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.

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

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

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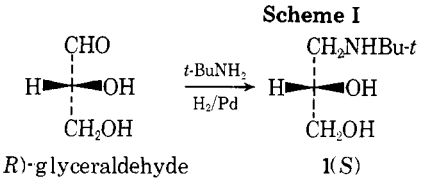
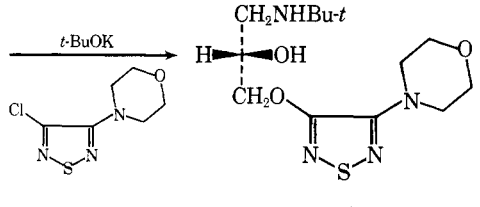
The synthesis of the β-adrenergic blocking agent, timolol, from optically active precursors is described and confirmation of its absolute configuration is presented.

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*)

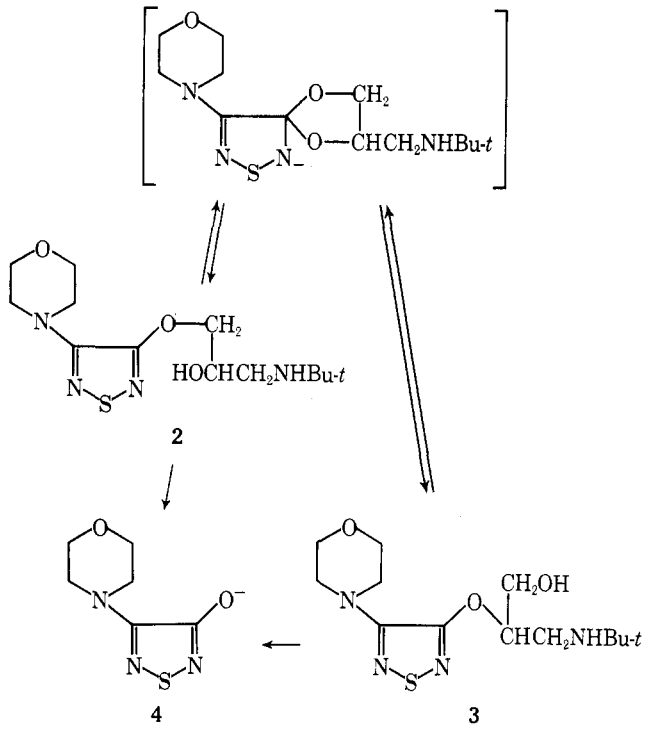
was condensed with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole in the presence of potassium *tert*-butoxide to afford a low yield of optically pure timolol, isolated as the levorotatory maleate salt.

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.

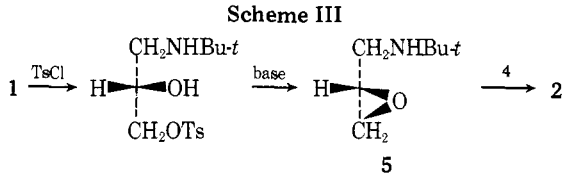
Scheme III depicts an alternate mode for introducing the aminopropanediol side chain utilizing optically active epoxide **5**. When the epoxide **5** was allowed to react with the sodium salt of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole, **2** was produced in 36% yield.

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-

Scheme II



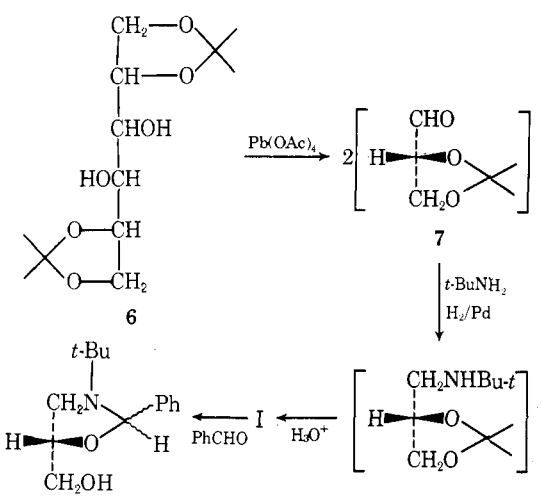
Scheme III



hyde to *tert*-butylamine during the course of the catalytic reduction.[6] In this manner, reduction of the aldehyde as well as racemization of the intermediate imine were minimized.

In conclusion, a practical synthesis of timolol has been achieved through the agency of optically active precursors and its absolute configuration has been confirmed. These procedures are also of potential utility in the synthesis of other β-adrenergic blocking agents in the biologically active *S* configuration utilizing either electrophilic or nucleophilic optically active reagents for elaboration of the side chain. These methods coupled with the method used by Danilewicz and Kemp[3] for the synthesis of (*R*)-practolol via **7** allow the introduction of the aminopropanol side chain in either the *R* or *S* configuration.

Scheme IV



Experimental Section

All melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Boiling ranges are similarly uncorrected. Infrared spectra were determined on a Perkin-Elmer Infracord Model 137 as Nujol mulls. Rotations were measured on a Perkin-Elmer Model 141 polarimeter. NMR spectra were determined on a Varian Model A-60A; proton shifts, δ, are relative to internal Me_4Si reference. Uv spectra were obtained on a Perkin-Elmer Model 202.

3-Chloro-4-(*N*-morpholino)-1,2,5-thiadiazole. 3,4-Dichloro-1,2,5-thiadiazole[4] (100.0 g, 0.645 mol) was added dropwise over a 30-min period at 105–110 °C to 224 ml (2.58 mol) of morpholine (mild exotherm). After addition the reaction mixture was stirred for 2 h at 105–110 °C, cooled to 15 °C, and quenched with 250 ml of water. The mixture was made acidic with 250 ml of concentrated hydrochloric acid. The insoluble oil soon crystallized to a heavy solid which was isolated by filtration and washed well with water. After drying in vacuo at 35 °C, 125.5 g (97%) of the morpholine derivative was obtained, mp 43–45 °C. NMR ($CDCl_3$) showed two symmetrical multiplets, δ 3.5 ppm (CH_2NCH_2), the second at 3.9 ppm ($-CH_2OCH_2-$). An analytical sample was prepared by recrystallization from ethanol, mp 43–45 °C. Anal. Calcd for $C_6H_8ClN_3OS$: C, 35.04; H, 3.92; N, 20.43; Cl, 17.24. Found: C, 35.27; H, 3.88; N, 19.90; Cl, 17.30.

3-Hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (4). 3-Chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (125.5 g, 0.610 mol) was added to 1 l. of 2.5 N sodium hydroxide and 100 ml of dimethyl sulfoxide. The reaction mixture was refluxed with stirring for 3 h. The solution was cooled to 15 °C and rendered acidic with 250 ml of concentrated hydrochloric acid. The precipitated hydroxy compound was filtered at 15 °C, washed well with water, and dried in a Dietert dryer, yielding 108.7 g (95%) of **4**, mp 198–200 °C dec, equiv wt 189 (calcd, 187). The NMR (Me_2SO-d_6) showed two symmetrical multiplets at δ 3.3 ($-CH_2NCH_2-$) and 3.45 ppm ($-CH_2OCH_2-$). The active proton was too broad to be observed. Anal. Calcd for $C_6H_9N_3O_2S$: C, 38.49; H, 4.85; N, 22.44. Found: C, 38.64; H, 4.76; N, 22.49.

(*S*)-(−)-3-*tert*-Butylamino-1,2-propanediol (1). Method A. To a solution of 12.48 g (0.17 mol) of *tert*-butylamine in 50 ml of methanol was added 1.0 g of 5% palladium on carbon and the mixture shaken under hydrogen (45 psi initial) as a solution of 5.0 g (0.056 mol) of (*R*)-glyceraldehyde in 20 ml of methanol was added dropwise. Hydrogen uptake ceased after 24 h (48 of 53 lb theory consumed). After separation of the catalyst by filtration and washing twice with 5-ml portions of methanol the combined filtrates were concentrated in vacuo to a viscous, yellow oil. This oil was covered with 25 ml of ether and scratched to induce crystallization. The resulting solid was isolated by filtration and dried in vacuo at 25 °C to afford 7.1 g of crude **1**, mp 55–65 °C. After recrystallizing from *n*-hexane 4.47 g (54%) of **1**, mp 81–83 °C, $[\alpha]_D$ −30.1° (1 N aqueous HCl), was obtained. The NMR showed a singlet at δ 1.1 ppm [$-C(CH_3)_3$], a distorted doublet at 2.6 ppm ($-CH_2N-$), a complex multiplet at 3.6 ppm (CHOH, NH), distorted singlet at 4.0 ppm ($-CH_2O-$). Anal. Calcd for $C_7H_{17}NO_2$: C, 57.10; H, 11.64; N, 9.51. Found: C, 57.36; H, 11.58; N, 9.73.

Method B. A solution of 36.4 g (0.138 mol) of 1,2,5,6-diisopropylidenemannitol[5] in 175 ml of anhydrous tetrahydrofuran was treated with 61.6 g (0.139 mol) of lead tetraacetate. The addition was made in portions over a 20-min period at 15–20 °C (slightly exothermic). After the addition the mixture was stirred for 40 min at 25 °C and the reaction tested negative with potassium iodide–starch paper. The mixture was cooled to 0 °C, aged 10 min, and filtered into an ice-cooled receiver, washing the precipitate with 35 ml of cold tetrahydrofuran. The filtrate (containing isopropylidene-(*R*)-glyceraldehyde) was added dropwise over a 1-h period during hydrogenation to a mixture of 103 ml of *tert*-butylamine, 103 ml of methanol, and 7.2 g of 5% palladium on carbon in a hydrogenation apparatus under 3 atm hydrogen pressure. The mixture was hydrogenated at ambient temperature until the absorption of hydrogen ceased. The catalyst was filtered (ice-cooled receiver) and washed with 52 ml of methanol. The filtrate was treated with 350 ml of 6 N hydrochloric acid (cooling), and the mixture was distilled until a vapor temperature of 98 ± 1 °C was reached, and then refluxed for 1 h. The solution was cooled to 0 °C and treated with 140 g of sodium hydroxide pellets keeping the temperature under 35 °C. The mixture was treated with 140 ml of water and extracted four times with 175-ml portions of methylene chloride. The combined extracts were dried over magnesium sulfate and evaporated to a thick crystalline slurry. The residue was flushed twice with 50 ml of ether and filtered at 0–5 °C and the product dried at 35 °C in vacuo yielding 28.5 (70%) of *S*-**1**, mp 83.5–85 °C, $[\alpha]_D$ −30.3° (1 N aqueous HCl), equiv wt 150 (calcd, 147).

This material was identical in all respects with that prepared from (*R*)-glyceraldehyde.

(*S*)-(−)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole (2) Hemimaleate Salt. Method A. A mixture of 20.57 g (0.100 mol) of 3-(*N*-morpholino)-4-chloro-1,2,5-thiadiazole and 14.72 g (0.100 mol) of (*S*)-(−)-3-*tert*-butylamino-1,2-propanediol (1) in 50 ml of anhydrous *tert*-butyl alcohol was heated to reflux under nitrogen. Then 100 ml of 1 M potassium *tert*-butoxide in *tert*-butyl alcohol was added in 10-ml portions 10 min apart. After the last addition the mixture was refluxed for an additional 10 min, cooled to 60 °C, and treated with 50 ml of 6 N hydrochloric acid with cooling. An additional 50 ml of water was introduced and the *tert*-butyl alcohol evaporated in vacuo, leaving an oil–water residue. The mixture was extracted twice with 35 ml of methylene chloride and the combined organic phases back-extracted twice with 50 ml of 4 N hydrochloric acid. The acid layers were rendered alkaline with excess potassium carbonate and extracted twice with 50 ml of ether. The ether layers were washed twice with 20 ml of water, dried over magnesium sulfate, and evaporated in vacuo to an oil, 13.7 g. This oil was dissolved in 50 ml of tetrahydrofuran, treated with 1.5 g of Merck charcoal, and filtered, and the cake was washed with 20 ml of fresh tetrahydrofuran. To this solution was added a solution of 5.0 g (0.043 mol) of maleic acid in 25 ml of tetrahydrofuran. The mixture was seeded and aged for 1 h at 25 °C. The resulting salt was filtered, washed with 5 ml of tetrahydrofuran, and dried at 50 °C in vacuo, yielding 7.3 g (13%) of **2** hemimaleate, mp 195–198 °C. The product was recrystallized from 60 ml of ethanol (0.5 g charcoal treatment), mp 198.5–199.5 °C dec (lit.[1] mp 201–202 °C), $[\alpha]_{405}$ −11.52° (*c* 4, 1 N aqueous HCl).

The NMR (1.0 N DCl/D_2O) showed a singlet at δ 1.5 ppm [$-C(CH_3)_3$], a doublet at 3.25 ppm ($-CH_2N-$), one-half of a symmetrical pair of multiplets at 3.6 ppm ($-CH_2NCH_2-$), the second half at 3.9 ppm ($-CH_2OCH_2-$), a broad multiplet at 4.5 ppm (–OCH–), a broad singlet at 4.6 ppm ($-CH_2O-$), and a sharp singlet at 6.5 ppm (HC=CH). Anal. Calcd for $C_{17}H_{28}N_4O_7S$: C, 47.21; H, 6.53; N, 12.95; S, 7.41. Found: C, 47.30; H, 6.59; N, 12.78; S, 7.55.

Method B. A mixture of 11.3 ml of 0.885 M potassium *tert*-butoxide in *tert*-butyl alcohol (10 mmol), 2.35 g (10 mmol) of (*S*)-(−)-2-phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (**8**), and 2.05 g (10 mmol) of 3-chloro-4-morpholino-1,2,5-thiadiazole was stirred at 25 °C for 16 h. The solvent was evaporated in vacuo and the residue treated with 20 ml of 1.0 N hydrochloric acid at 60 °C for 1 h. The mixture was cooled to 25 °C and extracted twice with 10 ml of ether. The aqueous layer was made alkaline with excess potassium carbonate and extracted twice with 70 ml of ether. These ether extracts were dried over magnesium sulfate and evaporated to an oil residue of 1.80 g (57%) of the desired free base. This material was dissolved in 10 ml of tetrahydrofuran and treated with 0.7 g (6 mmol) of maleic acid, producing 2.17 g (50%) of **2** hemimaleate, mp 199–201 °C, $[\alpha]_{405}$ −11.9° (*c* 4, 1 N HCl).

The mother liquor from which **2** had been crystallized was concentrated in vacuo to a gummy residue. This residue was partitioned between 40 ml of 5% aqueous sodium bicarbonate and 40 ml of ether. After drying over magnesium sulfate, evaporation of the ether in vacuo gave 6.0 g of a tan oil which was chromatographed on 400 g of Merck neutral alumina. Elution with glyme–THF (1:1) provided 1.9 g of crude **3** which was recrystallized from *n*-hexane affording pale yellow needles, mp 120–121.5 °C. The mass spectrum indicated a molecular ion of 316; NMR (Me_2SO-d_6) showed a multiplet at δ 4.8 ppm (–OCH), poorly resolved doublet at 3.7 ppm ($-CH_2OH$), multiplet at 3.45 ppm ($-CH_2N$, plus morpholino), and a singlet at 1.0 ppm [$-C(CH_3)_3$]. Addition of D_2O did not alter the splitting pattern of the single methine proton, indicating that it was not α to a slowly exchanging active proton. Anal. Calcd for $C_{13}H_{24}N_4O_3S$: C, 49.35; H, 7.65; N, 17.71; S, 10.13. Found: C, 49.53; H, 7.63; N, 17.84; S, 10.24.

Method C. A mixture of 0.92 g (2.5 mmol) of (*S*)-(−)-3-*tert*-butylammonium-1,2-epoxypropane *d*(10)-camphorsulfonate, 0.52 g (2.5 mmol) of the sodium salt of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (from NaOMe in MeOH), plus 0.467 g (2.5 mmol) of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole in 2 ml of dimethyl sulfoxide was aged for 4 days at room temperature. The solution was quenched into 35 ml of distilled water and the aqueous solution brought to pH 9 with sodium carbonate. The aqueous solution was then extracted three times with 40 ml of methylene chloride, and these extracts back extracted with 20 ml of water. After drying over magnesium sulfate, evaporation of the methylene chloride left a tan oil. This oil was dissolved in 8 ml of tetrahydrofuran and was added to a solution of 0.29 g (2.5 mmol) of maleic acic in 3 ml of tetrahydrofuran. After aging for 1 h at room temperature, the precipitate was isolated and dried in vacuo. This afforded 0.63 g (58.5%) of **2** hemimaleate, mp 183–193 °C. Recrystallization from 4 ml of absolute ethanol gave 0.35 g (32.5%), mp 197–198 °C, $[\alpha]_{405}$ −11.49° (*c* 4, 1 N HCl).

(*S*)-(−)-2-Phenyl-3-*tert*-butyl-5-hydroxymethyloxazolidine (8). A mixture of 7.5 g (0.051 mol) of (*S*)-(−)-3-*tert*-butylamino-1,2-propanediol and 10 ml (0.999 mol) of benzaldehyde was heated to 150 °C. Water plus benzaldehyde distilled from the reaction as fresh benzaldehyde was added to maintain constant volume. After 30 min distillation of volatiles ceased and the mixture was cooled to 30 °C. The excess benzaldehyde was distilled at 0.5 mm. Four fractions were collected: (1) bp 115–117 °C (0.2 g); (2) bp 117–120 °C (0.5 g); (3) bp 120–122 °C (5.3 g of **8**, 85% pure by VPC); (4) bp 122–124 °C (4.0 g of **8**, 93% pure by VPC). The combined yield of fractions 3 and 4 was 77%. The NMR spectrum ($CDCl_3$) (both enantiomers) exhibited a doublet at δ 1.05 ppm [$-C(CH_3)_3$], a singlet at 2.4 ppm (–OH), a doublet at 5.5 ppm (aminal methine), and a multiplet at 7.4 ppm (Ph). The remaining potons form a complex group of multiplets between 2.7 and 4.3 ppm.

(*S*)-(−)-1,2-Dihydroxy-3-*tert*-butylaminopropane 1-*p*-Toluenesulfonate. A solution of 4.0 g (0.027 mol) of (*S*)-(−)-3-*tert*-butylamino-1,2-propanediol and 3.14 g (0.027 mol) of pyridine hydrochloride in 8 ml of pyridine was treated with 5.31 g (0.027 mol) of *p*-toluenesulfonyl chloride. The mixture was stirred for 0.5 h at 25–30 °C and poured into 50 ml of cold water. The solution was treated with 1.92 g (0.014 mol) of potassium carbonate and the pyridine was evaporated at 55–60 °C in vacuo. The aqueous residue was treated with 4.5 g (0.033 mol) of potassium carbonate and the mixture extracted with 50 ml of methylene chloride. Evaporation of the magnesium sulfate dried extract gave a residue of 6.2 g (75%) of the desired tosylate, mp 91–93 °C.

The NMR ($CDCl_3$) exhibited a singlet at δ 1.08 ppm [$-C(CH_3)_3$], a singlet at 2.45 ppm ($-CH_3$), a complex multiplet centered at 2.6 ppm (NCH_2), a singlet at 3.3 ppm (NH, OH), a multiplet centered at 4.0 ppm (CH_2O, OCH), and an A_2B_2 pattern at 7.25 and 7.75 ppm.

(*S*)-(−)-3-*tert*-Butylammonium-1,2-epoxypropane (5) *d*(10)-Camphorsulfonate Salt. A solution of 2.0 g (6.6 mmol) of the above tosylate in 30 ml of benzene was treated with 0.39 g (7.3 mmol) of sodium methoxide. This mixture was aged for 2.5 h at room temperature and was then filtered, the insolubles being washed with 10 ml of benzene. This solution was then treated with a solution of 1.62 g (7 mmol) of *d*(10)-camphorsulfonic acid in 10 ml of acetone. The solution was seeded and evaporated to a volume of 20 ml under a stream of nitrogen. The resulting precipitate was isolated by filtration and dried in vacuo, yielding 0.95 g (38.5%) of the *d*(10)-camphorsulfonate of **5**, mp 141–142 °C. Anal. Calcd for $C_{17}H_{31}NO_5S$: C, 56.47; H, 8.64; N, 3.87. Found: C, 56.44; H, 8.50; N, 3.80. The NMR (Me_2SO-d_6) showed two singlets at δ 0.76 and 1.05 ppm (C_7 geminal CH_3's of camphorsulfonic acid), a singlet at 1.29 ppm [$-C(CH_3)_3$], a multiplet centered at 1.30 ppm (C_5 CH_2 of camphorsulfonic acid), a multiplet centered at 1.85 ppm (C_6 CH_2 plus one H from C_3 CH_2 of camphorsulfonic acid), a multiplet centered at 2.19 ppm (C_4 CH of camphorsulfonic acid), an AB pattern centered at 2.67 ppm ($-CH_2SO_3^-$), a multiplet centered at 2.60 ppm (one proton from C_3CH_2 of camphorsulfonic acid), a multiplet centered at 2.84 ppm (terminal epoxide), a multiplet centered at 3.30 ppm (substituted epoxide and $CH_2N<$), and a broad singlet at 8.92 ppm ($-SO_3H$, –NH–).

Equilibration of Compounds 2 and 3. Demonstration of the Instability of 2 and 3 toward Strong Base. A solution of 0.316 g (1.0 mmol) of **2** base was prepared in 2.0 ml of anhydrous *tert*-butyl alcohol. To this was added 1.12 ml of 0.89 N potassium *tert*-butoxide (1 mmol) in *tert*-butyl alcohol and the mixture digested at ambient temperature. Samples were taken at intervals and after silylation were analyzed by VPC. After 20 min the presence of **3** was detected. Likewise, when pure **3** was treated with potassium *tert*-butoxide at room temperature approximately 18% of **2** was detected in 20 min.

Both **2** and **3** were quantitatively converted into **4** when these compounds were treated with 1.5 molar equiv of potassium *tert*-butoxide in refluxing *tert*-butyl alcohol for 3 h.

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Registry No.—**1**, 30315-46-9; **2** hemimaleate, 33305-95-2; **3**, 59697-06-2; **4**, 30165-97-0; **5** *d*-(10)-camphorsulfonate, 30315-52-7; **6**, 1707-77-3; **7**, 59697-07-3; **8**, 59697-08-4; 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole, 30165-96-9; 3,4-dichloro-1,2,5-thiadiazole, 5728-20-1; morpholine, 110-91-8; *tert*-butylamine, 75-64-9; (*R*)-glyceraldehyde, 453-17-8; 3-hydroxy-4-(*n*-morpholino)-1,2,5-thiadiazole sodium salt, 59697-09-5; benzaldehyde, 100-52-7; (*S*)-(−)-1,2-dihydroxy-3-*tert*-butylaminopropane 1-*p*-toluenesulfonate,

30315-51-6; *p*-toluenesulfenyl chloride, 98-59-9; *d*-(10)-camphorsulfonic acid, 3144-16-9.

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Synthesis of C-Nucleosides. 13.[1] *s*-Triazolo[4,3-*a*]- and -[1,5-*a*]pyridine Derivatives

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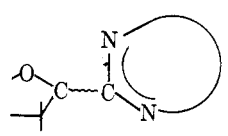
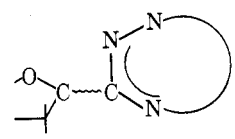
s-Triazolo[4,3-*a*]- and -[1,5-*a*]pyridine C-nucleosides are obtained in one step from 2-pyridylhydrazines and ribofuranosyl thioformimidate. The structures of these compounds are determined with ultraviolet, ^1H and ^{13}C NMR, mass, and circular dichroism spectra.

Glycosyl thioformimidates have proved in our hands to be convenient intermediates for the total synthesis of C-nucleosides. Their condensation with α or ortho aminonitrile derivatives, for instance, gave nucleosides of type **1** (imidazoles, purines, pyrazolopyrimidines)[2] in one step. We decided then to study the feasibility of using the same thioimidates to prepare heterocycles of type **2**, i.e. 1,2,4-triazoles[3] and fused triazoles.



1



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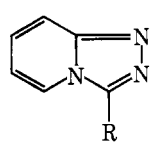
Representative of this new class of heterocycles is the triazolo[4,3-*a*]pyridine **3**. This structure is of particular in-



3

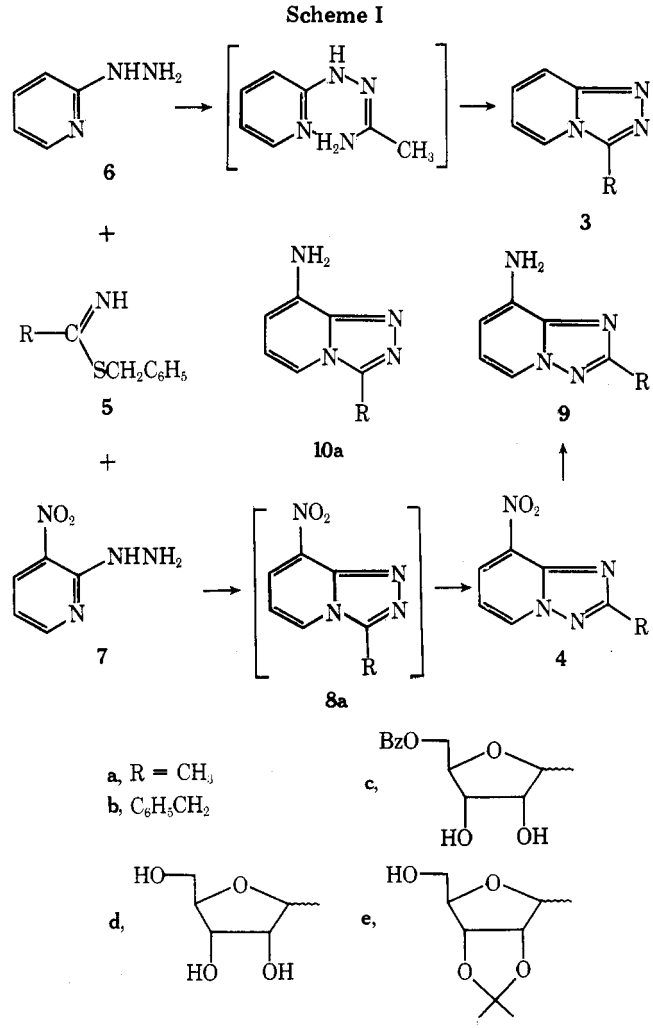
terest since on one hand it contains the 1,2,4-triazole moiety of ribavirine, and on the other hand it may be regarded as an unusual deaza analogue of formycines. C-Nucleosides containing a bridgehead nitrogen atom are unknown.[17] Their synthesis was undertaken in view of their possible biological activities.

3-Alkyl and aryl *s*-triazolo[4,3-*a*]pyridines **3** have been synthesized by cyclization of 2-pyridylhydrazines with carboxylic acid derivatives: anhydrides,[4] chlorides,[5,6] ortho esters,[5] or from the 2-pyridylhydrazone of aromatic aldehydes.[6-8] When the 2-pyridylhydrazine is substituted with an electron-withdrawing NO_2 group in position 3, the ring closure with ortho esters gives the expected 3-alkyl-8-nitro-*s*-triazolo[4,3-*a*]pyridines **3** which isomerized easily into *s*-triazolo[1,5-*a*]pyridines **4**.[9]

Results

In order to develop a reaction that could be extended to carbohydrate chemistry, we condense benzyl thioacetimidate (**5a**) (Scheme I) with 2-pyridylhydrazine (**6**): with 10% of pyridine in chloroform at room temperature, the reaction

Scheme I



yields the noncyclized intermediate acetamidrazone whereas using reflux in pyridine, the yield of cyclization goes up to 79% of 3-methyl-*s*-triazolo[4,3-*a*]pyridine (**3a**), previously described.[4] In the same conditions, benzyl phenylthioacetim-

† Research chemist of INSERM, deceased on September 14, 1975.