ment of the oxygen atom in the nitrosyl ligand, well established to be a three-electron donor, with a *p*-anisylimino group produces the *p*-anisylazo ligand present in the new complex just as replacement of the oxygen atom in the carbonyl ligand with a *p*-anisylimino group produces the *p*-anisyl isocyanide ligand, which has been shown to form complexes with many transition metals[10] similar to metal carbonyls in many respects. Thus the relationship between $C_5H_5Mo(CO)_2NO$[3,6] and $p$-$CH_3OC_6H_4N_2Mo(CO)_2C_5H_5$ appears to be especially close.

Further studies on arylazo derivatives of transition metals are in progress and will be reported in detail in the future.

(10) For a review of isocyanide complexes of metals see L. Malatesta, *Progr. Inorg. Chem.*, **1**, 283 (1959).

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RECEIVED OCTOBER 21, 1964

## 1,4-Phenyl Migration in a Base-Catalyzed Elimination–Rearrangement Reaction

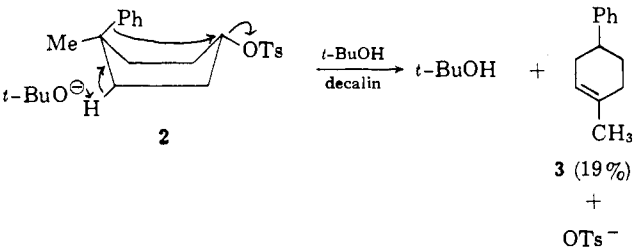
*Sir:*

Treatment of 4,4-diphenylcyclohexyl *p*-toluenesulfonate (**1**) with sodium *t*-butoxide in refluxing *t*-butyl alcohol solution for 4 hr. gave 4,4-diphenylcyclohexanone (7%), 4,4-diphenylcyclohexanol (9%), 1,4-diphenylcyclohexene (14%), and 4,4-diphenylcyclohexene (64%). These products were separated by elution chromatography and identified by comparing their melting points, infrared spectra, and g.l.c. retention times with those of authentic samples.[1] A comparable experiment in which dimethyl sulfoxide was used as the solvent increased the yield of 1,4-diphenylcyclohexene to 21%. When a refluxing *t*-butyl alcohol–decalin solvent mixture was used, the yield of 1,4-diphenylcyclohexene was 16% (determined by g.l.c. analysis).

There is ample mechanistic analogy for the formation of all these products, except 1,4-diphenylcyclohexene. Since the rearrangement reaction fails in the absence of base, a carbonium ion mechanism is unlikely. This view is supported by the failure of 1,4-phenyl migration to occur during solvolysis (acetolysis or formolysis) of tosylate **1**, or during deamination of the corresponding amine. Rearrangement *via* a radical or methylene intermediate appears unlikely, and we have some evidence against the latter inasmuch as preliminary experiments on the base-catalyzed decomposition of the *p*-tolylsulfonylhydrazone of 4,4-diphenylcyclohexanone have failed to reveal the presence of rearrangement products.

Examination of molecular models shows that the boat form of **1**, or of *cis*-4-methyl-4-phenylcyclohexyl *p*-toluenesulfonate (**2**),[2] has one of the C-3 hydrogen atoms, the C-3 and C-4 carbon atoms, and the C–$C_6H_5$ bond in the correct coplanar orientation for a concerted $\beta$-eliminative process. Furthermore, the phenyl group is in a favorable location to initiate bonding at the face of the carbon atom opposite to that holding the *p*-toluenesulfonate grouping. Conceivably, then, 1,4-diphenylcyclohexene could arise from **1** by a one-step concerted reaction—a merged elimination (E2) and intramolecular displacement (SNi) process.

This mechanism predicts that during the reaction the double bond is generated between the C-3 and C-4 carbon atoms, rather than between the C-1 and C-2 carbon atoms. The reaction of **1** gives no evidence on this point, but when applied to **2** this mechanism predicts that the rearrangement product will be 1-methyl-4-phenylcyclohexene (**3**), rather than 4-methyl-1-phenylcyclohexene.




**2** **3** (19%) + $OTs^-$

Treatment of **2** with sodium *t*-butoxide in a refluxing solution of *t*-butyl alcohol and decalin gave **3** (19%), 4-methyl-4-phenylcyclohexene (26%), 4-methyl-4-phenylcyclohexanone (~5%), and a mixture of *cis*- and *trans*-4-methyl-4-phenylcyclohexanol (36%). These products were separated by elution chromatography on silica gel. The isomeric 1-methyl-4-phenyl- and 4-methyl-4-phenylcyclohexenes were identified by comparing them with authentic samples using infrared, ultraviolet, and n.m.r. spectra and g.l.c. retention times.[1] For example, **3** has a series of maxima at 242, 247.5, 253, 257.5, 261, and 267.5 m$\mu$ with $\epsilon$ ~325, whereas 4-methyl-4-phenylcyclohexene has a broad maximum at 241 m$\mu$ ($\epsilon$ 700). There was no indication for the presence of 4-methyl-1-phenylcyclohexene ($\lambda_{max}$ 247 m$\mu$ ($\epsilon$ 21,000)), either in the ultraviolet or the n.m.r. spectrum or the g.l.c. analysis of **3**.

A search for merged E2–SNi reactions in other cyclic systems and in open-chain analogs is underway.[3]

**Acknowledgment.**—We are grateful to the National Science Foundation for their support of this investigation (NSF-G24095).

(1) Microanalyses consistent with the structures assigned were obtained for all new compounds.

(2) The *cis* designation refers to the first group mentioned, *i.e.*, *cis* $CH_3$ and OTs.

(3) Rearrangement products have been observed to be formed under similar conditions from neopentyl *p*-toluenesulfonate (elimination with methyl migration).

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RECEIVED OCTOBER 15, 1964

## Synthesis of 1(2,3,6-Trideoxy-$\beta$-D-*erythro*-hexopyranosyl)cytosine. The Deoxy Sugar Nucleoside Moiety of Amicetin

*Sir:*

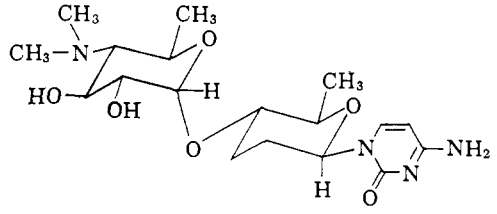
In this work the deoxy sugar nucleoside derived from amicetin[1,2] was synthesized starting from a readily available nucleoside of known $\beta$-configuration. More importantly, procedures were developed for the conversion of amicetose,[2] the naturally occurring deoxy sugar which has been synthesized conveniently in this

(1) (a) C. L. Stevens, K. Nagarajan, and T. H. Haskell, *J. Org. Chem.*, **27**, 2991 (1962); C. L. Stevens, P. Blumbergs, and F. A. Daniher, *J. Am. Chem. Soc.*, **85**, 1552 (1963).

(2) C. L. Stevens, P. Blumbergs, and D. L. Wood, *ibid.*, **86**, 3592 (1964).

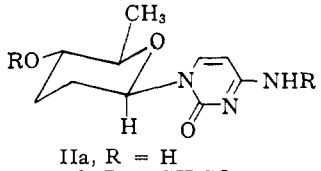
laboratory, into the naturally occurring nucleoside moiety.

Cytosamine, the disaccharide nucleoside moiety of the antibiotic amicetin,[1,2] has been shown to have structure I.[1-3] Most recently, the stereochemical con-



I

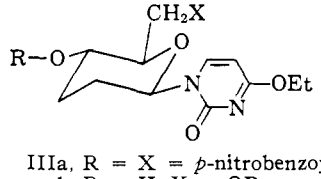
figuration of the O-glycosidic link has been established as $\alpha$.[3] In that same communication the nucleosidic link was deduced, *not* unequivocally, to be $\beta$.[3] The synthesis by two routes of the title nucleoside, IIa, allows the unambiguous assignment of the stereochemical configuration of the nucleoside link in I by



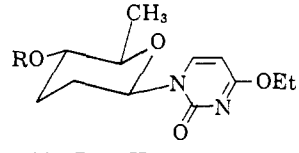
IIa, R = H
b, R = $CH_3CO$

comparison of the physical constants of synthetic IIa with the properties reported for IIa isolated from the natural source.[3]

The nucleoside IIIa, 1(2,3-dideoxy-4,6-di-O-*p*-nitrobenzoyl-$\beta$-D-*erythro*-aldohexosyl)4-ethoxy-2-(1H)pyrimidone, is readily synthesized and has been proven to have the $\beta$-configuration.[4] IIIa was converted in 75% yield to 1(6-O-*p*-bromobenzenesulfonyl-

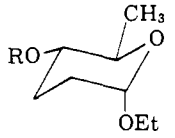


IIIa, R = X = *p*-nitrobenzoyl
b, R = H, X = OBs
c, R = H, X = I



IVa, R = H
b, R = *p*-nitrobenzoyl

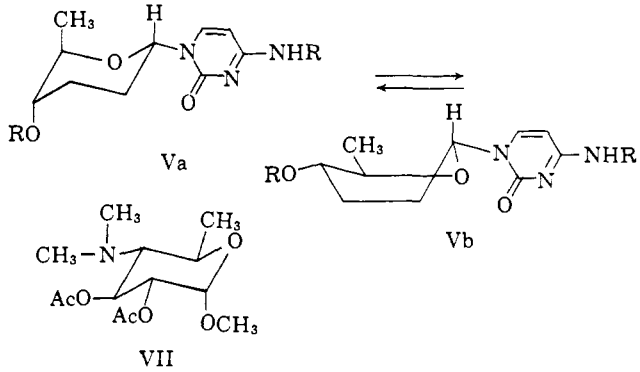
2,3-dideoxy-$\beta$-D-*erythro*-aldohexosyl)4-ethoxy-2(1H)-pyrimidone,[5] IIIb, m.p. 157–158°, $[\alpha]^{25}D$ +53.8° (*c* 1.19, $CHCl_3$), by successive treatments with barium hydroxide in 50% ethanol–water and 1.2 equiv. of brosyl chloride in pyridine–tetrahydrofuran solution (1:1 by volume). The primary 6-O-brosylate group of IIIb was then displaced with sodium iodide in acetone at 110° to give the corresponding 6-iodo compound, IIIc, in 86% yield, m.p. 171–173°, $[\alpha]^{23}D$ +36.4° (*c* 1.38, $CHCl_3$), which was, in turn, hydrogenated over 10% palladium on carbon affording, in 88% yield, 1(2,3,6-trideoxy-$\beta$-D-*erythro*-aldohexosyl)4-ethoxy-2(1H)pyrimidone, IVa, m.p. 157–158°, $[\alpha]^{23}D$ +101.3° (*c* 0.68, $CHCl_3$). The *p*-nitrobenzoyl derivative IVb was prepared in 82% yield, m.p. 197–198°, $[\alpha]^{25}D$ +71.8° (*c* 1.65, $CHCl_3$), by acylation of IVa in pyridine solvent and by the following alternate route. The ethyl glycoside of amicetose, ethyl 2,3,6-trideoxy-$\alpha$-D-*erythro*-hexopyranoside,[2] Va, was converted to its *p*-nitrobenzoyl derivative Vb, m.p. 73–75° (after a short-path distillation at 110° and 0.01 mm.), $[\alpha]^{25}D$



Va, R = H
b, R = *p*-nitrobenzoyl

+44.0° (*c* 0.75, 75% dioxane–water). Compound Vb was converted to the corresponding glycosyl chloride by treatment at 25° with acetyl chloride saturated with hydrogen chloride, and, without characterization, was condensed with 2,4-diethoxypyrimidine according to the classical procedure of Hilbert and Jansen.[6] After chromatography over neutral alumina, nucleoside IVb was isolated in 19% yield.

The assignment of the $\beta$-configuration to IIa by n.m.r. analysis[3] is not unambiguous. Thus, the $\alpha$-nucleoside VI[7] could be expected to give a signal similar to that of



VII

IIa for its anomeric hydrogen (diaxial and equatorial–axial splitting), and a similar chemical shift for the acetyl $CH_3$ signal[8] of its acetate (pseudo-equatorial in VIb). Also, at least one exception to the generalizations of ref. 8b is seen in the n.m.r. spectrum of the glucose derivative VII[9] which exhibits an "axial" acetoxy signal.

Treatment of nucleoside IVa with ethanolic ammonia at 110° converted it smoothly to the cytosine nucleoside IIa, m.p. 248–249° dec., $[\alpha]^{23}D$ −11.9° (*c* 0.52, $H_2O$); ultraviolet $\lambda_{max}$ 278 m$\mu$ (0.1 *N* HCl), 270 m$\mu$ (0.1 *N* NaOH); *R*(cytosine) 1.48 (2-propanol–water–ammonia, 7:2:1). Acetic anhydride treatment of IIa yielded the diacetate IIb in 78% yield, m.p. 201–202° dec., $[\alpha^{24}]D$ +180° (*c* 1.28, $CHCl_3$); infrared (KBr) 1740 and 1665 $cm.^{-1}$; ultraviolet $\lambda_{max}$ 299 and 248 m$\mu$. All the physical constants of synthetic IIa and b agreed with those reported for IIa and b prepared from the natural source.[3]

(3) S. Hanessian and T. H. Haskell, *Tetrahedron Letters*, **No. 36**, 2451 (1964).

(4) C. I. Stevens, N. A. Nielsen, and P. Blumbergs, *J. Am. Chem. Soc.*, **86**, 1894 (1964).

(5) All new compounds herein described had acceptable elemental analyses.

(6) G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **58**, 60 (1936).

(7) While the flexible or twist form, VIb, might be expected to be unstable relative to the chair form, VIa, the magnitude of their energy difference would be expected to be small so that the existence of appreciable equilibrium concentrations of VIb cannot conclusively be ruled out without a detailed conformational analysis.

(8) (a) The chemical shifts of axial *vs.* equatorial acetates are discussed in R. U. Lemieux, R. K. Kulnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958); (b) *cf.* also F. W. Lichtenthaler, *Ber.*, **96**, 2047 (1963).

(9) Prepared by acetylation of the corresponding diol,[1b] m.p. 199–201°.

The synthesis of IIa and b, therefore, *unequivocally* establishes the β-configuration for the nucleoside bond in I. This, together with the data of Hanessian and Haskell,[3] establishes the anomeric linkages of amicetin to be as shown in structure I.

**Acknowledgment.**—We are grateful to Professor N. A. Allinger for helpful discussions and to the Michigan Cancer Foundation for financial support.

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RECEIVED OCTOBER 28, 1964

## Kinetic Evidence for the Formation of a Tetrahedral Intermediate in the Aqueous Solvolysis of Ethyl Trifluorothiolacetate[1]

*Sir:*

A previous study provided kinetic evidence for the existence of tetrahedral intermediates in the reaction of methoxyl- and hydroxylamine with a series of thiol esters and lactones.[1c] In this communication we report kinetic evidence for the formation of a tetrahedral intermediate in the aqueous solvolysis of ethyl trifluorothiolacetate. This represents the first instance of the demonstration of a metastable intermediate in the reaction of a thiol ester with an oxygen nucleophile.

The hydrolysis of ethyl trifluorothiolacetate (temperature 30°, $\mu$ = 1 $M$ with KCl) in water in the pH range 0–8 is kinetically described by (1). The pH–rate

$$v = [[1/(2.31 + 6.6a_H)] + (5.25 \times 10^5)a_{OH}][\text{ester}] \quad (1)$$

profile (Fig. 1) was constructed from eq. 1 and the points were experimentally determined. The $k_{obsd}$ values in the acid region of Fig. 1 were obtained by following the disappearance of ester at 244 mμ in dilute hydrochloric acid. The $k_{obsd}$ values between pH 2.5 and 8.0 in Fig. 1 were obtained by extrapolation of linear plots of pseudo-first-order rate constants *vs.* total buffer concentration to zero buffer concentration, employing each of the buffers acetate, formate, phosphate, and imidazole at five concentrations at each pH. The relationship between rate and acidity from pH 0 to 6 is given by (2), which correctly predicts

$$v/[\text{ester}] = k_{obsd} = 1/(2.31 + 6.6a_H) \quad (2)$$

that a plot of $1/k_{obsd}$ *vs.* $a_H$ is linear, with slope 6.6 $M^{-1}$ min. and intercept 2.31 min. Of many possible mechanisms considered,[2] one is consistent with the experimental data. This mechanism involves general-base-catalyzed nucleophilic attack of water at the ester bond and the unsymmetrical partitioning of a tetrahedral intermediate which collapses spontaneously to products and is converted back to ester by hydronium ion *via* general-acid catalysis (eq. 3). Depending

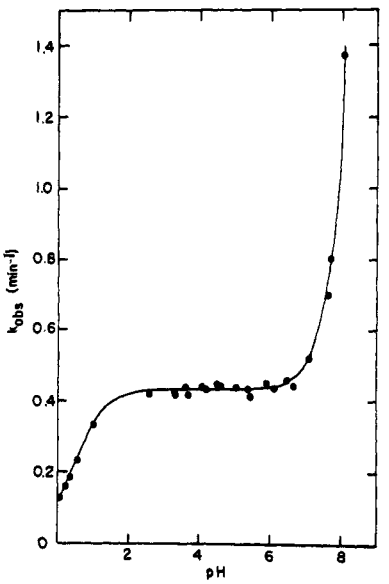


Fig. 1.—pH–rate profile for the solvolysis of ethyl trifluorothiolacetate in $H_2O$ at zero buffer concentration (30°; $\mu$ = 1.0 $M$). The solid line is constructed from eq. 1 and the points are experimentally determined values.

on whether one assumes steady state in T and TH or pre-equilibrium formation of T and TH, the rate ex-

$$CF_3COSC_2H_5 + H_2O \underset{k_2,\ H_3O^+}{\overset{k_1,\ H_2O}{\rightleftharpoons}} CF_3C(O^-)(OH)SC_2H_5\ (T) \xrightarrow{k_3} CF_3CO_2H + C_2H_5SH$$

$$T + H^+ \rightleftharpoons TH + H^+ \quad K_a$$

$$TH = CF_3C(OH)_2SC_2H_5 \quad (3)$$

pressions (4) or (5), respectively, can be derived.

$$v/[\text{ester}][H_2O] = k_{obsd} = \frac{k_1k_3}{k_3 + k_2[H_3O^+]} = 1/[1/k_1 + (k_2/k_1k_3)[H_3O^+]] \quad (4)$$

$$v/[\text{ester}][H_2O] = k_{obsd} = \frac{k_3k_1K_a}{k_1K_a + (k_2K_a + k_1)[H_3O^+]} = 1/[1/k_3 + (k_2/k_1k_3 + 1/k_3K_a)[H_3O^+]] \quad (5)$$

Either expression has the form of (2).[3] The steady-state derivation leading to (4) is preferred to the assumption of the pre-equilibrium formation of T and TH leading to (5). The preference is based on $k_{H_2O}/k_{D_2O}$ = 3.3 for the neutral water rate which corresponds to $k_1$ in (4) or $k_3$ in (5). No deuterium solvent kinetic isotope effect should be associated with the collapse of the tetrahedral intermediate. Also, the Arrhenius activation energy of 11.7 kcal. mole$^{-1}$, determined for $k_1$ in (4) or $k_3$ in (5), is more consistent with the general-base-catalyzed attack of a water molecule at

(1) A detailed presentation of results will appear as Thiol Esters. IV. For parts I–III see (a) T. C. Bruice, J. J. Bruno, and W. S. Chou, *J. Am. Chem. Soc.*, **85**, 1659 (1963); (b) L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 4117 (1964); (c) T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 738, 739, 4886 (1964).

(2) A detailed consideration of possible mechanisms will be given in Thiol Esters IV.

(3) A mechanism involving attack of hydroxide ion at the ester bond to form a tetrahedral intermediate which is converted to products by hydronium ion catalysis also gives a steady-state derivation which has the form of (2). However, it can be shown that the second-order rate constant for hydroxide attack would be *ca.* $10^{13}$, a value greater than the rate constant for a diffusion-controlled process.