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An Efficient Synthesis of 1-β-D-Arabinofuranosylcytosine

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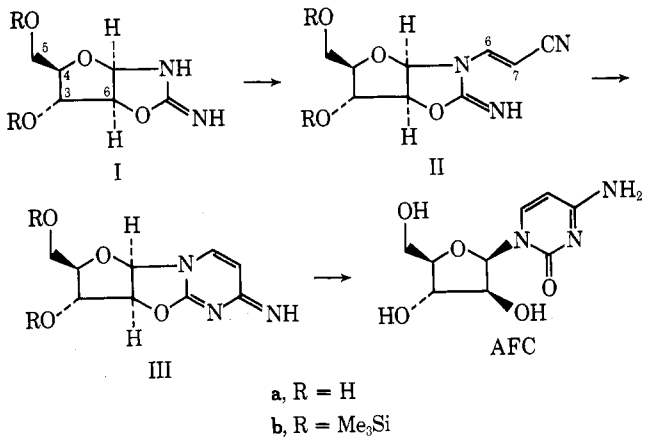
Isoxazole is treated with strong base at low temperature to form in high selectivity the cis enolate salt of cyanoacetaldehyde. Tosylation, followed by reaction with trimethylamine, furnishes *cis*-β-trimethylammoniumacrylonitrile tosylate in high yield. This product is treated with 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline to form the desired cis cyanovinyl adduct which is further converted to 1-β-D-arabinofuranosylcytosine.

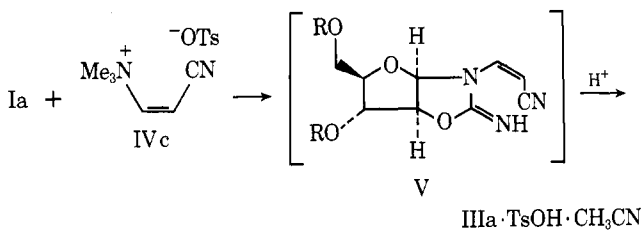
Cytosine arabinoside (1-β-D-arabinofuranosylcytosine, AFC) has been proven effective in the treatment of acute leukemias. Additionally, *anhydro*-AFC is being investigated as an antitumor agent. Since increasing amounts of AFC are being used medicinally a low-cost synthesis of AFC has been pursued in this and other laboratories. Very recently Sanchez and co-workers[1] published an elegant method to prepare AFC. The reaction of D-arabinose with cyanamide to form 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (Ia) is followed by reaction of Ia with propiolonitrile to yield a cyanovinyl adduct which Sanchez formulates as the trans adduct IIa.



a, R = H
b, R = Me_3Si

Treatment of the cyanovinyl adduct with aqueous ammonia gave a high yield of AFC, presumably via 2,2′-anhydro-1-β-D-arabinofuranosylcytosine (IIIa). Our goal was to prepare AFC by a procedure that could ultimately be used in large-scale manufacture and by a procedure that allowed isolation of *anhydro*-AFC (III), if possible. Use of oxazoline I as an intermediate was favored since the oxazoline is of the correct configuration at C-1 of the arabinose moiety. Unfortunately the above process utilizes propiolonitrile, a compound that was judged too hazardous for large-scale synthesis. Our specific goal then became to find a substitute for the key reagent, propiolonitrile.

It was found that *cis*-β-trimethylammoniumacrylonitrile tosylate (IVc), a stable, white, crystalline solid, can be substituted for propiolonitrile in the synthesis. Reaction of IVc with oxazoline Ia was carried out best in DMF at 50 °C. Use of protic solvents such as water, methanol, or 2-propanol for the reaction gave only poor yields of AFC. However, dipolar aprotic solvents were effective, with DMF giving the highest yields. Addition of acetonitrile at the end of the reaction caused crystallization of a white solid isolated in 70–74% yield, which is assigned the acetonitrile solvate of 2,2′-*anhydro*-AFC tosylate salt (IIIa TsOH CH_3CN) by NMR comparison to authentic[1] 2,2′-*anhydro*-AFC hydrochloride. It is very likely that the *cis*-cyanovinyl adduct Va is generated as an intermediate which then cyclizes to IIIa in the presence of tosic acid.

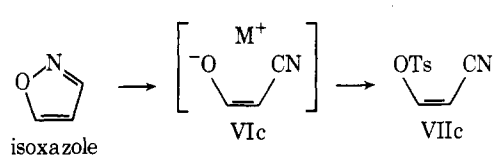


AFC crystallizes very poorly in the presence of impurities. Since 2,2′-*anhydro*-AFC tosylate salt IIIa crystallizes so well, a great deal of purification is accomplished at this stage; additionally, the desired isolation of *anhydro*-AFC (III) is accomplished by crystallization.

Hydrolysis of IIIa TsOH CH_3CN to AFC occurs readily in dilute aqueous ammonia as reported earlier by Sanchez.[1] The product mixture consists of AFC, tosic acid, and a trace of a less polar component which has been tentatively assigned as 1-β-D-arabinofuranosyluracil by TLC comparison. Purification of AFC is achieved by adsorption, then elution from a sulfonic acid ion exchange resin.

Crystallization is accomplished from aqueous methanol to give AFC in 90% yield from IIIa. AFC prepared in this way was shown to be identical with authentic AFC by ir, uv, TLC, optical activity, and elemental analysis.

The key reagent for this synthesis is quaternary salt IVc. This compound is synthesized in high yield by reaction of isoxazole with base. According to the early literature,[2] isoxazole reacts with sodium methoxide–methanol to give an equilibrium mixture of enolate salts VIc + VIt (45:55) in quantitative yield. This equilibration must surely occur via protonation of cis enolate salt VIc to form cyanoacetaldehyde, followed by proton abstraction to give VIc + VIt in the equilibrium ratio. Cis enolate VIc is the sole product from reaction of isoxazole with potassium *tert*-butoxide–THF, if the reaction is carried out at −40 °C or lower. Temperature control of this step is crucial; if the temperature of the reaction is −28 °C, ca. 30% of the unwanted trans enolate salt VIt forms. Product VIc crystallizes out of the reaction mixture. Since it must be kept cold in order to avoid isomerization it is not isolated, but treated directly with tosyl chloride–acetonitrile. The enolate salt reacts upon dissolution to form *cis*-β-tosyloxyacrylonitrile (VIIc) before any significant isomerization occurs.



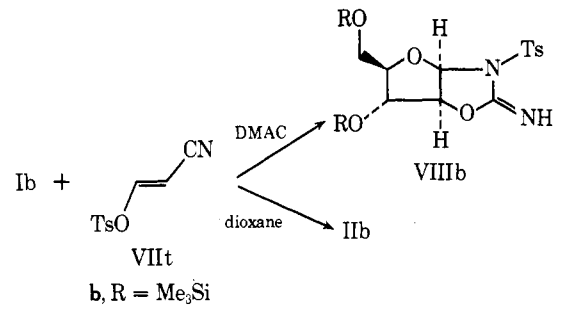
Compound VIIc is converted directly to quaternary salt IVc without isolation in the above reaction. The overall yield of IVc from isoxazole is 85–95%. The reaction with trimethylamine was expected on the basis of the reported[3] reaction of trimethylamine with β-chloroacrylonitrile.[4] It is a stereospecific addition–elimination process that occurs with retention, a result that parallels earlier published work[5] which described nucleophilic displacements of β-chlorocrotonate esters. Thus, cis tosylate VIIc yields only cis quaternary salt IVc (substantiated by NMR data; see Table I).

Other Approaches to AFC. In an earlier synthetic study the equilibrium mixture of enolate salts VIc + VIt was converted to the mixture of *cis*- and *trans*-β-tosyloxyacrylonitrile (VIIc + VIIt). These were separated and purified by silica gel chromatography.

The reaction of oxazoline I as its di-*O*-trimethylsilyl (Me_3Si) ether derivative (Ib) with VIIc and VIIt was examined. Curiously no reaction was observed with cis tosylate VIIc.[6] Reaction of oxazoline Ib with trans tosylate VIIt in the polar solvent *N*,*N*-dimethylacetamide (DMAC) produced, as the major product, a compound tentatively assigned the *N*-tosyloxazoline VIIIb. In nonpolar solvents such as dioxane a cyanovinyl adduct was produced, which was assigned the trans cyanovinyl adduct IIb.

Table I. Vinylic Coupling Constant Data

		τ H–C–CN	*J*, Hz
(II)	Tosylate cyanovinyl adduct	4.90	14.5
(V)	Propiolonitrile cyanovinyl adduct	5.43	10.5
(IVc)	Cis quaternary salt	3.45	10
(IVt)	Trans quaternary salt	3.23	14.5



Compound VIIIb, after silylation to the tri-Me_3Si derivative, showed intense *m/e* 529 and 480 peaks in its mass spectrum.[7] This is rationalized as follows: M^+ at *m/e* 544 not present; M − 15 (−Me) at *m/e* 529, and M − 64 ($-SO_2$) at *m/e* 480. The high-resolution mass spectral determination of the *m/e* 529 peak confirmed the elemental composition of VIIIb Me_3Si: calcd for *m/e* 529, 529.1680 ($C_{21}H_{37}O_8N_2SSi_3$), and found, 529.1673. We are not certain which nitrogen atom contains the tosyl group. Since the ring nitrogen atom is more nucleophilic, we assume that it is tosylated.

Compound IIb, designated the tosylate cyanovinyl adduct, after silylation to the tri-Me_3Si derivative, was analyzed by GLC and GLC–MS. A molecular ion of *m/e* 441 was observed. The high-resolution mass spectral determination of the *m/e* 441 peak confirmed the elemental composition for the cyanovinyl adduct (IIb Me_3Si): calcd for *m/e* 441, 441.1935 ($C_{18}H_{35}O_4N_3Si_3$) and found, 441.1927. It was assigned the trans stereochemistry by data presented below.

Because the tosylate cyanovinyl adduct had the correct molecular ion, we examined the known reaction[1] of propiolonitrile with oxazoline Ia in DMF, or with oxazoline Ib in Me_2SO, DMF, or $CHCl_3$. In all cases the reaction products were silylated and examined by GLC. Reaction in all the solvents gave a single product, designated as the propiolonitrile cyanovinyl adduct, which had a *different* retention time than that of the tosylate cyanovinyl adduct. However, the mass spectrum of the silylated propiolonitrile cyanovinyl adduct was identical with the mass spectrum of the silylated tosylate cyanovinyl adduct. Moreover, when the propiolonitrile cyanovinyl adduct from reaction of Ib in Me_2SO with propiolonitrile is treated with aqueous ammonia, conversion to AFC (by TLC) is rapid at room temperature, as already reported[1] for the nonsilylated cyanovinyl adduct. However, when the tosylate cyanovinyl adduct was treated with aqueous ammonia at room temperature, the only reaction that occurred is the hydrolysis of the silyl groups to give IIa. Uv and ir analysis of IIa indicated the presence of the cyanovinyl adduct unchanged; there was no AFC formed (by TLC). However, if the tosylate cyanovinyl adduct was stirred with aqueous ammonia at 90 °C, conversion to AFC did occur, presumably via thermal isomerization to the cis adduct Va, and then cyclization and hydrolysis to AFC. Presence of AFC

in the product was proven by preparative TLC, uv, and GLC/MS analysis.

NMR analysis of the tosylate cyanovinyl adduct and the propiolonitrile cyanovinyl adduct showed the vinylic proton coupling constants in Table I. The NMR analysis shows that the larger coupling constant, normally assigned to trans isomers, occurs for the tosylate cyanovinyl adduct.

The Sanchez group has suggested in their latest publication[1] that the propiolonitrile cyanovinyl adduct is a trans cyanovinyl adduct (as in II). Our data (NMR analysis and reactivity of the two isomers) require that the cyanovinyl adduct from propiolonitrile is cis (as in V) and the cyanovinyl adduct from *trans*-β-tosyloxyacrylonitrile is trans (as in II).[8]

Although the trans cyanovinyl adduct II can be converted to AFC by photoisomerization in aqueous ammonia, or by thermal isomerization, we discarded this approach because isolation of β-*trans*-tosyloxyacryonitrile is very cumbersome. Investigation of the reactions of the *cis*- and *trans*-β-trimethylammoniumacrylonitrile tosylates then led to the final procedure.

Experimental Section[9]

After study of the reported[1] procedure to prepare oxazoline Ia, the reaction conditions were modified considerably. Reaction of D-arabinose with cyanamide is best carried out in DMF. Potassium bicarbonate is required in catalytic quantities.

2-Amino-β-D-arabinofurano[1′,2′4,5]-2-oxazoline (Ia). A mixture of 90.0 g (600 mmol) of D-arabinose, cyanamide (31.0 g, 740 mmol, 1.23 equiv), and mortared potassium bicarbonate (3.60 g, 36 mmol, 0.06 equiv) was stirred at 90 °C in 600 ml of DMF. After ca. 5 min, the mixture was a pale yellow solution, and after another 6 min, the solution deposited crystals of product. It was stirred for 75 min at 90 °C after the product precipitated, then was cooled to 30 °C. Ethyl acetate (360 ml) was added over ~15 min, and the suspension was stirred for 30 min at 25 °C and 1 h at 0 °C. The crystals were filtered, washed with 2 × 100 ml of 1:1 ethyl acetate–DMF and then 150 ml of ethyl acetate, and dried at 60 °C under house vacuum (27 in. Hg) overnight to give 88.1 g (85%) of off-white crystalline oxazoline II, mp 173.5–174.5 °C. This material is suitable for the next step, although purest quality oxazoline is a white solid of mp 181–183 °C.

2-Amino-β-D-arabinofuran[1′,2′:4,5]-2-oxazoline Di-*O*-trimethylsilyl Ether (Ib). D-Arabinose (30.0 g, 0.20 mol), cyanamide (8.6 g, 0.205 mol), 200 ml of DMF, and 2.0 g of mortared potassium bicarbonate were stirred at 90 °C for 50 min. The mixture was cooled to room temperature, 0.60 ml of concentrated sulfuric acid was added, and the mixture was stirred for 5 min. Hexamethyldisilizane (100 ml, 0.48 mol) and trimethylsilyl chloride (1.0 ml, 0.008 mol) were added and ammonia gas was evolved vigorously. After stirring for ~25 min the reaction mixture was a clear yellow solution. It was cooled to 0 °C and toluene (500 ml) was added. The mixture was extracted with 500 ml and then 200 ml of 10% aqueous potassium carbonate and the aqueous phases back-extracted with 100 ml of toluene. The total toluene was dried over magnesium sulfate, stirred with 2.0 g of activated carbon for 15 min, filtered, washed, and concentrated to a total weight of 160 g. Hexane (700 ml) was added and the semisolid dissolved upon warming to 65 °C. The solution was slowly cooled with stirring to 0 °C; the crystals were collected by filtration, washed with hexane–toluene (9:1), and dried to give 50.0 g of colorless needles (79%), mp 129.5–130 °C. The NMR spectrum (CCl_4) showed the following: τ 3.63 (2 H, broad peak, 2 NH), 4.28 (1 H, doublet, J = 5.5 Hz, C_1 proton), 5.50 (1 H, doublet, J = 5.5 Hz, C_2 proton), 5.81 (1 H, partially resolved triplet, J = 0.8 Hz, C_3 proton), 6.2–6.7 (3 H, multiplet, C_4 proton and C_5 methylene group), 9.83 and 9.95 (each 9 H, two singlets, 2 $SiMe_3$ groups).

***cis*-β-Trimethylammoniumacrylonitrile Tosylate (IVc).** Into a 1.0-l. jacketed, three-necked flask was added a THF solution of potassium *tert*-butoxide (273 g, 55.4 g of KO-*t*-Bu, 495 mmol; this material had been assayed as 20.3% KO-*t*-Bu, 0.40% KOH, 0.9103 g/ml). The solution was cooled to −45 °C and then a solution of isoxazole (Rayco Chemical Co., 27.60 g, 400 mmol) in dry THF (50 ml) was added dropwise at such a rate that temperature was maintained at −39 °C or lower (addition took 31 min). After approximately 5 min of addition, a white precipitate of the enolate salt developed and by the end of the addition the mixture was a thick slurry. The slurry was stirred for 30 min further at −40 to −45 °C. Solid tosyl chloride (92.5 g, 485 mmol) was added in portions at such a rate that the temperature stayed below −38 °C (required ca. 13 min to add) and the white suspension turned black. Acetonitrile was added (300 ml) dropwise over 6 min and the temperature stayed at −43 °C. After stirring overnight at −10 °C, the mixture was concentrated to a small volume (131 g), 750 ml of toluene was added, and the mixture was extracted with 2 × 500 ml of 5% Na_2CO_3. This was back extracted with 100 ml of toluene. (Note: the backwash gave an emulsion and was filtered to remove a black solid.) The toluene extracts were combined, dried over sodium sulfate, and stirred with 10 g of activated carbon for 30 min. This was filtered and washed well to give a pale brown solution of enol tosylate VII. The isomer ratio can be determined readily at this point by running an NMR of an aliquot of the toluene solution. The ratio of VIIc and VIIt is ca. 95:5. The toluene solution was concentrated to 1000 g and stirred at 35–40 °C. A solution of trimethylamine (50 ml, 32.8 g, 560 mmol) in 150 ml of cold toluene was added dropwise over ~30 min. During this addition crystals of cis quaternary salt IVc precipitated. The slurry was stirred for 2 h at room temperature, filtered, and washed with 75 ml of toluene, 75 ml of 2:1 toluene–methylene chloride, then 2× 75 ml of pentane, and dried to give 106.1 g of off-white solid (94%), mp 138–145 °C. This material was suitable for further reactions. Purest cis tosylate VIIc can be obtained by crystallization of the tosylate prior to addition of trimethylamine. After crystallization from methylene chloride–hexane, a white solid is obtained, mp 96.5–97 °C. Pure VIIc caused skin irritation on one occasion and should be handled cautiously. Conversion of this to the cis quaternary salt IVc gave a snow-white, crystalline solid, mp 152.5–154 °C. The NMR spectrum of pure IVc (Me_2SO-d_6) showed the following: τ 2.3–3.0 (5 H, multiplet, aromatic protons and proton on corbon β to cyanomoiety), 3.45 (1 H, doublet, J = 10 Hz, proton on carbon α to the cyano moiety), 6.45 (3 H, singlet, protons on the toluene methyl group).

2,2′-Anhydro-1-β-D-arabinofuranosylcytosine Tosylate (IIIa TsOH CH_3CN). A mixture of oxazoline Ia (13.051 g, 75 mmol), cis quaternary salt IVc (25.4 g, 90 mmol), and 75 ml of DMF was stirred at 50 °C for 10.5 h with a nitrogen sparge at 1 ft^3/min and through a DMF bubbler to presaturate the nitrogen with DMF. Acetonitrile (300 ml) was added rapidly and the solution was seeded to develop crystals of IIIa. The slurry was slowly cooled to room temperature over 30 min, then to 0 °C and stirred for 1 h at 0 °C. The crystals were collected by filtration and washed with 2 × 20 ml of acetonitrile–DMF (9:1), then 2 × 25 ml of acetonitrile and dried under vacuum to give 23.30 g (71%) of white solid. Melting point determinations were meaningless because the material first lost the acetonitrile (of solvation), then decomposed from 90 to 110 °C. The NMR spectrum (Me_2SO-d_6) showed the following: τ 0.8 (1 H, broad peak, NH or OH), 1.72 [1 H, doublet, J = 7 Hz, olefinic proton (probably C-6)], 2.4–2.8 (4 H, multiplet, aromatic protons of the tosylate moiety), 3.39 [2 H, 2 doublets, J = 6 and 7 Hz, proton on C_1 of sugar, and olefinic proton (probably C-7)], 3.9 (1 H, broad peak, NH or OH), 4.53 (1 H, doublet, J = 6 Hz, C_2 proton), 4.95 (1 H, broad peak, NH or OH), 5.47 (1 H, singlet, C_3 proton), 5.71 (1 H, singlet, C_4 proton), 6.55 (3 H, poorly resolved multiplet, OH or NH, and C_5 methylene proton), 7.71 (3 H, protons on the toluene methyl group), 7.95 (5 H, acetonitrile protons). Those signals assigned to NH or OH were shown to disappear by addition of deuterium oxide followed by redetermination of the NMR spectrum. A sample of authentic 2,2′-anhydro-1-β-D-arabinofuranosylcytosine hydrochloride prepared by the method of Sanchez[1] showed the following NMR spectrum (Me_2SO-d_6) after admixture with deuterium oxide: τ 1.70 [1 H, doublet, J = 7 Hz, olefinic proton (probably C_6)], 3.38 [2 H, 2 doublets, J = 6 and 7 Hz, proton on C_1 and olefinic proton (probably C_7)], 4.55 (1 H, doublet, J = 6 Hz, C_2 proton), 5.45 (1 H, singlet, C_3 proton), 5.70 (1 H, broadened singlet, C_4 proton), 6.55 (2 H, broad singlet, C_5 methylene protons).

1-β-D-Arabinofuranosylcytosine (AFC). Tosylate salt IIIa $TosOHCH_3CN$ (8.002 g, 18.25 mmol) and 80 ml of 2 N ammonium hdroxide were stirred at 58 °C for 80 min. The solution was concentrated to a weight of 40 g and added to a Dowex MSC-1 resin column (1.5 × 28 cm, 20–50 mesh, H^+ form, 55 ml of resin equivalent to 94 mequiv): loading phase, 40 g of solution and 2 × 5 ml of water all at 1.0 ml/min flow rate (fraction 1); wash phase, 80 ml of water at 1.0 ml/min (fraction 2, 80 ml); elution phase, 4.5 N ammonium hydroxide at 1.0 ml/min (fraction 3, 35 ml; fraction 4, 125 ml; and fraction 5, 20 ml). TLC analysis indicated that AFC was present only in fraction 4; uv analysis of fraction 4 indicated 101% of the theoretical amount of AFC (4.52 g). Fraction 4 was concentrated to 40 g, 100 ml of methanol was added, and the solution was stirred with 0.50 g of activated charcoal for 30 min. The mixture was filtered and the carbon washed with methanol–water (70:30). The filtrate was concentrated to 9.40 g; 3.0 ml of methanl was added and the mixture warmed to 85 °C to achieve complete solution. This was slowly diluted with 90 ml

of methanol at reflux over 1.5 h. The crystal slurry was cooled to 0 °C over a period of 1.5 h, and stirred at 0. °C for 1 h. The crystals were collected by filtration, washed and dried to give 3.567 g of crystalline AFC. From concentration of the mother liquors a second crop of AFC was obtained, 0.45 g, to give a total yield of 90% from IIIa $TosOHCH_3CN$. The first and second crops of AFC were shown to be identical with authentic AFC by ir, uv, TLC, elemental analysis, and optical activity.

Equilibrium Mixture of *cis*- and *trans*-β-Tosyloxyacrylonitrile (VIIIc and VIIt). To a stirred solution of sodium methoxide (5.35 g, 99 mmol) in reagent 2-propanol (120 ml) was added dropwise over 15 min isoxazole (6.90 g, 100 mmol) and this was stirred under nitrogen for 1 h. The slurry was concentrated to dryness and suspended in 100 ml of acetone at 0 °C and a solution of recrystallized tosyl chloride (17.80 g, 94 mmol) in 50 ml of acetone was added dropwise over 30 min. The mixture was stirred at 25 °C overnight, concentrated to dryness, added to 500 ml of benzene, and extracted with 2 × 50 ml of 10% potassium bicarbonate, then with 250 ml of 25% aqueous sodium chloride. The aqueous phases were back extracted with 2 × 250 ml of benzene. The total benzene extracts were dried ($MgSO_4$) and concentrated to a solid, 21.64 g (97% crude). *Caution:* The crude mixture as well as the crystalline compounds described below easily cause a rash and are skin irritants.

Chromatographic Separation of VIIc and VIIt. A mixture (2:1) of VIIc:VIIt (30.5 g) was mixed with 60 g of silica gel (G. F. Smith Co., which had been deactivated by the addition of 6% water) in ethyl acetate and the mixture concentrated to dryness. This was added to a column of silica gel–6% water (1440 g, 6 × 80 cm) packed in cyclohexane–ethyl acetate (95:5). Elution was continued with 1.5 l. of 95:5, 2.0 l. of 90:10, then 16 l. of 85:15 cyclohexane–ethyl acetate and the progress of the chromatography was followed by TLC (silica gel GF, with 3:1 benzene–ethyl acetate). The earlier 7 l. of the 85:15 system contained pure trans VIIt; this was concentrated to give 9.4 g of the pure trans VIIt. The latter 8 l. of the 85:15 system contained cis VIIc. This was concentrated to give 18.5 g of pure VIIc. Tosylate VIIc was crystallized from ethyl acetate–hexane, mp 94.0–95.5°C. Tosylate VIIt was crystallized from methylene chloride–hexane, mp 87–88.5 °C. The NMR spectra ($CDCl_3$) showed the following. VIIc: τ 2.18–2.6 (4 H, multiplet, aromatic protons), 2.75 (1 H, doublet, J = 6.5 Hz, assigned to olefinic proton on β-carbon atom of the acrylonitrile moiety), 5.02 (1 H, doublet, J = 6.5 Hz, olefinic proton on α carbon of the acrylonitrile moiety), 7.51 (3 H, singlet, protons of the toluene methyl group). VIIt: τ 2.2–2.6 (4 H, aromatic proton), 2.53 (1 H, doublet, J = 12.5 Hz, proton on β carbon), 4.75 (1 H, doublet, J = 12.5 Hz, proton on α carbon), 7.51 (3 H, singlet, protons on the toluene methyl group).

Trans Cyanovinyl Adduct IIb. Oxazoline Ib (3.9776 g, 12.5 mmol), trans tosylate VIIt (3.067 g, 13.75 mmol), 50 ml of dry dioxane, and sodium carbonate (1.541 g, 14.5 mmol) were stirred at 92°C under nitrogen for 19 h. An aliquot (0.050 ml was silylated by stirring with 0.50 ml of bis(trismethylsilyl)trifloroacetamide (BSTFA) for 1 h at 25°C. This was analyzed by GLC (F & M Model 800, 210° C, 6 ft 2% SE-30); a trace of tosylate VIIt was present at 0.5 min retention time, 8% of oxazoline Ib $2Me_3Si$ at 1.0 min, and 92% of the trans cyanovinyl adduct IIb Me_3Si at 4 min.

The reaction mixture was cooled to 15°C, and trimethylamine–tetrahydrofuran (THF) (1.80 ml, 2.0 N) was added to destroy the excess trans tosylate VIIt. After the mixture was stirred for 40 min, it was filtered and the residue washed with THF. The filtrate was concentrated to a brown glass (4.274 g). An NMR spectrum ($CDCl_3$) showed the following: τ 2.45 (1 H, doublet, J = 14.5 Hz, assigned to the olefinic proton on the β-carbon atom of the acrylonitrile moiety), 4.13 (1 H, doublet, J = 5.5 Hz, proton at C_1 of the sugar moiety), 4.90 (1 H, doublet, J = 14.5 Hz, olefinic proton on the α-carbon atom of the acrylonitrile moiety), 5.16 (1 H, doublet, J = 5.5 Hz, proton at C_2), 5.60 (1 H, broadened singlet, proton at C_3), 5.8 (1 H, broadened singlet, proton at C_4), 6.2–6.6 (2 H, multiplet, methylene protons at C_5), 9.81 and 9.90 (9 H each, two singlets, protons on the trimethylsilyl groups).

Reaction of Oxazoline Ib with Propiolonitrile to Form the Cis-Cyanovinyl Adduct Vb. Oxazoline Ib (80 mg, 0.25 mmol) in 0.40 ml of $CDCl_3$ was stirred at room temperature for 2 h after addition of propiolonitrile (14.7 mg, 0.29 mmol). The NMR spectrum ($CDCl_3$) showed the following: τ 2.80 (1 H, doublet, J = 10.5 Hz, olefinic proton on the β-carbon atom of the acrylonitrile moiety), 3.44 (1 H, doublet, J = 5.5 Hz, proton at C_1 of the sugar moiety), 4.1–4.3 (2 H, broad peak, NH), 5.23 (1 H, doublet, J = 5.5 Hz, proton at C_2), 5.43 (1 H, doublet, J = 10.5 Hz, olefinic proton at the α carbon), 5.55 (1 H, broadened singlet, proton at C_3), 5.85 (1 H, multiplet, proton at C_4), 6.3–6.8 (2 H, multiplet, methylene protons at C_5), 9.87 and 9.95 (9 H each, two singlets, protons on the trimethylsilyl groups). An aliquot of this NMR sample (0.020 ml) and 0.50 ml of BSTFA was stirred at 25 °C for 1 h. This sample was analyzed by GLC: trace of oxazoline I at 1.0 min, and major peak at 2.5 min retention time corresponding to Vb Me_3Si.

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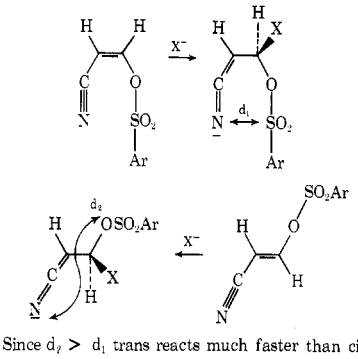
Registry No.—Ia, 36994-58-8; Ib, 58311-70-9; IIb, 58311-71-0; IIIa TsOH, 58342-55-5; IVc, 58311-73-2; Vb, 58342-56-6; *cis*-VII, 58311-74-3; *trans*-VII, 58311-75-4; AFC, 147-94-4; D-arabinose, 10323-20-3; cyanamide, 420-04-2; isoxazole, 288-14-2; tosyl chloride, 98-59-9; propiolonitrile, 107-13-1.

References and Notes

(1) D. H. Shannahoff and R. A. Sanchez, *J. Org. Chem.*, **38**, 593 (1973), & references cited therein.
(2) L. Claisen, *Chem. Ber.*, **25**, 1787 (1892).
(3) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).
(4) We prepared β-chloroacrylonitrile by the method described in ref 3, but found it too irritating to our skin to be handled conveniently. Further work with it was then discontinued.
(5) D. E. Jones, R. D. Morris, C. A. Vernon, and R. F. M. White, *J. Chem. Soc.*, 2349 (1960).
(6) Professor J. E. Baldwin recently suggested to me a plausible explanation for the difference in reactivity of the cis tosylate VIIc and the trans tosylate VIIt based on dipole–dipole interactions of the sulfonyl and nitrogen moieties in the molecules.



Since $d_2 > d_1$ trans reacts much faster than cis

(7) GLC-mass spectra were all run on a CH-7 mass spectrometer.
(8) Sanchez[1] had used DMAC as the solvent in his studies and we used DMF, Me_2SO, or chloroform. We do not think that the different solvent used in Sanchez's case made any difference, however, because his cyanovinyl adduct (corresponding to II) cyclized so readily; this indicates again that his cyanovinyl adduct was cis.
(9) Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. NMR spectra were recorded on a Varian A-60A spectrometer and reported values are relative to tetramethylsilane.