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Absolute Configuration of Glycerol Derivatives. 6.[1] Cupra A Circular Dichroism Spectra of 3-(Aryloxy)-1-(alkylamino)-2-propanol β-Adrenergic Blocking Agents

Wendel L. Nelson,* Mark L. Powell, and John E. Wennerstrom

Department of Pharmaceutical Sciences, School of Pharmacy, University of Washington, Seattle, Washington 98195

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Cupra A circular dichroism spectra of 16 optically active 3-(aryloxy)-1-(alkylamino)-2-propanol structures have been examined. All 2*R* isomers show negative Cotton effects (ε 250–690) in the 285-nm region and two weaker Cotton effects in the longer wavelength regions. Negative transitions are observed in the 500-nm region (usually ε 5–50) and positive transitions in the 620-nm region (ε 50–95). 2*S*-Enantiomers show inverted spectra. The method was applicable to all compounds tried in this class which contained an *N*-isopropyl or primary alkyl substituent. In one case where the N substituent was *tert*-butyl, no Cupra A CD spectrum was observed.

Effects related to absolute configuration are significant and fundamental factors contributing to the intensity and duration of pharmacological responses to drugs, neurotransmitters, and hormones. An excellent example of a series of compounds where effects of absolute configuration are observed in several aspects of drug action is the sympathetic agonists and antagonists related to norepinephrine and epinephrine.[2] Changes in the absolute configuration of the α carbon alter the potency of β-adrenergic agonists in in vitro assays (in reserpinized tissues) 5–25-fold. Among competitive β-adrenergic antagonists differences of up to 500-fold are noted. Differences in rates of cardiac tissue uptake and in overall metabolic rate have been noted between optical isomers of β-adrenergic antagonists.[3] Thus, determination of the absolute configuration of these agents is an important dimension of studies relating chemical characteristics to pharmacological activity.

Recently we reported the use of Cupra A circular dichroism spectra for the unambiguous determination of absolute configuration of several drug-related 3-(aryloxy)-1,2-propanediols and 3-(aryloxy)-1-amino-2-propanols.[4] In that study preparation of a variety of enantiomers of known absolute configuration from chiral glycerol derivatives allowed a relatively complete investigation of the method as applied to these related glycols and 1,2-amino alcohols. The Cupra A CD techniques have also been applied successfully to other 1,2-glycols and 1,2-amino alcohols,[5–15] a few 1,3-glycols,[16] and certain mandelic acid derivatives.[17]

Assignment of the absolute configuration of β-adrenergic antagonists of the aryloxypropanolamine type has previoulsy been done primarily on an empirical basis. The positive rotating hydrochloride salts of propranolol were known to be of the 2*R* configuration because (+)-(2*R*)-3-chloro-2-hydroxypropanolamine was stereochemically related to (+)-(2*S*)-lactic acid by Dukes and Smith.[18] Additionally, these workers reported the application of the Horeau method to several related systems which gave consistent results. At the present time there are no known exceptions to those observations. In only a few cases has stereospecific synthesis from starting materials of known chirality been applied to such systems.[4,19–21]

In this paper we report the Cupra A CD spectra of a number of aryloxypropanolamines which have been obtained from several sources, including chiral synthesis and resolution. Analyses of the results of these studies indicate that the method is generally applicable to most 3-(aryloxy)-1-(alkylamino)-2-propanols.

The results obtained are reported in Table I. An example of the Cupra A CD spectra obtained is given in Figure 1. The first six entries in Table I are compounds of known absolute configuration. These compounds were synthesized from chiral glycerol derivatives of known absolute configuration. Other entries are data obtained on compounds from several pharmaceutical industrial sources. In only a few cases was the absolute configuration known on the basis of synthesis (see Experimental Section). As noted, all compounds which provide a negative Cotton effect at 280–290 nm are correlated with the 2*R* absolute configuration, either known or assigned on this basis. All 2*S* enantiomers give positive Cotton effects in this region. All compounds gave Cupra A CD spectra with the exception of the enantiomers of tolamolol (**15** and **16**), for which no spectral changes were observed. Optical isomers **15** and **16** contain an *N*-*tert*-butyl group. These results are consistent with the work of Mitscher,[15] who did a systematic study of *N*-alkyl-2-amino-1-phenylethanols. As the N substituent became larger, the amplitude of the Cupra A CD Cotton effect decreased. Compounds with N secondary alkyl or cycloalkyl substituents gave low ε values (ε 35–75). Their study did not include compounds bearing a *tert*-butyl group.

As noted both in Figure 1 and Table I, an intermediate

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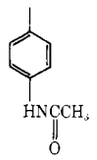
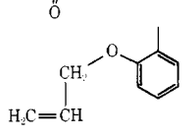
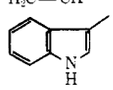
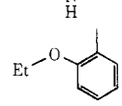
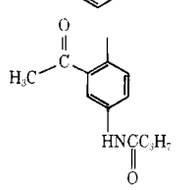
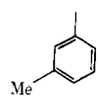
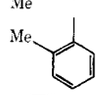
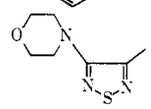
Table I. Cupra A CD Spectra of Chiral 3-(Aryloxy)-1-(alkylamino)-2-propanols

$$ArOCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2NH\text{-}i\text{-}Pr$$

compd	stereochemistry	Ar	rel $[\theta]_x$ max		
1[a]	2R		$[\theta]_{320}$ −250	$[\theta]_{500}$ −18	$[\theta]_{620}$ +56
2[a]	2S		$[\theta]_{320}$ +295	$[\theta]_{500}$ +15	$[\theta]_{620}$ −59
3	2R		$[\theta]_{300}$ −625	$[\theta]_{500}$ −46	$[\theta]_{620}$ +95
4	2S		$[\theta]_{300}$ +570	$[\theta]_{500}$ +46	$[\theta]_{620}$ −77
5	2R		$[\theta]_{290}$ −560	$[\theta]_{500}$ −10	$[\theta]_{600}$ +36
6	2S		$[\theta]_{290}$ +580	$[\theta]_{500}$ +13	$[\theta]_{600}$ −34
7	2R		$[\theta]_{295}$ −250	$[\theta]_{490}$ −10	$[\theta]_{620}$ +25
8	2S		$[\theta]_{295}$ +390	$[\theta]_{490}$ +12	$[\theta]_{620}$ −38
9	2R		$[\theta]_{280}$ −690	$[\theta]_{490}$ −5	$[\theta]_{620}$ +29
10	2S		$[\theta]_{280}$ +490	$[\theta]_{490}$ +7	$[\theta]_{620}$ −30
11	2R		$[\theta]_{280}$ −570	$[\theta]_{500}$ −25	$[\theta]_{620}$ +57
12	2S		$[\theta]_{280}$ +590	$[\theta]_{500}$ +25	$[\theta]_{620}$ −46
13	2R		$[\theta]_{270}$ −545	$[\theta]_{490}$ −23	$[\theta]_{630}$ +47
14[b]	2S		$[\theta]_{290}$ +690	$[\theta]_{500}$ +26	$[\theta]_{630}$ −44
15[c]	2R			none observed	
16[c]	2S			none observed	

[a] See ref 22. [b] A 2-(4-carboxamidophenyl)ethyl substituent replaces *N*-isopropyl. [c] A *tert*-butyl substituent replaces *N*-isopropyl.

wavelength transition is noted which we had not seen previously in our study of diols and primary amino alcohols.[4] This transition had been noted by Mitscher[15] and by Gillard and Wootten[12] only in compounds with N substituents. It may be related to the addition of another conformational variable in the system and/or manifestation of other possible d→d* transitions of Cu(II), as suggested by Gillard and Wootten.[12]

Based on the model studies of Bukhari[5-8] the (2*S*)-amino alcohol–Cupra A complexes are assigned the λ conformations and thus (−) chiralities as designated by the method of Dillon and Nakanishi[23] and the (2*R*)-amino alcohol–Cupra A complexes assigned δ conformations and (+) chiralities (Figure 2). These assignments assume that the aryloxyalkyl substituent adopts an equatorial position in the chelate as would be expected.[24] These results are analogous with our previous results and in agreement with the results of Mitscher in *N*-alkyl-2-amino-1-phenylethanols, with the appropriate changes in the Cahn–Ingold–Prelog sequence as encountered in these two systems.

In summary, the method as applied to aryloxypropanolamine β-adrenergic antagonists of this important class is a general one. Only one limitation was noted: evidently in cases of severe steric hindrance about the amine nitrogen (*tert*-butyl) no complexation of significance occurs. However, since most β-adrenergic antagonists of this class bear *N*-isopropyl substituents, this limitation is not a major one.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Circular dichroism spectra were recorded on a Jobin Yvon Dichrographe R. J. Mark III instrument. Intensities are not absolute, since the reaction between the amino alcohols and Cupra A is an equilibrium process. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England.

Cupra A Spectra. Cupra A solution was prepared by the method of Reeves,[25] consisting of 0.01 M Cu(II) dissolved in 3.17 M NH_3 in H_2O-EtOH. All spectra were run in Cupra A. In some cases small amounts of EtOH were added to facilitate solubilization.

(2*R*)- and (2*S*)-3-(1-Naphthyloxy)-1-(isopropylamino)-2-propanol (1 and 2). These compounds were prepared from 2*S* and 2*R* isomers of 3-(tosyloxy)-1,2-propanediol acetonide, as previously described.[4] (2*R*)-1:[22] CD (*c* 0.120, Cupra A) $[\theta]_{700}$ +25, $[\theta]_{620}$ +56, $[\theta]_{530}$ 0, $[\theta]_{500}$ −18, $[\theta]_{440}$ 0; $[\theta]_{350}$ −23, $[\theta]_{320}$ −250, $[\theta]_{310}$ 0. (2*S*)-**2**:[22] CD (*c* 0.120, Cupra A) $[\theta]_{700}$ −29, $[\theta]_{620}$ −59, $[\theta]_{530}$ 0, $[\theta]_{500}$ +15, $[\theta]_{440}$ 0, $[\theta]_{350}$ +45, $[\theta]_{320}$ +295, $[\theta]_{310}$ 0.

(2*R*)-3-(4-Acetamidophenoxy)-1-(isopropylamino)-2-propanol (3). *p*-Toluenesulfonyl chloride, 4.75 g (0.025 mol), was added slowly to a cold (0 °C) solution of 5.0 g (0.022 mol) of (2*R*)-3-(4-acetamidophenoxy)-1,2-propanediol[4] and the mixture was stirred at room temperature for 24 h. The mixture was poured over ice and stirred 1 h, and the resulting oil was extracted with $CHCl_3$ (3 × 100 mL). The extracts were combined and cooled to yield 4.02 g (48%) of

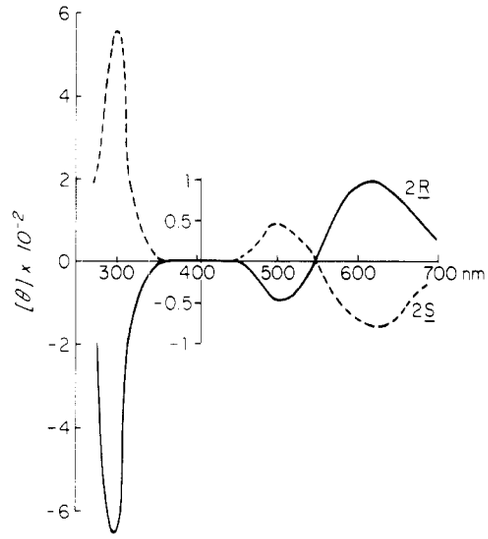


Figure 1. Cupra A CD spectra of practolol enantiomers (2*R*)-**3** and (2*S*)-**4**.

the corresponding 1-tosylate as a crystalline solid, mp 120–121 °C (lit. mp 118–120 °C, racemic mp 132–134 °C).[19] To a solution of 0.50 g (0.01 mol) of NaOMe in 10 mL of MeOH was added 3.79 g (0.01 mol) of the 1-tosylate in 10 mL of MeOH and the resulting mixture was refluxed for 30 min. The solvent was removed, 200 mL of ether was added, and the NaOTs was removed by filtration. Evaporation of the solvent gave an oil which slowly solidified. Recrystallization from benzene yielded 1.60 g (80%) of (2*R*)-3-(4-acetamidophenoxy)-1,2-epoxypropane as a white solid, mp 101–103 °C (lit. mp 104–106 °C).[19] The epoxide, 1.0 g (0.005 mol), was dissolved in 10 g (0.17 mol) of isopropylamine and the mixture was stirred for 3 days at room temperature. Evaporation of the solvent and crystallization of the residue from methyl ethyl ketone yielded 0.60 g (46%) of a white solid: mp 129–131 °C (lit. mp 130–131.5 °C, racemic mp 134–136 °C);[19] CD (*c* 0.10, Cupra A) $[\theta]_{700}$ +26, $[\theta]_{620}$ +95, $[\theta]_{550}$ 0, $[\theta]_{500}$ −46, $[\theta]_{430}$ 0, $[\theta]_{370}$ 0, $[\theta]_{320}$ −290, $[\theta]_{300}$ −625, $[\theta]_{290}$ 0.

(2*S*)-3-(4-Acetamidophenoxy)-1-(isopropylamino)-2-propanol (4). Compound **4** was prepared by a procedure analogous to **3**. Starting from (2*S*)-3-(4-acetamidophenoxy)-1,2-propanediol[4] and TsCl, the 1-tosylate was obtained in 51% yield, mp 119–120 °C. The 1-tosylate was converted to the epoxide using NaOMe in 95% yield, mp 100–102 °C. The epoxide was allowed to react with isopropylamine, affording **4** in 50% yield: mp 129–131 °C (methyl ethyl ketone); CD (*c* 0.10, Cupra A) $[\theta]_{700}$ −19, $[\theta]_{620}$ −77, $[\theta]_{550}$ 0, $[\theta]_{500}$ +46, $[\theta]_{430}$ 0, $[\theta]_{370}$ 0, $[\theta]_{320}$ +230, $[\theta]_{300}$ +570, $[\theta]_{290}$ 0.

(2*R*)- and (2*S*)-3-(2-Allyloxyphenoxy)-1-(isopropylamino)-2-propanol (5 and 6). These compounds were prepared from the *R* and *S* isomers of 3-(tosyloxy)-1,2-propanediol acetonide as described.[1] (2*R*)-**5**: CD (*c* 0.088, Cupra A) $[\theta]_{700}$ +14, $[\theta]_{600}$ +36, $[\theta]_{540}$ 0, $[\theta]_{500}$ −10, $[\theta]_{430}$ 0, $[\theta]_{360}$ 0, $[\theta]_{330}$ −90, $[\theta]_{290}$ −560, $[\theta]_{280}$ 0. (2*S*)-**6**: CD (*c* 0.098, Cupra A) $[\theta]_{700}$ −13, $[\theta]_{600}$ −34, $[\theta]_{540}$ 0, $[\theta]_{500}$ +13, $[\theta]_{430}$ 0, $[\theta]_{360}$ 0, $[\theta]_{330}$ +85, $[\theta]_{290}$ +580, $[\theta]_{280}$ 0.

(2*R*)- and (2*S*)-3-(3-Indolyl)-1-(isopropylamino)-2-propanol (7 and 8). These compounds were obtained as (+)-(*R*)- and (−)-(*S*)-pindolol, courtesy of Drs. H. Weidmann and H. Friedlie, Sandoz A. G., Basel, Switzerland. (2*R*)-**7**: CD (*c* 0.10, Cupra A) $[\theta]_{700}$ +11, $[\theta]_{620}$ +25, $[\theta]_{540}$ 0, $[\theta]_{490}$ −10, $[\theta]_{450}$ 0, $[\theta]_{360}$ 0, $[\theta]_{330}$ −39, $[\theta]_{295}$ −250, $[\theta]_{290}$ 0. (2*S*)-**8**: CD (*c* 0.096, Cupra A) $[\theta]_{700}$ −17, $[\theta]_{620}$ −38, $[\theta]_{540}$ 0, $[\theta]_{490}$ +12, $[\theta]_{450}$ 0, $[\theta]_{360}$ 0, $[\theta]_{330}$ +78, $[\theta]_{295}$ +390, $[\theta]_{290}$ 0.

(2*R*)- and (2*S*)-3-(2-Ethoxyphenoxy)-1-(isopropylamino)-2-propanol (9 and 10). These compounds were obtained as (+)-(*R*)-ICI-65941 and (−)-(*S*)-ICI-66836, through the courtesy of Drs. L. H. Smith and J. D. Fitzgerald, ICI Industries, Cheshire, England. The absolute configuration of the (+) enantiomer has been assigned by the method of Dukes and Smith, using the Horeau method.[18] (2*R*)-**9**: CD (*c* 0.103, Cupra A) $[\theta]_{700}$ +15, $[\theta]_{620}$ +29, $[\theta]_{530}$ 0, $[\theta]_{490}$ −5, $[\theta]_{440}$ 0, $[\theta]_{370}$ 0, $[\theta]_{340}$ −46, $[\theta]_{280}$ −690, $[\theta]_{255}$ 0. (2*S*)-**10**: CD (*c* 0.102, Cupra A) $[\theta]_{700}$ −16, $[\theta]_{620}$ −30, $[\theta]_{530}$ 0, $[\theta]_{490}$ +7, $[\theta]_{440}$ 0, $[\theta]_{370}$ 0, $[\theta]_{340}$ +48, $[\theta]_{280}$ +490, $[\theta]_{255}$ 0.

(2*R*)- and (2*S*)-3-[2-Acetyl-4-(butyrylamido)phenoxy]-1-(isopropylamino)-2-propanol (11 and 12). These compounds were obtained as the (+)-*R* and (−)-*S* enantiomers of acebutolol hydrochloride, $[\alpha]^{30}_D$ +12° and $[\alpha]^{30}_D$ −12.9°, respectively, from Dr. K. R. H. Wooldridge, May and Baker, Ltd., London. (2*R*)-**11**: CD (*c* 0.094, Cupra A) $[\theta]_{700}$ +14, $[\theta]_{620}$ +57, $[\theta]_{545}$ 0, $[\theta]_{500}$ −25, $[\theta]_{430}$ 0, $[\theta]_{350}$ 0, $[\theta]_{325}$ −195, $[\theta]_{280}$ −570, $[\theta]_{255}$ 0. (2*S*)-**12**: CD (*c* 0.108, Cupra A) $[\theta]_{700}$ −14, $[\theta]_{620}$ −46, $[\theta]_{545}$ 0, $[\theta]_{500}$ +25, $[\theta]_{430}$ 0, $[\theta]_{350}$ 0, $[\theta]_{325}$ +185 $[\theta]_{280}$ +590, $[\theta]_{255}$ 0.

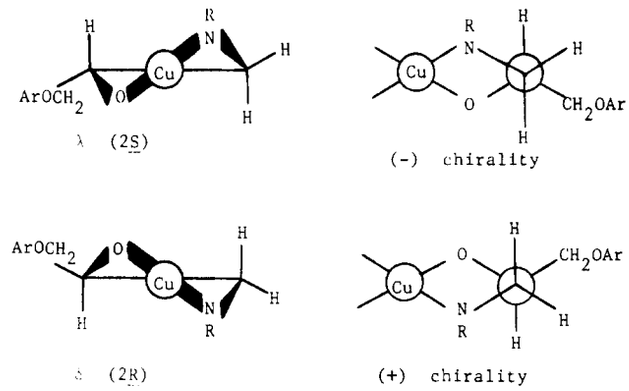


Figure 2.

(2*R*)-3-(3-Methylphenoxy)-1-(isopropylamino)-2-propanol (13). This compound was obtained as (+)-ICI-49526 from Drs. L. H. Smith and H. D. Fitzgerald, ICI Industries, Cheshire, England. The absolute configuration of the (−)-*S* isomer has been assigned by synthesis:[21] CD (*c* 0.097, Cupra A) $[\theta]_{700}$ +14, $[\theta]_{630}$ +47, $[\theta]_{555}$ 0, $[\theta]_{490}$ −23, $[\theta]_{440}$ 0, $[\theta]_{370}$ 0, $[\theta]_{310}$ −145, $[\theta]_{270}$ −545, $[\theta]_{245}$ 0.

(2*S*)-3-(2-Methylphenoxy)-1-[2′-(4-carboxamidophenyl)-ethyl]-2-propanol (14). This compound was obtained as the (−) isomer of tolamolol (UK-17,100-01) courtesy of Drs. T. K. Devon and D. A. Faulkner, Pfizer Central Research, Sandwich, England: CD (*c* 0.097, Cupra A) $[\theta]_{700}$ 0, $[\theta]_{630}$ −44, $[\theta]_{555}$ 0, $[\theta]_{500}$ +26, $[\theta]_{430}$ 0, $[\theta]_{370}$ 0, $[\theta]_{340}$ +65, $[\theta]_{290}$ +690, $[\theta]_{280}$ 0.

(2*R*)- and (2*S*)-3-(4-*N*-Morpholino-1,2,5-thiadiazol-3-yloxy)-1-(*tert*-butylamino)-2-propanol (15 and 16). These compounds were obtained as (+)-(*R*)- and (−)-(*S*)-timolol maleate, courtesy of Dr. L. M. Weinstock, Merck, Sharp and Dohme, Rahway, N.J. The absolute configurations have previously been assigned by synthetic methods.[20] No Cupra A CD spectra were observed.

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Registry No.—**1**, 5051-22-9; **2**, 4199-09-1; **3**, 37936-66-6; **4**, 37936-65-5; **5**, 31576-00-8; **6**, 22972-96-9; **7**, 68050-98-6; **8**, 68050-99-7; **9**, 27480-08-6; **10**, 27480-06-4; **11**, 68107-81-3; **12**, 68107-82-4; **13**, 4198-88-3; **14**, 68051-00-3; **15**, 26839-76-9; **16**, 26839-75-8; (2*S*)-3-(4-acetamidophenoxy)-1,2-propanediol, 56715-20-9; isopropylamine, 75-31-0; (2*R*)-3-(4-acetamidophenoxy)-1,2-propanediol, 41432-48-8; (2*R*)-3-(4-acetamidophenoxy)-1,2-epoxypropane, 39219-48-2; (2*R*)-3-(4-acetamidophenoxy)-1,2-propanediol 1-tosylate, 56761-03-6; (2*S*)-3-(4-acetamidophenoxy)-1,2-propanediol 1-tosylate, 41349-60-4; (2*S*)-3-(4-acetamidophenoxy)-1,2-propanediol epoxide, 68051-01-4.

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5-Amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (1-Deaza-8-azaguanosine) and Certain Related Derivatives[1,2]

Barry L. Cline, Raymond P. Panzica, and Leroy B. Townsend*

Department of Medicinal Chemistry (ARB) and Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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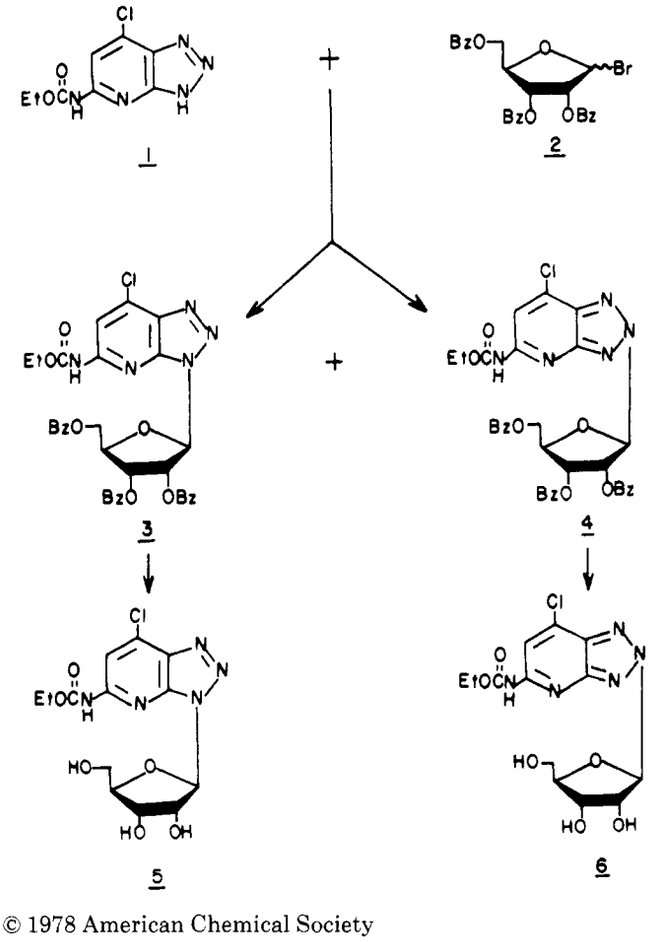
The synthesis of 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (1-deaza-8-azaguanosine) has been accomplished by a condensation of the silyl derivative of ethyl 7-chloro-*v*-triazolo[4,5-*b*]pyridine-5-carbamate and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide using the mercuric cyanide procedure. The 6-thioguanosine analogue 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-7-thione (1-deaza-8-aza-6-thioguanosine) has been prepared by a nucleophilic displacement of the chloro group from ethyl 7-chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate with sodium hydrogen sulfide, which also effected a concomitant removal of the blocking group from the 5-amino group. A rearrangement of 1-deaza-8-aza-6-thioguanosine was observed under various conditions and has furnished 6-amino-4-(α- and β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[4,5-*c*]pyridine as determined by ultraviolet and ^{1}H NMR spectroscopy. The syntheses of various nucleoside precursors and derivatives of the above compounds are also described. Procedures used to unequivocally determine the site of ribosylation and anomeric configuration are also discussed.

8-Azaguanine was the first purine analogue shown to be incorporated into RNA.[3] The wide spectrum of biological activity exhibited by 8-azaguanine and its nucleoside–nucleotide derivatives[4] influenced investigations which subsequently led to other azapurine analogues.[5] As part of our continuing research efforts involving the synthesis of aza- and deazapurine nucleoside analogues as potential chemotherapeutic agents, we wish to report the synthesis of certain *v*-triazolo[4,5-*b*]pyridines related not only to guanine and guanosine but also to the important chemotherapeutic agents[6] 6-thioguanine and 6-thioguanosine. These types of nucleosides have also been used as valuable biochemical tools for the elucidation of enzyme–substrate specificity.

The heterocycle ethyl 7-chloro-*v*-triazolo[4,5-*b*]pyridine-5-carbamate[7,8] (**1**) was chosen as our starting material for the synthetic sequence which should lead to 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (**14**, 1-deaza-8-azaguanosine). The envisaged purpose of using **1** was twofold; ribosylation and subsequent chemical modification[9] of the heterocyclic moiety would eventually furnish a nucleoside [3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine[10]] whose structure had been previously established. This would provide a structure proof, i.e., the site of ribosylation and determination of anomeric configuration, for all nucleosides synthesized in this investigation, and second, the 7-chloro substituent was expected to undergo a facile nucleophilic displacement to afford the desired 5-amino-7-substituted *v*-triazolo[4,5-*b*]-pyridine nucleosides.

The silyl derivative of ethyl 7-chloro-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (**1**) (prepared by the reaction of **1** with



* Address correspondence to this author at the Division of Medicinal Chemistry, College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48109.

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