# The SN1 Hydrolysis of Isothioureas. 2

D. R. Flanagan* and A. P. Simonelli

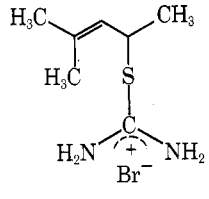
*School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268*

*Received December 2, 1975*

The hydrolysis of an allylic isothiourea and the hydrolytic effect of structural modifications on the isothiourea moiety were studied. The allylic isothiourea 1,3-dimethyl-2-butenylisothiourea (1) was found to be much more reactive than arylmethylisothioureas. Various *N*-methylisothioureas (2–4) and an isoselenourea (5) were studied to determine how alterations directly on the isothiourea affect reactivity. Such studies further support an SN1 mechanism for isothiourea hydrolysis proposed previously.[1]

In the preceding paper,[1] evidence was presented for an SN1 hydrolysis of certain arylmethylisothioureas in a purely aqueous medium. Our previous work indicated that thiourea is a new leaving group for SN1 hydrolyses. These compounds offer the opportunity to study hydrolysis in pure water because of their moderate aqueous solubility. This advantage is significant, because the correlation of SN1 hydrolysis studies from one investigator to another is made difficult by the wide variety of mixed solvent systems employed.

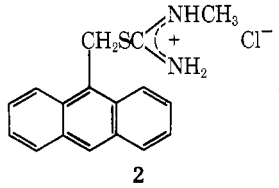
This report will extend the applicability of our proposed mechanism to a wider variety of compounds. An allylic isothiourea, 1,3-dimethyl-2-butenylisothiourea hydrobromide (1), was studied to further investigate a previous proposal[2]



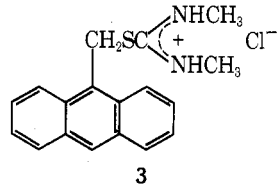
1

that 1 hydrolyzed by an SN1 mechanism. No detailed study of the mechanism of the hydrolysis was undertaken but 1 was found to hydrolyze quickly in water producing an allylic alcohol, thiourea, and hydrogen ion.

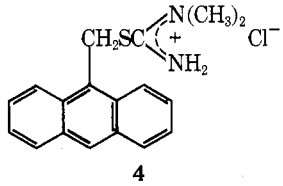
We also will report on the effect of modifications of the isothiouronium moiety on hydrolytic reactivity. Various *N*-methyl-substituted 9-anthrylmethylisothioureas (2–4) were



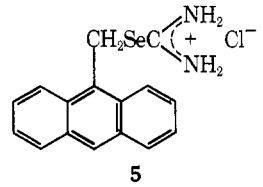
2



3



4



5

studied as well as 9-anthrylmethylisoselenourea (5), in which selenium substitutes for sulfur in the isouronium moiety.

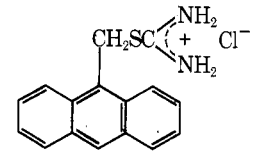
## Experimental Section

**1,3-Dimethyl-2-butenylisothiourea Hydrobromide (1).** The procedure of Saville[2] was used to synthesize 1 by the reaction of thiourea with 2-methylpenta-1,3-diene catalyzed by concentrated hydrobromic acid. The 2-methylpenta-1,3-diene was prepared by dehydration of 2-methylpentane-2,4-diol using aniline and hydrobromic acid. The 2-methylpenta-1,3-diene (bp 76 °C) was purified by fractional distillation.

Crude 1 was washed with cold dilute hydrobromic acid, suspended in acetone, filtered, and dried over paraffin chips in a desiccator. The white, crystalline product melts at 124–125 °C (Saville reports 133.5–134.3 °C). Anal. Calcd for $C_7H_{15}BrN_2S$: C, 35.15; H, 6.32. Found: C, 35.21; H, 6.25.

Two similar allylic isothioureas, allylisothiourea hydrochloride (6) and 2-methylallylisothiourea hydrochloride (7), were used as received from Eastman Organic Chemicals.

***N*-Methyl-Substituted 9-Anthrylmethylisothiourea Hydrochlorides (2–4).** *N*-Methyl, *N,N*-dimethyl, and *N,N'*-dimethyl analogues of 9-anthrylmethylisothiourea hydrochloride were synthesized in a manner similar to 9-anthrylmethylisothiourea hydrochloride (8)



8

reported in our previous paper.[1] The appropriate N-substituted thiourea was used in place of thiourea.

*N*-Methyl-9-anthrylmethylisothiourea hydrochloride (2) melted with decomposition at 206–209 °C. Anal. Calcd for $C_{17}H_{17}ClN_2S$: C, 64.44; H, 5.41. Found: C, 64.25; H, 5.25.

*N,N'*-Dimethyl-9-anthrylmethylisothiourea hydrochloride (3) melted with decomposition at 205–207 °C. Anal. Calcd for $C_{18}H_{19}ClN_2S$: C, 65.34; H, 5.79. Found: C, 63.43; H, 5.60. The impurity in this compound did not affect the hydrolysis kinetic data.

*N,N*-Dimethyl-9-anthrylmethylisothiourea hydrochloride (4) melted with decomposition at 204–207 °C. Anal. Calcd for $C_{18}H_{19}ClN_2S$: C, 65.34; H, 5.79. Found: C, 65.22; H, 5.83.

**9-Anthrylmethylisoselenourea Hydrochloride (5).** The synthesis of 5 is analogous to the synthesis of 9-anthrylmethylisothiourea hydrochloride (8)[1] except that thiourea is replaced by selenourea. Selenourea is difficult to use because of its instability. It apparently decomposes in solution by reacting with dissolved oxygen and, therefore, reaction solutions were deoxygenated prior to the introduction of selenourea. Commercial samples of selenourea were contaminated with free selenium, which was removed by filtration of the selenourea before adding it to the reaction solution. The resulting yellow isoselenourea hydrochloride (5) melted with decomposition at 185–188 °C. Anal. Calcd for $C_{16}H_{17}ClN_2OSe$ (monohydrate): C, 52.26; H, 4.66; $H_2O$, 4.91. Found: C, 52.18; H, 4.54; $H_2O$, 5.17.

**Kinetic Method.** The pH-stat technique described in the preceding paper[1] was used for each compound. The titrant volume added as a function of time was used to obtain first-order rate constants. The thiourea effect was studied, for 1, by adding thiourea to reaction solutions of 1 and measuring the apparent reduction in hydrolysis rate. The analysis of the results for the thiourea effect has been previously discussed.[1]

## Results and Discussion

**1,3-Dimethyl-2-butenylisothiourea Hydrobromide (1).** 1 hydrolyzes much faster (50–300-fold) than any of the arylmethylisothioureas reported on previously.[1] Using the pH-stat technique, anthrylmethylisothioureas require reaction temperatures greater than 50 °C for hydrolysis to occur at an appreciable rate, while 1 is so reactive that its hydrolysis can only be followed conveniently at temperatures below 40 °C. Table I summarizes the hydrolysis rate constants and activation parameters obtained for 1. The higher reactivity of 1 is encompassed in the activation entropy, which is +21.22

**Table I. Hydrolysis Rate Constants for Various Isothioureas and an Isoselenourea**

| | $10^4 k$, $s^{-1}$ | | | | | |
|---|---|---|---|---|---|---|
| | | 9-Anthrylmethyl | | | | |
| Temp, °C | 1,3-dimethyl-2-butenyl (1) | Unsubstd (8)[a] | *N*-Methyl (2) | *N,N'*-Dimethyl (3) | *N,N*-Dimethyl (4) | Seleno (5) |
| 74 | | | 11.6 | 20.9 | | |
| 67 | | 7.00 | 5.4 | 9.8 | 7.3 | 15.6 |
| 62 | | | 2.5 | 5.3 | 3.7 | 9.6 |
| 57 | | 1.70 | 1.3 | 2.7 | 2.0 | 4.1 |
| 52 | 290.5 | | | | | 1.6 |
| 47 | 142.2 | 0.43 | | | | 0.7 |
| 42 | 68.0 | | | | | |
| 37 | 31.8 | 0.10 | | | | |
| 27 | 6.4 | 0.03 | | | | |
| 17 | 1.2 | | | | | |
| $E_a$, kcal/mol | 28.9 | 28.2 | 28.2 | 28.2 | 28.2 | 36.8 |
| $S_a$, cal/mol K | +21.2 | +7.8 | +7.0 | +8.4 | +7.8 | +35.3 |
| $pK_a$[b] | | −1.19 | −1.12 | −1.32 | −1.08 | |

[a] See ref 1. [b] $pK_a$ of the N-substituted thiourea.

**Table II. Kinetic Salt and Thiourea Effects on the Hydrolysis of 1,3-Dimethyl-2-butenylisothiourea Hydrobromide (1)[a]**

| Concn, M | $10^4 k$, $s^{-1}$ | Concn, M | $10^4 k$, $s^{-1}$ |
|---|---|---|---|
| 0 | 12.8 | 1.00 $NaClO_4$ | 19.9 |
| 0.10 KCl | 12.8 | 0.01 Thiourea | 12.5 (2.6)[b] |
| 0.50 KCl | 16.2 | 0.10 Thiourea | 10.6 (2.0) |
| 1.00 KCl | 21.1 | 1.00 Thiourea | 6.6 (0.9) |
| 0.10 $NaClO_4$ | 13.3 | | |

[a] 30 °C. [b] Parenthetical values are $\alpha$ ($k_{-1}/k_2[H_2O]$).

cal/(mol K) compared to +7.77 cal/(mol K) for **8**. Similar hydrolysis studies with **6** and **7** gave no hydrolysis under the same conditions where **1** hydrolyzed readily, and even by elevating the temperature to force hydrolysis, only the thiol-producing reaction was detected.[3]

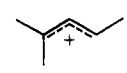
It has been shown that an increase in ionic strength assists reactions in which a molecule dissociates into ions in the rate-determining step.[4] The ionic strength effect on the hydrolysis of anthrylmethylisothioureas could not be studied because the addition of salt depresses their solubility appreciably, but **1** is very soluble in water and its solubility is relatively unaffected by the addition of salt. It was, therefore, thought that it would be worthwhile to investigate the effect of added salt on the hydrolysis rate of **1** as a further test of the SN1 mechanism proposed for isothiourea hydrolysis. Table II summarizes the hydrolysis rate constants obtained at various concentrations of potassium chloride and sodium perchlorate up to 1.0 M.

The effect of thiourea added to reaction solutions of arylmethylisothioureas[1] was used as a measure of the "common ion" effect, which is observed with the SN1 solvolysis of organic halides. The effect of initially added thiourea on the hydrolysis rate of **1** was investigated up to 1.0 M thiourea and Table II summarizes the observed hydrolysis rate constants.

The kinetic information presented for **1** indicates hydrolytic properties that are quite different from those of the arylmethylisothioureas. Its behavior can best be discussed in relation to the hydrolysis of allylic halides, which have shown evidence for both SN1 and SN2 mechanisms.[5] Allyl chloride was observed to be more reactive than the corresponding saturated alkyl chloride, but its solvolysis rate is dependent on the entering nucleophile in certain solvents.[5] The higher reactivity is attributed to the allyl cation in which the positive charge is resonantly distributed, while the dependency upon the entering nucleophile indicates that under some solvolytic conditions the allyl carbonium ion is not fully developed and allyl chloride requires nucleophilic assistance.

Methyl-substituted allyl chlorides show definite SN1 character and diminishing SN2 character. In 50% aqueous ethanol, $\alpha,\alpha$-dimethylallyl chloride and $\gamma,\gamma$-dimethylallyl chloride are $1.3 \times 10^5$ and $5.5 \times 10^5$ times more reactive than allyl chloride, respectively.[6] They are also less sensitive to the nature of the entering nucleophile, while being more sensitive to the solvent ionizing power. In formic acid, containing 0.5% water, a common ion effect was observed in the hydrolysis of various substituted allyl chlorides due to the chloride ion produced in the reaction.

The available evidence indicates that, while allyl halides may react by SN1 or SN2 mechanisms, alkyl substituted allyl halides react by an SN1 mechanism except under extreme conditions where only the SN2 mechanism is possible. Hydrolysis of **1** by an SN1 reaction would produce, as an intermediate, the trimethylallyl carbonium ion (**9**) which would be



**9**

quite stable. The lack of hydrolysis for allylisothiourea (**6**) and 2-methylallylisothiourea (**7**) indicates that a sufficiently stable carbonium ion is not produced from these isothioureas.

The modest acceleration for the hydrolysis of **1** due to the addition of salt does not apparently correlate with the significant positive salt effects seen in other SN1 hydrolyses. Typically, Ingold has observed rate accelerations of 30–50% at 0.1 M salt concentrations for the hydrolysis of *tert*-butyl bromide and benzhydryl halides.[7] Recently a more detailed study of specific salt effects on SN1 solvolyses has been reported[8] and, generally, it was observed that the rate of hydrolysis increases linearly with ionic strength for halide salts, while with perchlorates greater rate accelerations are observed.

For **1** only a 4–6% increase in hydrolysis rate is seen up to a 0.1 M concentration of either potassium chloride or sodium perchlorate. Above 0.1 M the increase in rate seems to be more pronounced with an increase of 60–70% at a 1.0 M concentration. These results indicate that the SN1 hydrolysis of an isothiourea does not follow the ionic strength behavior of alkyl halide hydrolysis. For alkyl halides the SN1 transition state involves the separation of two charged species—the carbonium ion and anionic halide. For the isothioureas, on the other

hand, the transition state involves only one charged species—the carbonium ion—and one dipolar species—thiourea. The ionic strength effect on such a dissociation would be smaller than that expected for the separation of two charged species.

Above a salt concentration of 0.1 M, the observed rate accelerations could be due to either an effect on the transition state or the initial state. It is unlikely that an increased salt concentration would assist in a transition state that is dispersing charge. In proceeding from the cationic isothiourea to the transition state in which the carbon–sulfur bond is being stretched, positive charge is being actually spread over a larger area as depicted below. Increasing ionic strength should de-


crease slightly the stability of the transition state of such a molecule. The salt effect on the initial state (cationic isothiourea) may be the important factor in the observed rate acceleration, since at high ionic strengths, it is known that the activity coefficients of many salts increase rather than decrease. Such an effect could be operative in increasing the activity of the cationic isothiourea, which would be reflected in a hydrolysis rate acceleration. In general, the kinetic effect of high concentration salt cannot be predicted, a priori, and thus the origin of the ionic strength effect is only speculative.

In addition to an apparently anomalous salt effect on hydrolysis, **1** exhibits only a minor "common ion" effect. With 0.1 M thiourea the reduction in hydrolysis rate is only 15% while other arylmethylisothioureas exhibit reductions of 85–99% at this concentration.[1] Even at the highest concentration of 1.0 M thiourea, the rate reduction is only 50%. Values for $\alpha$ ($k_{-1}/k_2[H_2O]$) are also given in Table II and it appears that $\alpha$ decreases as the thiourea concentration increases but it is questionable whether these decreases are significant. At low thiourea concentrations the rate reductions are small and small errors in the apparent rate constants would produce large deviations in $\alpha$. Additionally, at a high thiourea concentration (1.0 M), the hydrolytic properties of the aqueous solution have changed due to the large amount of added solute and thus $\alpha$ would depend on both the thiourea effect and the effect of the altered solvent on the hydrolysis rate.

For **1**, $\alpha$ is at least an order of magnitude lower than $\alpha$ determined for other arylmethylisothioureas.[1] Apparently, although the trimethylallyl carbonium ion produced in this reaction is very stable, it poorly discriminates between thiourea and water nucleophiles, which may be the result of a strongly held hydration layer hindering penetration by a potential nucleophile. In the trimethylallyl carbonium ion, the positive charge is shared by fewer atoms than in the anthrylmethyl carbonium ion, where the positive charge is delocalized over 15 atoms. The trimethylallyl carbonium ion could hold its hydration sphere more strongly because of its higher charge density. Such a hydration sphere around carbonium ions has been suggested by the pioneering work of Ingold,[9] which indicated that the reaction of the carbonium ion with water is a multimolecular cooperative reaction of the hydration sphere with the carbonium ion. With a strongly held hydration layer an effective barrier to entering nucleophiles is present. Also a strong interaction between the carbonium ion and its hydration layer should facilitate surmounting the activation barrier for the reaction of water and carbonium ion.

Even though **1** exhibits its own unusual kinetic behavior, its behavior can be rationalized in terms of the previously proposed SN1 mechanism for arylmethylisothioureas. These studies on **1** extend the general applicability of the proposed SN1 hydrolysis mechanism to a different class of isothioureas. Thus the carbonium ion mediated hydrolysis of arylmethylisothioureas is not peculiar to them alone, but can be applied to other isothioureas which produce sufficiently stable carbonium ions.

**N-Substituted 9-Anthrylmethylisothiourea Hydrochlorides (2, 3, 4).** Table I summarizes the hydrolysis rate constants and activation parameters obtained for each *N*-methylmonoisothiourea (**2–4**). These compounds apparently have the same activation energy (28.2 kcal/mol) as **8** with the differences in hydrolysis rate being encompassed in their activation entropies.

In considering solvolysis reactions, the relative ability of various leaving groups to depart from carbon is an important factor in controlling hydrolysis rates. The ability of a group to leave a developing carbonium ion can be correlated with the $pK_a$ of the conjugate acid of the leaving group.[10] This correlation is reasonable, since the $pK_a$ of an acid represents the ability of a base to separate from a hydronium ion, which is analogous to a base separating from a carbonium ion.

The hydrolysis rate of **3** is significantly faster than that for **8** while **2** hydrolyzes significantly slower. These results correlate well with the $pK_a$'s of the corresponding thioureas (Table I)[11] except for **4**. Apparently, **4** does not follow the reactivity correlation with $pK_a$, because its hydrolysis rate is identical with **8** at the three temperatures studied, while the $pK_a$ correlation predicts that **4** should hydrolyze slower than **2**. The anomaly in this case may be due to steric factors arising from the two methyl groups being attached to the same nitrogen. Isothioureas have been shown to be freely rotating about the alkyl carbon–sulfur bond,[12] but substituents on the isothiourea nitrogens or in the alkyl moiety hinder this rotation[12] and may hold the molecule in one conformation, if they are sufficiently bulky. Molecular models show that the substitution of two methyl groups on one nitrogen can hinder free rotation in **4**. Steric hindrance could create an energy barrier to rotation creating a strain upon rotation in the alkyl carbon–sulfur bond which would facilitate bond breaking in the SN1 ionization step.

Other than the abnormality in reactivity observed for **4**, methyl additions to the isothiourea moiety add further confirmation to the proposed carbonium ion mechanism.[1] Minor alterations in leaving group structure would not produce such a pronounced effect on the hydrolysis rate in an SN2 reaction. Only a small charge separation is involved in the transition state for a SN2 mechanism which would not be as sensitive to the individual ionization properties of each methyl-substituted thiourea.

**9-Anthrylmethylisoselenourea Hydrochloride (5).** The hydrolysis rate constants and activation parameters for **5** are summarized in Table I. With the N-substituted isothioureas (**2–4**) there is a correlation between reactivity and $pK_a$ of the corresponding thiourea. This $pK_a$ relationship is applicable because only small perturbations are made in the leaving group. The methyl substitutions influence the carbon–sulfur bond indirectly through an inductive effect, while replacement of sulfur by selenium is a more significant perturbation of the leaving group. The isoselenourea (**5**) has a larger activation energy than its corresponding sulfur analogue (**8**), which is in keeping with the isouronium moiety being the leaving group in a SN1 hydrolysis mechanism. Selenium is larger and more polarizable than sulfur, and it is reasonable to assume that energetically it should be more difficult for selenourea to depart from the developing carbonium ion. This greater energy requirement is seen in the 8 kcal/mol higher activation energy for the isoselenourea (**5**) over the equivalent isothiourea (**8**). The very positive activation entropy may indicate higher

initial solvation for **5**, contributing to the high activation entropy when hydration water is released in the activated state.

## Conclusions

The evidence presented in this and the previous report[1] supports our proposal that thiourea is a new leaving group for SN1 hydrolyses. In this report we have included studies on a reactive allylic isothiourea and the effect of alterations of the leaving group. These additional studies extend the applicability of the SN1 mechanism originally proposed for arylmethylisothioureas and indicate that perturbations of the leaving group are in agreement with a carbonium ion mediated mechanism.

**Acknowledgments.** Supported in part by Contract PH43-68-1284, with Chemotherapy, National Cancer Institute, National Institutes of Health.

**Registry No.**—**1**, 59473-89-1; **2**, 59473-90-4; **3**, 59473-91-5; **4**, 59473-92-6; **5**, 59473-93-7.

## References and Notes

(1) D. R. Flanagan and A. P. Simonelli, *J. Org. Chem.*, preceding paper in this issue.
(2) B. Saville, *Proc. Chem. Soc., London*, 214 (1961); 18 (1962); *J. Chem. Soc.*, 5040 (1962).
(3) B. Rathke, *Ber.*, **17**, 297 (1884).
(4) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 979 (1940).
(5) C. A. Vernon, *J. Chem. Soc.*, 423 (1954).
(6) A. Streitwieser, "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, p 78.
(7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2d ed, Cornell University Press, Ithaca, N.Y., 1969, p 491.
(8) C. A. Bunton, T. W. Del Pasco, A. M. Dunlop, and K.-U. Yang, *J. Org. Chem.*, **36**, 887 (1971).
(9) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 979 (1940).
(10) M. D. Bentley and M. J. S. Dewar, *J. Am. Chem. Soc.*, **92**, 3991 (1970).
(11) M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **79**, 1066 (1960).
(12) H. Kessler and H. O. Kalinowski, *Angew. Chem., Int. Ed. Engl.*, **9**, 641 (1970).

# Synthesis of the β-Adrenergic Blocking Agent Timolol from Optically Active Precursors

Leonard M. Weinstock,* Dennis M. Mulvey, and Roger Tull

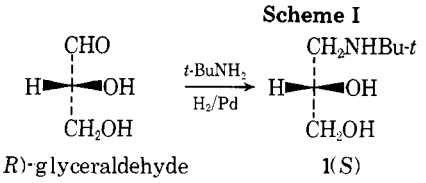
*Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065*

*Received April 9, 1976*

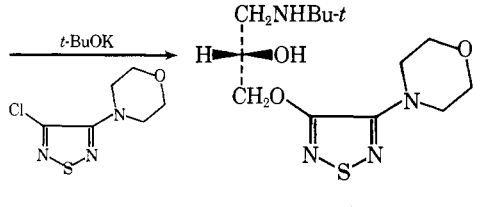
The synthesis of the β-adrenergic blocking agent, timolol, from optically active precursors is described and confirmation of its absolute configuration is presented.

The biological activity of 3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole (**2**),[1] a potent β-adrenergic blocking agent, resides mainly in one of the enantiomers, the levorotatory hemimaleate salt. The active isomer, timolol maleate, was previously obtained via chemical resolution, and on the basis of the stereochemistry of compounds interacting with the adrenergic receptor was presumed to have the *S* configuration[1]. Since other β-blocking agents such as propranolol[2] and practolol[3] possess the *S* configuration, it seems likely that the stereoisomeric relationship of timolol with (*R*)-glyceraldehyde as depicted in Scheme I should obtain. We have indeed found this to be the case and wish to report a convenient synthesis of timolol from optically active precursors. Catalytic hydrogenation of (*R*)-glyceraldehyde over palladium in the presence of *tert*-butylamine produced 54% of (*S*)-3-*tert*-butylamino-1,2-propandiol (**1**). This in turn

**Scheme I**




(*R*)-glyceraldehyde **1**(*S*)




**2**(*S*)

was condensed with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole in the presence of potassium *tert*-butoxide to afford a low yield of optically pure timolol, isolated as the levorotatory maleate salt.

This procedure was short and convenient for laboratory purposes but suffered from two shortcomings: low yields and the commercial unavailability of glyceraldehyde. Low yields in the etherification step (**1** → **2**) were found to be a consequence of the base instability of compound **2**. Strong base effects the equilibration of **2** and **3** (Smiles rearrangement) as well as the concomitant loss of the side chain from **2** and **3** giving the anion of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**4**). These transformations are illustrated in Scheme II. In order to circumvent these side reactions the secondary alcohol functionality of **1** was protected by reaction with benzaldehyde yielding oxazolidine **8**. Subsequent reaction of **8** with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole in the presence of potassium *tert*-butoxide followed by acid hydrolysis gave timolol in 50% yield.

Scheme III depicts an alternate mode for introducing the aminopropanediol side chain utilizing optically active epoxide **5**. When the epoxide **5** was allowed to react with the sodium salt of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole, **2** was produced in 36% yield.

To obviate the need for (*R*)-glyceraldehyde, an alternate synthesis of aminoglycol **1** was devised (Scheme IV). Cleavage of D-mannitol-1,2,5,6-bisacetonide (**6**)[5] with lead tetraacetate conveniently afforded 2 equiv of (*R*)-glyceraldehyde acetonide (**7**). Reductive alkylation with *tert*-butylamine and subsequent hydrolysis gave a 70% overall yield of **1** without isolation of the intermediates. Optimum conditions for conducting the reductive alkylation were achieved by slow addition of alde-