ppm.

Due to the presence of unequal amounts of *cis*- and *trans*-isomers, two sets of nmr signals of disproportional intensity are seen in the spectra of the mixtures. In searching for ^{1}H and ^{13}C nmr data from model unsymmetrical *cis*- and *trans*-2,2,5-trisubstituted 1,3-oxathiolanes, akin to **7** and **24**, there are available ^{1}H and ^{13}C nmr parameters for many 2,5-disubstituted or symmetrical 2,2,5-trisubstituted 1,3-oxathiolanes [4,11,23-29]. The structural similarity of *cis*- and *trans*-**6** (and **8**) to that of *cis*- and *trans*-**7** suggests that ^{1}H and ^{13}C chemical shift differences of H-5 and C-5 might follow the same trend. On this basis, ^{1}H and ^{13}C chemical shifts of the *trans*-isomers should be downfield to those of the *cis*-isomers of **7**.

In examining chemical shift differences ($\Delta\delta$, Table 2) of C-5 and H-5 in each pair of diastereomers, **7a** to **7h**, the more deshielded of the two H-5 methine signals is assigned to the *trans*-isomer. We had hoped that the chemical shift differences of C-5 signals of *cis*- and *trans*-**7** would follow suit. They do, with some exceptions. This premise falters when it was discovered that in three pairs of isomers, **5b**, **5c**, and **24c**, ^{13}C chemical shifts of *cis*- and *trans*-C-5 are reversed. A common trait to these three sets of isomers is that each has a C-2 aryl group bearing an *ortho*-chloro group. It is conceivable that such an *ortho*-substituent might inhibit certain conformational equilibria and perhaps also free rotation about the aryl-C-2 bond thereby exerting unexpected anisotropic effects on the 1,3-oxathiolane ring carbons. Since the chemical shift differences for these *cis*- and *trans*-isomers are in general only of the order of 1 to 2 ppm, small conformational changes could bring about these small chemical shift changes. In order to establish the stereochemistry of *cis*-and *trans*-iso-

mers of **7** unequivocally, we resorted to a number of nuclear Overhauser enhancement (noe) experiments. Since the CH_3 group at C-2 of **7** (R = H) is in relatively close proximity to either the 2-CH_2 group of the *cis*-isomer or the H-5 methine of the *trans*-isomer, it is conceivable that observable noe effects could settle the structure. Irradiation of the 2-CH_3 signal of a number of *cis*- and *trans*-isomers of **7** (R = H) produces notable enhancement of proton nmr signals of *trans*-H-5 protons, but not at all the *cis*-5-CH_2 signals (Table 2). The only other protons(s) experiencing noe's (not calculated) are sometimes *o*-protons (H-2, H-6) of **7** or **24** which is in keeping with the spatial arrangements of the affected protons. Significant noe effect are also observed when the 2-CH_2 protons of *trans*-**24g** are irradiated causing noe effects of the neighboring *trans*-methine proton (H-5), as well as of the vicinal CH_2 protons, as depicted in the figure below. In addition, there were noe enhancements of a number of the aromatic protons. Since we did not establish the chemical shifts of either H-2 or H-5 of the imidazole group, or those of the *ortho*-protons of either phenyl ring of *trans*-**24g**, we did not assign these additional noe's. Irradiation of the 2-CH_2 group of *cis*-**24g** showed no noe on either the neighboring methine (H-5) or methylene (5-CH_2) groups, effecting only the adjacent CH_2 and some aromatic protons signals.



trans **24g**

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All research chemicals were purchased from Aldrich Chemical Co., Milwaukee, Wisconsin, unless specified otherwise, and were used as supplied. Pyridine and DMF were stored over 4 Å molecular sieves once the original container had been opened. Evaporation or removal of solvents, *in vacuo*, implies that solvents were removed by means of a rotary flash evaporator at the water pump (20-30 torr) at about 40°, unless specified otherwise. Analytical samples were dried first at room temperature, and if necessary at higher temperature, *in vacuo*, before microanalyses were carried out by Midwest Microlab, Indianapolis, Indiana. Analytical data are in Table 3.

Table 3

Microanalytical Data

Compound	Molecular Formula	Analyses Calcd./Found C%	H%	N%
5h	$C_{13}H_{13}BrN_2O$	53.26	4.47	9.56
		53.26	4.38	9.48
6f-*cis* & *trans*	$C_{13}H_{14}ClN_3O_3 \cdot H_2O$	49.77	5.14	13.39
		49.96	4.89	13.49
7a-*cis* & *trans*	$C_{11}H_{13}ClO_2S$	53.99	5.35	–
		54.20	5.39	–
7b-*cis* & *trans*	$C_{11}H_{13}ClO_2S$	53.99	5.35	–
		54.03	5.34	–
7c-*cis* & *trans*	$C_{11}H_{12}Cl_2O_2S$	47.32	4.33	–
		47.13	4.34	–
7d-*cis* & *trans*	$C_{17}H_{18}O_2S$	71.30	6.33	–
		71.32	6.35	–
8e-*cis*	$C_{14}H_{14}Cl_2N_2O_2S$	48.71	4.09	8.11
		49.00	4.05	7.89
8f-*cis* & *trans*	$C_{13}H_{14}ClN_3O_2S$	50.08	4.53	13.48
		50.04	4.49	13.42
8g-*cis* & *trans* Oxalate	$C_{17}H_{19}ClN_2O_6S$	49.22	4.61	6.75
		49.38	4.62	6.55
20	$C_{11}H_{11}ClO_2S$	54.43	4.57	–
		54.43	4.52	–
22f-*cis* & *trans*	$C_{14}H_{16}ClN_3O_5S$	44.92	4.31	11.22
		44.73	4.34	10.96
23e-*cis*	$C_{16}H_{16}Cl_2N_2O_3S$	49.62	4.16	7.23
		49.60	4.05	7.15
23f-*cis* & *trans*	$C_{15}H_{16}ClN_3O_3S$	50.92	4.56	11.88
		50.65	4.58	11.65
24a-*cis*	$C_{18}H_{17}ClO_3S$	61.98	4.91	–
		62.01	4.89	–
24a-*cis* & *trans*	$C_{18}H_{17}ClO_3S$	61.98	4.91	–
		62.05	4.91	–
24e-*cis*	$C_{18}H_{16}Cl_2O_3S$	56.41	4.21	–
		56.53	4.36	–
24e-*cis* & *trans*	$C_{18}H_{16}Cl_2O_3S$	56.41	4.21	–
		56.32	4.10	–
24d-*cis* & *trans*	$C_{24}H_{22}O_3S$	73.82	5.68	–
		73.93	5.60	–
24g-*cis*	$C_{22}H_{21}ClN_2O_3S$	61.61	4.93	6.53
		61.67	4.89	6.46
24g-*trans* 4-Toluenesulfonate	$C_{29}H_{29}ClN_2O_6S_2$	57.94	4.86	4.66
		57.93	4.83	4.60
24h-*cis*	$C_{23}H_{23}BrN_2O_3S$	56.68	4.76	5.75
		56.72	4.80	5.75
24h-*cis* & *trans* Oxalate	$C_{25}H_{25}BrN_2O_7S$	52.00	4.36	4.85
		51.92	4.38	4.86
25a-*cis* & *trans*	$C_{18}H_{18}ClNO_3S$	59.42	4.99	3.85
		59.51	4.90	3.90
25b-*cis* & *trans*	$C_{18}H_{18}ClNO_3S$	59.42	4.99	3.85
		59.29	5.00	3.64
25c-*cis* & *trans*	$C_{18}H_{17}Cl_2NO_3S$	54.28	4.30	3.52
		54.09	4.27	3.48
25d-*cis*	$C_{24}H_{23}NO_3S$	71.09	5.72	3.45
		70.99	5.77	3.50
25d-*cis* & *trans*	$C_{24}H_{23}NO_3S$	71.09	5.72	3.45
		70.99	5.60	3.50

The nmr spectra were recorded in deuteriochloroform, unless specified otherwise. Proton nmr spectra were obtained on a Varian XL-300 or Nicolet NT-360 spectrometer. Carbon nmr spectra were determined at 75.4 MHz on the Varian XL-300 spectrometer, or at 90.8 MHz on a Nicolet NT-360 spectrometer. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are described as s, singlet, d, doublet, t, triplet, q, quartet and m, multiplet. The abbreviation br is used to describe broad signals. While proton nmr spectra were obtained for all compounds, they were not necessarily analyzed because of their inherent complexity. Centers of complex multiplets are taken as chemical shifts. Certain signals were useful in structure or isomer determinations and these are mentioned in the text. Attached proton tests (APT) were utilized when necessary. For noe experiments, all nmr samples were flushed with pure dry nitrogen for 10 minutes prior to determinations.

Thin layer chromatography was performed on Aldrich aluminum-backed plates (silica gel coated with 254 nm fluorescent indicator). Column chromatography utilized silica gel (60-200 mesh, J. T. Baker), unless noted otherwise. Solvents for chromatographic methods are designated as follows: Solvent A, dichloromethane; solvent B, dichloromethane-methanol, 99:1; solvent C, dichloromethane-methanol, 98:2; solvent D, dichloromethane-methanol, 97:3; solvent E, dichloromethane-methanol, 95:5; solvent F, dichloromethane-methanol, 90:10; solvent G, chloroform; solvent H, chloroform-methanol, 99:1; solvent I, chloroform-methanol, 98:2; solvent J, chloroform-methanol, 97.5:2.5.

1-(4-Chlorophenyl)-3-(1*H*-imidazol-1-yl)-1-propanone (**5g**).

Although this ketone had been prepared by the Mannich reaction of 4-chloropropiophenone, formaldehyde and imidazole (in lesser yield) [30], this synthesis presents a viable alternate route. A mixture of 3,4'-dichloropropiophenone (14.2 g, 0.07 mole) and imidazole (23.8 g, 0.35 mole) in DMF (70 ml) was stirred at 25° (72 hours) until tlc showed the disappearance of the starting ketone. The mixture was poured into water (500 ml) from which **5g** crystallized (13.3 g, 81%), mp 107°. Recrystallization from benzene raised the mp to 111°, lit [30] mp 104°; ^{1}H nmr: δ 3.14 (t, CH_2CH$_2$N), 4.43 (t, CH$_2$N, J = 6.5 Hz), imidazole signals as narrow complex multiplets at 6.97 (H-5), 7.04 (H-4), 7.55 (H-2), phenyl proton signals as an AA'BB' system, centered at 7.45 and 7.85 (complex m); ^{13}C nmr: δ 39.4 (CH$_2$CH$_2$N), 41.0 (CH$_2$N), imidazole carbons at 137.2 (C-2), 128.8 (C-4), 119.0 (C-5), phenyl carbons at 128.6, 129.2, 134.3, 139.4, 195.5 (C=O).

1-(4-Bromophenyl)-4-(1*H*-imidazol-1-yl)-1-butanone (**5h**).

A solution of 4'-bromo-4-chlorobutyrophenone (19.6 g, 0.075 mole) and imidazole (25.6 g, 0.375 mole) in DMF (100 ml) was stirred at 95-100° (monitored by tlc, 48 hours). After cooling, the bulk of the solvent was evaporated, (*ca.* 5 torr). The residue was diluted with water (500 ml), extracted by chloroform (3 x 100 ml), the extract washed with brine (100 ml), dried (magnesium sulfate) and evaporated, *in vacuo*. Chromatography on silica gel (500 g) and elution by solvent C furnished pale yellow crystals (10.90 g, 50%), which were recrystallized from benzene, mp 88-89°; tlc, R_f = 0.24 (solvent E); ^{1}H nmr: δ 2.21 (q, CH$_2$CH_2CH$_2$N, J = 6.8 Hz), 2.87 (t, CH_2CH$_2$CH$_2$N, J = 6.8 Hz), 4.05 (t, CH$_2$N, J = 6.8 Hz), imidazole proton signals as narrow complex m, 6.91 (H-5), 7.06 (H-4), 7.45 (H-2), phenyl proton signals AA'BB' at 7.58, 7.74; ^{13}C nmr: δ 25.1 (CH$_2$CH$_2$CH$_2$N), 34.3 (CH$_2$CH$_2$CH$_2$N), 45.9 (CH$_2$N), imidazole carbons at 137.1 (C-2), 129.8 (C-4), 118.7 (C-5), phenyl carbons at 128.5, 129.4, 132.0, 135.1, 197.5 (C=O).

Method A. General Method of Ketalization by 3-Mercapto-1,2-propanediol (**1**).

(i) From 4-Chloroacetophenone (**5a**).

The general procedure is illustrated for the synthesis of *cis*- and *trans*-2-(4-chlorophenyl)-2-methyl-5-(hydroxymethyl)-1,3-oxathiolane (**7a**) and *cis*- and *trans*-2-(4-chlorophenyl)-2-methyl-4-(mercaptomethyl)-1,3-dioxolane (**8a**). All *cis*- and *trans*- mixtures were obtained as oils, unless otherwise specified.

A mixture of **5a** (4.64 g, 0.03 mole), **1** (4.05 g, 0.0375 mole) and 4-toluenesulfonic acid monohydrate (TsOH·H$_2$O, 0.12 g, 0.006 mole) was refluxed in benzene (50 ml, Dean-Stark apparatus for azeotropic removal of water, 30 minutes). Solvents were evaporated, *in vacuo*, the residue neutralized with saturated sodium bicarbonate solution (100 ml) and extracted into dichloromethane (3 x 100 ml). The extract was washed with brine (100 ml), dried (magnesium sulfate) and dichloromethane removed, *in vacuo*, to provide a colorless oil 7.2 g). The product was chromatographed on silica gel (140 g). Fractions (100 ml) were collected until tlc indicated complete elution. Fractions whose tlc indicated the presence of the same compound(s) were combined and evaporated, *in vacuo*.

Elution with solvent A (600 ml) yielded *cis*- and *trans*-**8a** (60:40, 2.0 g, 27%); tlc, R_f = 0.56 (solvent A). Further elution with solvent B (1200 ml) gave *cis*- and *trans*-**7a** (58:42, 4.66 g, 64%); tlc, R_f = 0.14 (solvent A).

In a cognate reaction, using a more concentrated solution and increasing the time, the following results were obtained: from **5a** (15.5 g, 0.1 mole), **1** (21.6 g, 0.02 mole), TsOH·H$_2$O (0.38 g, 0.002 mole) in benzene (100 ml, 1.5 hours), there was isolated (after chromatography on 500 g silica gel, *cis*- and *trans*-**8a** (70:30, 0.72 g, 3%) and *cis*- and *trans*-**7a** (70:30, 21.0 g, 86%).

(ii) From 2-Chloroacetophenone (**5b**).

A mixture of **5b** (4.64 g, 0.03 mole), **1** (4.05 g, 0.0375 mole) and TsOH·H$_2$O (0.12 g, 0.0006 mole) was refluxed in benzene (50 ml, with azeotropic removal of water, 2.5 hours). After workup and chromatography, according to Method A, there was obtained *cis*- and *trans*-**8b** (70:30, 1.2 g, 16%), tlc, R_f = 0.57 (solvent A); *cis*- and *trans*-**7b** (65:35), which was recrystallized from benzene to provide 5.44 g (74%), mp 92-94°; tlc, R_f = 0.15 (solvent A).

(iii) From 2,4-Dichloroacetophenone (**5c**).

A mixture of **5c** (18.9 g, 0.1 mole), **1** (13.5 g, 0.125 mole) and TsOH·H$_2$O (0.38 g, 0.02 mole) was refluxed in benzene (50 ml, 1.5 hours). Upon workup and chromatography (Method A), there was isolated (elution with solvent A), *cis*- and *trans*-**8c** [70:30, 7.27 g, 26%, tlc, R_f = 0.62 (solvent A)] and (with solvent B) *cis*- and *trans*-**7c** [30:70, 19.26 g, 69%); tlc, R_f = 0.15 (solvent A)].

When the time of a similar reaction was extended to 8 hours, the following results were obtained. From **5c** (5.67 g, 0.03 mole), **1** (5.07 g, 0.0375 mole) and TsOH·H$_2$O (0.12 g, 0.0006 mole) in refluxing benzene (15 ml), there was obtained *cis*- and *trans*-**8c** [70:30, 1.67 g, 20%) and *cis*- and *trans*-**7c** [60:40, 5.85 g, 70%).

Upon standing at room temperature for 6 months, a sample of *cis*- and *trans*-**8c** (70:30, 1.4 g) was reexamined for contents. The early chromatographic fractions contained some **5c**, unchanged **8c** and some disulfides and were not examined further. The more polar fraction consisted of pure *trans*-**7c** (0.1 g, 7%), whose structure was confirmed by noe experiments.

(iv) From Deoxybenzoin (**5d**).

After a mixture of **5d** (3.9 g, 0.02 mole), **1** (2.7 g, 0.025 mole) and TsOH·H_2O (0.08 g, 0.004 mole) was refluxed in benzene (50 ml, 2 hours), it was worked up according to Method A. Chromatography on silica gel (120 g) and elution with solvent A gave *cis*- and *trans*-**8d** (70:30, 1.7 g, 30%), tlc, R_f = 0.70 (solvent A) and *cis*- and *trans*-**7d** [65:35, 3.6 g, 63%); tlc, R_f = 0.24 (solvent A).

(v) From 1-(4-Chlorophenyl)-3-(1*H*-imidazol-1-yl)-1-propanone (**5g**).

A mixture of **5g** (4.7 g, 0.02 mole), **1** (5.4 g, 0.05 mole) and TsOH·H_2O (4.4 g, 0.0232 mole) in benzene (80 ml), was refluxed (24 hours) with azeotropic removal of water and was worked up according to Method A. Chromatography (silica gel, 200 g) and elution with solvent C provided *cis*- and *trans*-**8g** (75:35, 5.75 g, 89%) as a colorless oil; tlc, R_f = 0.52 (solvent F).

From another preparative run, but using a shorter reaction time, **5g** (14.0 g, 0.06 mole), **1** (16.2 g, 0.15 mole) and TsOH·H_2O (13.2 g, 0.07 mole) was boiled in benzene (100 ml, 8 hours) with removal of water. The crude product (28.0 g, which contained some polymer of **1** was chromatographed on silica gel (300 g), eluted with solvent H (2500 ml) to yield *cis*- and *trans*-**8g** [75.25, 1.0 g, 5%, tlc, R_f = 0.66 (Solvent F)]. Further elution with solvent J (2500 ml) brought forth *cis*- and *trans*-**7g** (70:30, 15.5 g, 80%).

A solution of **8g** (1.0 g) in 2-propanol (10 ml) was treated with oxalic acid (0.27 g) in 2-propanol (5 ml) and the resultant salt was recrystallized from the 2-propanol, to furnish *cis*- and *trans*-**8g** oxalate (75:25, 1.0 g), mp 142-146°.

(vi) From 1-(4-Bromophenyl)-4-(1*H*-imidazol-1-yl)-1-butanone (**5h**).

A mixture of **5h** (2.93 g, 0.01 mole), **1** (2.16 g, 0.02 mole) and TsOH·H_2O (2.2 g, 0.0116 mole) was refluxed in benzene (50 ml) with azeotropic removal of water (2 hours) and worked up as *per* Method A. Chromatography on silica gel (100 g), eluting with solvent D furnished *cis*- and *trans*-**7h** (70:30, 3.5 g, 91%) as a viscous light yellow oil; tlc, R_f = 0.48 (solvent F).

In another experiment, **5h** (10.26 g, 0.035 mole) was boiled with **1** (4.76 g, 0.044 mole), TsOH·H_2O (7.72 g, 0.041 mole) in benzene (60 ml) for 2.5 hours. Workup according to Method A, after chromatography on silica gel [210 g, solvent H (2000 ml), then solvent J (2000 ml)] provided *cis*- and *trans*-**7h** (12.0 g, 90%).

(vii) From 2-Bromo-1-(4-chlorophenyl)ethanone (**18**).

A mixture of **18** (5.37 g, 0.023 mole), **1** (2.7 g, 0.025 mole) and TsOH·H_2O (0.1 g, 0.0005 mole) was refluxed in benzene (50 ml) with azeotropic removal of water (1 hour). Workup according to Method A gave an oil (mainly of **20**, and starting ketone). Chromatography (silica gel, 150 g, solvent A) produced a gum which was triturated with petroleum ether-ether (2:1) to afford 1-(4-chlorophenyl)-2,8-dioxa-thiabicyclo[3.2.1]octane, (**20**, 1.1 g, 18%), mp 108°; ^{1}H nmr: δ 2.26 (dd, eq H-5), 2.51 (d, eq H-7), 3.16 (d, ax H-7), 3.33 (d, ax H-5), 4.13 (t, exo H-3), 4.53 (d, endo H-3), 4.94 (m, H-4), 7.3-7.5 (m, aromatic protons), $J_{3,3}$ = 6.83, $J_{5,5}$ = 13.3, $J_{7,7}$ = 13.1, $J_{3\,endo,4}$ = 0.0, $J_{3\,exo,4}$ = 6.24, $J_{5\,ax,4}$ or $J_{5\,eq,4}$ = 2.34 or 2.44 Hz; ^{13}C nmr: δ 28.8 (C-5), 38.3 (C-7), 69.6 (C-3), 74.9 (C-4), 106.1 (C-1), aromatic carbons, 126.5 (C-2, C-6), 128.5 (C-3, C-5), 134.4 (C-1), 139.0 (C-4).

Method B. Synthesis and Separation of *cis*- and *trans*-Benzoates **24**.

(i) *cis*-**24a** From a Mixture of *cis*- and *trans*-**24a**.

To a stirred cold (<5°) solution of *cis*- and *trans*-**7a** (70:30, 7.34 g, 0.03 mole) in dry pyridine (20 ml) was added dropwise, benzoyl chloride (4.62 g, 0.033 mole) over 20 minutes. The reaction mixture was allowed to warm to room temperature and stirred for another 4 hours. Pyridine was removed, *in vacuo* (<40°, 5 torr), and the residue diluted with water (100 ml). The mixture was extracted with chloroform (3 x 50 ml). The extract was washed with dilute hydrochloric acid, then with water, dried (magnesium sulfate) and evaporated, *in vacuo*. The oily residue commences to crystallize after an unpredictable time period. In this experiment, after 24 hours a cream white solid formed and the mixture was layered with methanol (50 ml) and permitted to stand at least 18 hours. Colorless crystals were filtered, washed with cold methanol, dried and recrystallized from methanol to give *cis*-**24a** (4.0 g, 38%), mp 76-77°; ^{1}H nmr: δ 1.89 (s, CH_3), 3.12 (narrow AB m, CH_2S), 4.42 (m, H-5), 4.54 (narrow m, CH_2O) 7.28, 7.46, 7.56, 8.07 (m, aromatic protons). The mother liquor was evaporated, *in vacuo*, to give a colorless oil which was shown to be a mixture of *cis*- and *trans*-**24a** (40:60).

(ii) *cis*-**24c** From a Mixture of *cis*- and *trans*-**24c**.

Using Method B-i, *cis*- and *trans*-**7c** (60:40, 1.9 g, 0.0068 mole) was reacted with benzoyl chloride (1.05 g, 0.0075 mole) in pyridine (10 ml) to provide *cis*- and *trans*-**24c** (60:40, 2.57 g, 99%), as a colorless oil. Addition of methanol (50 ml) caused crystallization of *cis*-**24c** (0.8 g, 31%), mp 91-92°; ^{1}H nmr: δ 2.01 (s, CH_3), 3.07 (narrow AB m, CH_2S), 4.45 (m, H-5), 4.62 (narrow m, CH_2O), 7.22-8.11 (series of m, aromatic protons). The mother liquor was chromatographed to provide 1.42 g of a mixture of *cis-trans* of **24c** (40:60).

Hydrolysis of *cis*-**24c** (0.2 g) with sodium bicarbonate (0.05 g) in boiling methanol (5 ml, 15 minutes) afforded (after chromatography, silica gel, solvent A), *cis*-**7c** (0.13 g, 93%) as a colorless oil; ^{1}H nmr: δ 2.00 (s, CH_3), 2.49 (t, OH, J = 6.4 Hz), 2.89-3.09 (m, CH_2S), 3.91 (m, CH_2O), 4.25 (m, H-5), 7.21, 7.40, 7.52 (m, aromatic protons).

(iii) *cis*- and *trans*-**24d**.

Using Method B, and starting with *cis*- and *trans*-**7d** (2.86 g, 0.01 mole), benzoyl chloride (1.7 g, 0.012 mole) in pyridine (10 ml), there was obtained, after chromatography (100 g of silica gel, elution with solvent A) *cis*- and *trans*-**24d** (70:30, 3.2 g, 84%). The gum did not crystallize.

(iv) *cis*- and *trans*-**24g**.

To an ice-cold stirred solution of *cis*- and *trans*-**7g** (70:30, 16.2 g, 0.05 mole) in dry pyridine (40 ml) was added benzoyl chloride (8.4 g, 0.06 mole), dropwise, (15 minutes). After 5 hours at room temperature, the reaction was worked up according to Method B. There was obtained *cis*- and *trans*-**24g** (20.4 g, 96%, ratio of 70:30) as a colorless oil; tlc, R_f = 0.74 (solvent F). After stirring this mixture with ether (100 ml), colorless *cis*-**24g** precipitated. Recrystallization from benzene-hexane yielded pure *cis*-**24g** (7.5 g, 35%), mp 111°; ^{1}H nmr: δ 2.48 (m, part of an A_2BC system, 2-CH_2), 3.15 (m, AB part of an ABX system, CH_2S), 3.95-4.23 (2 m, BC part of A_2BC system, CH_2N), 4.44 (m, H-5), 4.55 (m, AB part of an ABC system, CH_2O), 6.83-8.09 (series of m, aromatic protons).

The mother liquors from *cis*-**24g** were evaporated, *in vacuo*, to give pale yellow oil, consisting of *cis*- and *trans*-**24g**, in the ratio of approximately 45:55. This oil (6.5 g) was boiled in benzene (50 ml) containing TsOH·H_2O (2.85 g, 0.15 mole) and was dried azeotropically. After cooling, the resulting clear solution was layered with an equal volume of ether. After several hours a colorless

crystalline solid was filtered and was washed a with benzene-ether (1:1). Recrystallization from benzene yielded *trans*-**24g** 4-toluenesulfonate (2.0 g, representing about 13% from *cis*- and *trans*-**24g**), mp 126-127°; ^{1}H nmr: δ 2.32 (s, CH_3), 2.67 (m, 2-CH_2), 2.99-3.26 (2 m, part of an ABX system, CH_2S), 4.09-4.34 (2 m, AB part of ABX_2 system, CH_2N), 4.40 (m, AB part of an ABC system, CH_2O), 4.75 (m, H-5), 7.00-7.96 (series of m, aromatic protons), 9.23 (s, NH^+).

Neutralization of this salt (1.8 g, 0.003 mole) with saturated aqueous sodium bicarbonate solution (25 ml), followed by extraction yielded (after the usual workup) *trans*-**24g** (1.24 g) as a colorless gum; ^{1}H nmr: δ 2.59 (t, J = 7.8 Hz, 2-CH_2), 3.03-3.28 (2 m, part of an ABX system, CH_2S), 3.76-4.08 (2 m, AB part of ABX_2 system, CH_2N), 4.49 (m, AB part of an ABC system, CH_2O), 4.75 (m, H-5), 6.82 (s), 7.00 (s), 7.25-8.00 (series of m, aromatic protons).

Hydrolysis of *cis*-**24g** (8.6 g, 0.02 mole) was carried out with sodium bicarbonate (1.85 g, 0.022 mole) in boiling methanol (100 ml) for 45 minutes. After removal of solvents, *in vacuo*, the residue was diluted with water (100 ml), extracted into chloroform (2 x 100 ml) and chromatographed on silica (100 g) to remove methyl benzoate. Elution first with solvent I (1000 ml), then with solvent J, (1000 ml) furnished pure *cis*-**7g** (6.25 g, 96%) as a gum; ^{1}H nmr: δ 2.47 (m, part of an A_2BC system, 2-CH_2), 3.06 (m, AB part of an ABX system, CH_2S), 3.70-3.92 (2 m, AB part of an ABC system, CH_2O), 4.10 (m, BC part of A_2BC system, CH_2N), 4.19 (m, H-5), 6.85-7.45 (series of m, aromatic protons).

(v) *cis*-**24h** From a Mixture of *cis*- and *trans*-**24h**.

Reaction of *cis*- and *trans*-**7h** (70:30, 10.5 g, 0.0275 mole), benzoyl chloride (4.9 g, 0.035 mole) in dry pyridine (25 ml), Method B-i, yielded an oil (13.16 g). Addition of anhydrous ether caused *cis*-**24h** (4.14 g, 31%) to crystallize out, mp 101°; ^{1}H nmr: δ 1.80-2.00 (m, C-CH_2CH_2CH_2-N part of AA'BB'XX' system), 3.08 (m, CH_2S, AB part of ABX), 3.82 (CH_2-N), 4.40 (m, H-5), 4.54 (m, CH_2O), 6.81, 7.00, 7.38 (H-5, H-4 and H-2 of imidazole), 7.27-8.07 (m, aromatic protons).

Mother liquors were evaporated and the resultant oil treated with oxalic acid (1.55 g) in 2-propanol (60 ml), when a solid (mixture of *cis*- and *trans*-**24h** oxalate, 50:50, 5.3 g) crystallized out, mp 143-146°.

Method C. Characterization of *cis*- and *trans*-**8** *via* their *N*-Phenylthiourethanes **25**.

(i) *cis*- and *trans*-**25a**.

To an ice-cold solution of *cis*- and *trans*-**8a** (0.5 g, 0.002 mole) in dry pyridine (2 ml) was added phenyl isocyanate (0.3 g, 0.0025 mole), dropwise. After stirring the mixture at room temperature (2 hours), pyridine was removed, *in vacuo*, at 25°. The residue was chromatographed on silica gel (30 g) and eluted with solvent A (500 ml) to provide *cis*- and *trans*-**25a** (65:35, 0.6 g, 82%); tlc, R_f = 0.20 (solvent A), mp 104-106°.

(ii) *cis*- and *trans*-**25b**.

These derivatives were prepared from **8b** (70:30, 0.38 g, 0.0016 mole), phenyl isocyanate (0.24 g, 0.002 mole) in 2 ml pyridine, as described in C-i, to yield *cis*- and *trans*-**25b** (70:30, 0.52 g, 89%) as an oil; tlc, R_f = 0.22 (solvent A).

(iii) *cis*- and *trans*-**25c**.

From *cis*- and *trans*-**8c** (70:30, 2.8 g, 0.01 mole), there was obtained the corresponding mixture of *cis*- and *trans*-**25c** (3.2 g, 80%), as an oil.

(iv) *cis*- and *trans*-**25d**.

Starting from *cis*- and *trans*-**8d** (70:30, 0.73 g) and using the general Method C, there was isolated *cis*- and *trans*-**25d** (70:30, 0.71 g, 87%), mp 158-160°. When this mixture was extracted with boiling ether, cooled, *cis*-**25d** (0.27 g, 30%) crystallized out, mp 165-166°.

cis-{2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-(dioxolan-4-yl)}methyl Thioacetate (**23e**).

A solution of *cis*-**22e** (2.54 g, 0.00625 mole) [22] in DMF (30 ml) and potassium thioacetate (0.86 g, 0.075 mole) was stirred at 50-55° (1 hour). After cooling to 25°, the mixture was diluted with water (150 ml), the product filtered and dried. It weighed 2.0 g (83%), mp 98-99°; tlc, R_f = 0.47 (solvent E); ^{1}H nmr: δ 2.33 (s, CH_3), 2.72 (d, J = 6.3 Hz, CH_2S), 3.42, 3.83 (2 m, AB part of ABK system, CH_2O), 4.09 (m, H-5), 4.25 (AB q, CH_2N), 6.98-7.53 (series m, aromatic protons).

cis-2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-4-(mercaptomethyl)-1,3-dioxolane (**8e**).

A solution of **23e** (0.2 g, 0.0005 mole) in methanol (5 ml) containing sodium bicarbonate (0.050 g, 0.0006 mole) was refluxed for 15 minutes, cooled, diluted with water (25 ml), neutralized to *p*H 7 with hydrochloric acid and extracted into chloroform (2 x 25 ml). After drying the extract (magnesium sulfate) it was evaporated *in vacuo*, to furnish *cis*-**8e** (0.13 g, 76%) as a light yellow oil; tlc, R_f = 0.58 (solvent E); ^{1}H nmr: δ 1.35 (t, SH, J = 9 Hz), 2.29, 2.50 (2 m, part of AB part of ABKX system, CH_2S), 3.50, 3.90 (2 m, AB part of ABC system, CH_2O), 4.06 (m, H-5), 4.43 (AB q, CH_2N), 6.97-7.60 (series m, aromatic protons).

cis- And *trans*-2-(4-Chlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-4-(hydroxymethyl)-1,3-dioxolane (**6f**).

A mixture of **5f** (4.4 g, 0.02 mole), glycerol (9.21 g, 0.1 mole) and methanesulfonic acid (38.4 g, 0.4 mole) in benzene (20 ml) was refluxed for 3 hours with azeotropic removal of water. The solvent was removed, *in vacuo*, and the residue was poured onto a mixture containing crushed ice (150 g) and 30% ammonium hydroxide (75 ml). The colorless solid (4.7 g, 80%) was filtered, washed with water, dried and consisted of a mixture of *cis*- and *trans*-**6f** (70:30), mp 123-127°.

cis- And *trans*-{2-(4-Chlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-(dioxolan-4-yl)}methyl Methanesulfonate (**22f**).

To a cooled (< 5°) and stirred solution of *cis*- and *trans*-**6f** (3.7 g, 0.0125 mole) in pyridine (20 ml) was added, dropwise, methanesulfonyl chloride (2.86 g, 0.025 mole) during 10 minutes. The reaction mixture was further stirred 5 hours at room temperature, then 10 minutes at 60°. The reaction mixture was diluted with water (100 ml), extracted with chloroform (2 x 30 ml), the combined extract washed with water (50 ml), dried (magnesium sulfate) and the solvent evaporated, *in vacuo*, to afford 4.4 g (99%) of *cis*- and *trans*-**22f** (70:30), which solidified to a light yellow solid, mp 105-109°.

cis- And *trans*-{2-(4-Chlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-(dioxolan-4-yl)}methyl Thioacetate (**23f**).

A mixture of *cis*- and *trans*-[2-(4-chlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl methanesulfonate **22f** (3.73 g, 0.01 mole) and potassium thioacetate (1.37 g, 0.012 mole) in DMF (35 ml) was stirred at 65-70° (2 hours). The reaction mixture was diluted with water (100 ml), extracted with dichloromethane (30 x 2 ml), the extracts washed with water (50 ml) and dried

(magnesium sulfate). Evaporation of solvent yielded a yellow oil which was chromatographed (silica gel, 70 g) and was eluted (solvent G) to produce *cis*- and *trans*-**22f** (70:30, 3.0 g, 85%) as an oil.

cis- And *trans*-2-(4-Chlorophenyl)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-4-(mercaptomethyl)-1,3-dioxolane (**8f**).

A mixture of *cis*- and *trans*-**22f** (0.7 g, 0.002 mole) and sodium bicarbonate (0.18 g, 0.0022 mole) was refluxed with methanol (15 ml) for 15 minutes. Workup according to the method described for the isolation of **8e** gave *cis*- and *trans*-**8f** (70:30, 0.53 g, 86%) as a pale yellow oil.

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REFERENCES AND NOTES

[1] D. L. Rakhmankulov, V. V. Zorin, F. N. Latypova, S. S. Zlomskii and R. A. Karakhanov, *Russ. Chem. Rev.*, **52**, 350 (1983).

[2] G. E. Wilson, Jr., M. G. Huang and W. W. Schloman, Jr., *J. Org. Chem.*, **33**, 2133 (1968).

[3] R. Böhm and E. Hannig, *Pharmazie*, **24**, 526 (1969).

[4] R. Böhm and E. Hannig, *Pharmazie*, **26**, 598 (1971).

[5] R. Böhm and E. Hannig, *Pharmazie*, **26**, 600 (1971).

[6] R. Böhm, *Pharmazie*, **33**, 465 (1978).

[7] R. Böhm and E. Hannig, *Pharmazie*, **33**, 27 (1978).

[8] R. Böhm, *Pharmazie*, **36**, 329 (1981).

[9] B. Burczyk and Z. Kortylewocz, *Synthesis*, 831 (1982).

[10] J. Gelas and M. Teppaz-Misson, *Can. J. Chem.*, **61**, 1487 (1983).

[11] P. Angeli, M. Giannella, M. Pigini, F. Gualtieri, E. Teodori, B. Valsecchi and G. Gaviraghi, *Eur. J. Med. Chem.*, **20**, 517 (1986).

[12] B. Sjöberg, *Chem. Ber.*, **75**, 13 (1942).

[13] D. R. Chapman and L. Bauer, *J. Heterocyclic Chem.*, **27**, 2053 (1990).

[14] D. R. Chapman, L. Bauer, D. P. Waller and L. J. D. Zaneveld, *J. Heterocyclic Chem.*, **27**, 2063 (1990).

[15] J. Heeres and J. Van Cutsem, *J. Med. Chem.*, **24**, 1360 (1981).

[16] T. H. Fife and L. K. Jao, *J. Am. Chem. Soc.*, **91**, 4217 (1969).

[17] F. Guinot, G. Lamaty and H. Munsch, *Bull. Soc. Chim. France*, 541 (1971).

[18] B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **41**, 2671 (1963).

[19] J. Heeres, L. J. J. Backx, J. B. A. Thijssen and A. G. Knaeps, European Patent Application, No. 228,125, December 10, 1986.

[20] B. T. Friedlander, R. A. Davis and A. R. Blem, Braz. Pedido PI Br 85 02,029 (December 31, 1985); *Chem. Abstr.*, **105**, 153062h (1986).

[21] B. T. Friedlander, A. R. Blem, R. A. Davis and D. L. Walker, European Patent Application, No. 224,998 (June 10, 1987); *Chem. Abstr.*, **107**, 217633w (1987).

[22] J. Heeres, L. J. J. Backx, J. H. Mostmans and J. Van Cutsem, *J. Med. Chem.*, **22**, 1003 (1979).

[23] D. J. Pasto, F. M. Klein and T. W. Doyle, *J. Am. Chem. Soc.*, **89**, 4368 (1967).

[24] M. Pigini, L. Brasili, M. Giannella and F. Gualtieri, *Eur. J. Med. Chem.*, **16**, 415 (1981).

[25] P. Angeli, M. Giannella, M. Pigini, F. Gualtieri and L. Cingolani, *Eur. J. Med. Chem.*, **19**, 495 (1984).

[26] I. Takeuchi, M. Sugiura, K. Yamamoto, T. Ito and Y. Hamada, *Yakugaku Zasshi*, **105**, 554 (1985).

[27] E. Teodori, F. Melani and F. Gualtieri, *J. Heterocyclic Chem.*, **23**, 1487 (1986).

[28] A. Cassinelli, P. Angeli, M. Giannella and F. Gualtieri, *Eur. J. Med. Chem.*, **22**, 5 (1987).

[29] E. Teodori, F. Gualtieri, P. Angeli, L. Brasili and M. Giannella, *J. Med. Chem.*, **30**, 1934 (1987).

[30] K. Takahashi, S. Shimizu and M. Ogata, *Synth. Commun.*, **17**, 809 (1987).