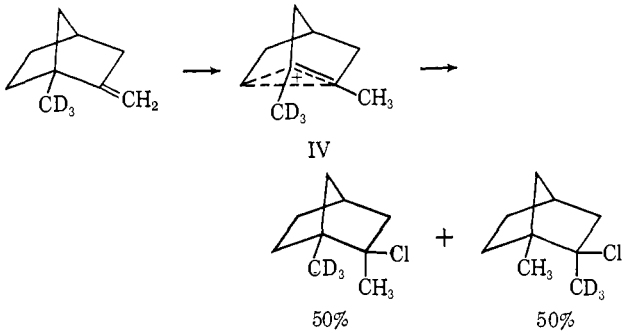
the presence of the 7,7-dimethyl substituents should, for steric reasons, result in the formation of *endo* product, except in cases where nonclassical bridging directs the entering nucleophile to the *exo* position.[8,9] If this argument is valid, the formation of the 2,7,7-trimethyl-*exo*-norbornyl chloride in the hydrochlorination of α-fenchene would appear to require the formation of a bridged cation.

On this basis, the hydrochlorination of a tagged 1-methyl-2-methylenenorbornane would be expected to proceed through a symmetrical bridged intermediate, requiring complete scrambling of the tag. Indeed, when hydrogen chloride was added to 1-methyl-d_3-2-methylenenorbornane under the usual reaction conditions, *i.e.*, slow addition and long reaction time, the product was completely scrambled as shown by nmr.[10] However, when the addition was carried out in ether or methylene chloride solution at 0° for 1–2 min, the initial product was predominantly 1-methyl-d_3-2-methyl-*exo*-norbornyl chloride, with the distribution of the methyl-d_3 tag corresponding to only 52–56% scrambling, instead of the 100% scrambling required by the symmetrical bridged ion (IV). Addition of hydrogen

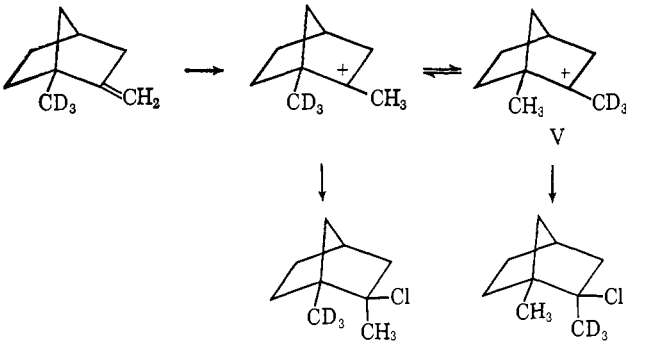


chloride to the neat olefin gave chloride which was even less scrambled, 35%. Exposure of the product to hydrogen chloride results in complete scrambling. These results are summarized in Table I.

Table I. Per Cent Scrambling in the Hydrochlorination of 1-Methyl-d_3-2-methylenenorbornane

Solvent	Temp, °C	Time, min	Scrambling, %
Ether	0	1	53
Ether	0	2	56
Ether	0	20	73
Ether	0	40	82
Ether	0	60	97
Ether	0	120	100
CH_2Cl_2	0	2	52
CH_2Cl_2	−20	2	55
Neat	0	2	42
Neat	0	1	35

Similarly, deuteriochlorination of 1-methyl-2-methylene-d_2-norbornane yielded predominantly 1-methyl-2-methyl-d_3-*exo*-norbornyl chloride. Therefore, the incomplete scrambling is not the results of an isotope effect. The above results make it clear that the bridged nonclassical ion cannot be the major intermediate involved in the hydrochlorination of 1-methyl-d_3-2-methylenenorbornane and related olefins. The results are consistent with the alternative proposal of a rapidly equilibrating pair of classical ions (V),[11] with the addition of chloride ion being somewhat faster than the equilibration.



It might be argued that the hydrochlorination reaction does not involve the formation of carbonium ions. However, we would then be faced with the dilemma of accounting for the almost exclusive formation of tertiary chlorides in these reactions. Moreover, this position would render untenable the argument that reactions of the 7,7-dimethylnorbornyl system must necessarily take an *endo* course in the absence of nonclassical bridging to control the reaction path for the entering nucleophile.

(8) J. A. Berson in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 130.

(9) A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *J. Am. Chem. Soc.*, 87, 378 (1965); R. Howe, E. C. Friedrich, and S. Winstein, *ibid.*, 87, 379 (1965).

(10) All nmr spectra were measured with a Varian A-60 spectrometer using carbon tetrachloride solution containing tetramethylsilane as internal standard. The distinct methyl peaks at δ 1.23 and 1.57 corresponded to the C_1-methyl and the C_2-methyl group, respectively. The ratio of 1-methyl-d_3-2-methyl-*exo*-norbornyl chloride to 1-methyl-2-methyl-d_3-*exo*-norbornyl chloride was calculated from peak height measurement.

(11) For a recent discussion of this problem, see H. C. Brown, *Chem. Brit.*, 2, 199 (1966).

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Synthesis of 3′-Thioadenosine and Compounds Derived from 3-Thio-D-ribose[1]

Sir:

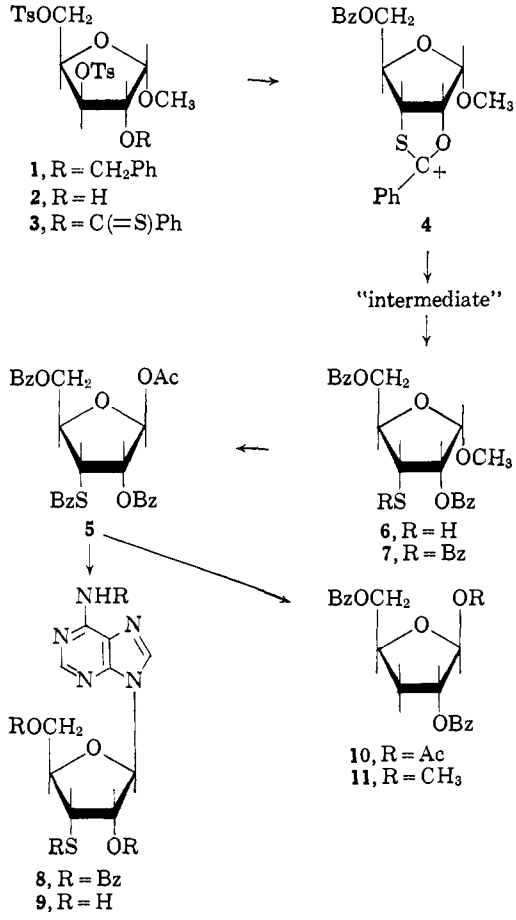
Chemical changes at C-3 of the D-ribose moiety of nucleosides can result in dramatic changes in biological activity; *e.g.*, the unique biological properties of the antibiotic puromycin have been attributed[2] to the presence of 3-amino-3-deoxy-D-ribose instead of the natural D-ribose moiety; it is noteworthy that change of functionality had to be at C-3, and the sugar of the ribose configuration, for activity. The similar substitution of a 3-thiol group in adenosine to give 3′-thioadenosine might be expected to lead to another biologically interesting nucleoside, but methods for preparing the *cis*-mercaptoalcohol system of 3-thio-D-ribofuranose derivatives have not been available to

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH 43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

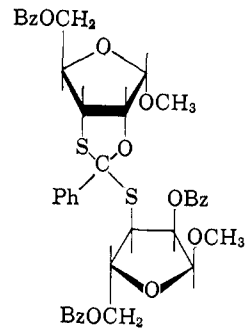
(2) B. R. Baker in "The Chemistry and Biology of Purines," Ciba Foundation Symposium, Little, Brown and Co., Boston, Mass., 1957, p 120.

date. Recently we were able to prepare a number of novel sugars by the neighboring-group participation reactions of *trans*-*O*-benzoates,[3-5] and we now wish to report the successful use of the related *trans*-*O*-thionbenzoate neighboring group in an intramolecular sulfonate displacement that has permitted the synthesis of 3′-thioadenosine.

Methyl 3,5-di-*O*-tosyl-α-D-xylofuranoside[6] (**2**), mp 97.5–99°, was prepared by hydrogenolysis of the 2-*O*-benzyl ether[3] (**1**) and converted with thionbenzoyl chloride[7] in pyridine to the thionobenzoate **3**, mp 121–122°, $[\alpha]^{22}D$ +152° ($CHCl_3$), λ_{max}^{EtOH} 415 mμ (ε 147). Treatment of **3** with 2 molar equiv of sodium benzoate in dimethylformamide at 110° for 6 hr caused complete ejection of the sulfonates (the 5-tosyloxy group by benzoate anion from the solution and the 3-tosyloxy group by the neighboring thionobenzoate), with the formation of a stable intermediate apparently derived from the bridged acylonium ion **4**. This intermediate



was dimeric, unsymmetrical ($[\alpha]^{25}D$ −79° (benzene); nmr signals: two singlets for C-1–OCH_3, two doublets for C-1–H, two quartets for C-2–H), and when purified was free of OH, SH, or SBz bands in the infrared. A structure obtained from the ion **4** by its S-alkylation of the dibenzoate **6** (obtainable from **4** with moisture) is suggested to explain these data.[8] This intermediate



was stable to moisture or to solution in methanol, but was converted in warm 80% acetic acid to the monomeric thiol dibenzoate **6**, which showed strong benzoate bands in the infrared and an SH band at 3.87 μ (weak), but little or no OH at 2.8–3.0 or SBz at 6.0. Benzoylation afforded the syrupy tribenzoate **7** (one singlet, doublet, and quartet, respectively, for C-1–OCH_3 C-1–H, and C-2–H in the nmr). Acetolysis with acetic acid–acetic anhydride–sulfuric acid afforded crystalline 1-*O*-acetyl-3-*S*-benzoyl-2,5-di-*O*-benzoyl-3-thio-β-D-ribofuranose (**5**), mp 136–137°, $[\alpha]^{24}D$ +155° ($CHCl_3$); in the nmr, a singlet (δ 6.41) for C-1–H was indicative of the β anomer. The position of the sulfur on the furanose ring was established by nickel desulfurization of **5**; the resultant crude 3-deoxy sugar **10** was treated with methanolic hydrogen chloride, and crystalline methyl 2,5-di-*O*-benzoyl-3-deoxy-β-D-ribofuranose[9] (**11**) was isolated by chromatography.

The acetate tribenzoate **5**, in the presence of titanium tetrachloride, was condensed[10] with chloromercuri-6-benzamidopurine to form *N*,*O*,*O*,*S*-tetrabenzoyl-3′-thio-D-adenosine (**8**) as foamed glass. The benzoyl groups were removed with methanolic sodium methoxide and an *S*-acetoxymercuri salt of the free nucleoside **9** was precipitated, as described recently for the epimeric 3-thio-D-arabino analog.[11] 3′-Thio-D-adenosine (**9**) was liberated from the salt in 80–90% acetic acid by the precipitation of mercuric sulfide with hydrogen sulfide, isolated from the filtrate, and crystallized from water. Dithioerythritol[12] was added to the solutions to prevent oxidation of **9** to its disulfide, but **9** (18.5% yield based on **5**) was stable when stored as the anhydrous powder; mp 179–181°; $[\alpha]^{25}D$ −13° (water); $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 14,400); $\lambda_{max}^{pH\ 7}$ 259 (ε 14,500); $\lambda_{max}^{pH\ 13}$ 259 (ε 15,100); SH found by iodine titration was 95% of theory. The β-anomeric configuration was assigned on the basis of the "*trans*" rule and the optical notation.

Further studies are in progress of the chemistry of *O*-thionobenzoate as a new neighboring group in intramolecular displacements.

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(6) Infrared spectra and nmr spectra were recorded for each compound. Satisfactory elemental analyses were obtained for **2**, **3**, **5**, and **9**. Optical rotations were determined in 1% solutions.

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(8) This structure was supported by comparison with a similar, but crystalline, intermediate obtained from the 5-deoxy analog of **3** with sodium benzoate–dimethylformamide. Mass spectrometry suggested a related such structure for the crystalline 5-deoxy intermediate, and other properties indicated the two intermediates were completely analogous.

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