Synthesis of 6-[[(Hydroxyimino)phenyl]methyl]-1-[(1-methylethyl)sulfonyl]-1*H*-imidazo[4,5-*b*]pyridin-2-amine. An Aza Analogue of Enviroxime

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6-[[(Hydroxyimino)phenyl]methyl]-1-[(1-methylethyl)sulfonyl]-1*H*-imidazo[4,5-*b*]pyridin-2-amine (**1**), an aza analogue of enviroxime, was synthesized in eight steps from 6-hydroxynicotinic acid (**2**). Acid **2** was nitrated, chlorinated with phosphorus pentachloride, and subjected to Friedel-Crafts aroylation to give 6-chloro-5-nitro-3-pyridyl phenyl ketone (**5**). Amination of **5** was followed by reduction of the nitro group and condensation with ethoxycarbonylisothiocyanate to give 6-benzyl-2-ethoxycarbonylamino-1*H*-imidazo[4,5-*d*]pyridine (**8**). The ethoxycarbonyl moiety of **8** was cleaved, N-1 was isopropylsulfonylated, and the carbonyl moiety was condensed with hydroxylamine to give **1**. Compound **1** was inactive against rhinovirus 1B and poliovirus type 1.

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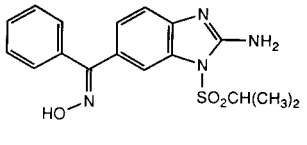
The rhinoviruses are the most common respiratory pathogens for humans and are responsible for the majority of common colds in adults [1]. There are over 100 serotypes of rhinovirus; such numbers have precluded the development of an adequate vaccine [2]. Several chemical agents with potent *in vitro* antirhinovirus activity were tested in humans for beneficial effect on the common cold. With one exception, these agents failed to show a significant clinical effect [3,4]. Enviroxime, a *N*(1)-sulfonyl benzimidazole, is a very potent inhibitor of rhinovirus replication *in vitro* with a uniform level of activity against more than 60 serotypes [5,6]. In clinical trials in England, intranasal and oral enviroxime had some beneficial effect on rhinovirus infections, although the oral form was poorly tolerated due to nausea and vomiting [7,8]. The inability of enviroxime to show highly significant oral clinical usefulness may be because therapeutic blood levels could not be achieved without CNS-associated side effects [9].



enviroxime

1

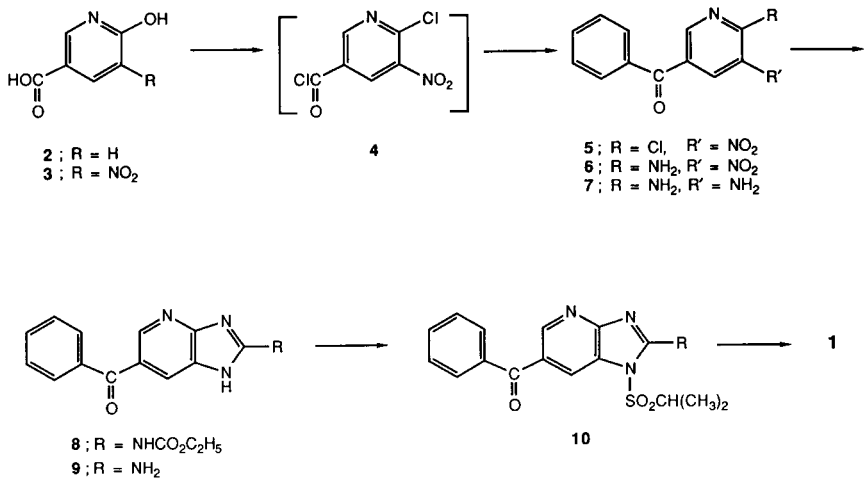
Enviroxime is a lipophilic compound; its measured log P is 3.1 [10]. Hansch has suggested that agents with a lower log P would have less CNS entry and better physiological distribution [11]. Consequently, we prepared 6-[[(hydroxyimino)phenyl]methyl]-1-[(1-methylethyl)sulfonyl]-1*H*-imidazo[4,5-*b*]pyridin-2-amine (**1**), an aza analogue of enviroxime, which should be less lipophilic and may have better bioavailability and fewer CNS-associated side effects. Synthesis of a thieno[2,3-*d*]imidazole analogue of enviroxime was recently reported, but it was less active against several rhinovirus serotypes [12].

The imidazo[4,5-*b*]pyridine **1** was prepared in eight steps from 6-hydroxynicotinic acid (**2**) (Scheme 1). Nitration of **2** with fuming nitric acid provided **3** in 39% yield [13]. Chlorination of **3** with phosphorus pentachloride in dry benzene gave the 6-chloronicotinoyl chloride **4**, which was treated *in situ* with aluminum chloride to effect a Friedel-Crafts aroylation with the benzene solvent. This reaction, which was based on the Binder, *et al.* approach to the thieno[2,3-*d*]imidazole [12], provided ketone **5** in 49% yield. Amination of **5** with ammonium hydroxide in methanol provided the aminopyridine **6** in 83% yield. The nitro group in **6** was reduced using platinum oxide and hydrogen in 95% ethanol. The diaminopyridine **7** was sensitive to air oxidation, although its hydrochloride was sufficiently stable to give an nmr. The diaminopyridine **7** was condensed with ethoxycarbonylisothiocyanate [14] and dicyclohexylcarbodiimide in acetonitrile to give **8** in 55% yield from **6**. The 2-aminoimidazo[4,5-*d*]pyridine **9** was prepared in 38% yield by hydrolysis of **8** with 4 *M* sodium hydroxide.

Selective sulfonylation of **9** was effected with isopropylsulfonyl chloride and potassium carbonate in dimethylformamide to give **10** in 31% yield. The ketone **10** was condensed with hydroxylamine hydrochloride in pyridine to give **1** in 30% yield as a mixture of the *syn*- and *anti*-oxime isomers in a ratio of 1 to 2.6, which were not separable by tlc.

The structure of **10** was assigned from nmr experiments and was substantiated by X-ray structure determination (Figure 1). Proton and carbon spectral data for **10** were obtained at 22° for a 40 mg/ml DMSO-d_6 solution using a Varian XL-300 NMR spectrometer. Assignment of the observed resonances was accomplished by a combination of homo and heteronuclear, one and two dimensional techniques. Inspection of the proton spectrum provided evidence for substitution at C-6 of the pyridine ring since H-5 and H-7 are observed as a resolved scalar coupling pair

Scheme 1



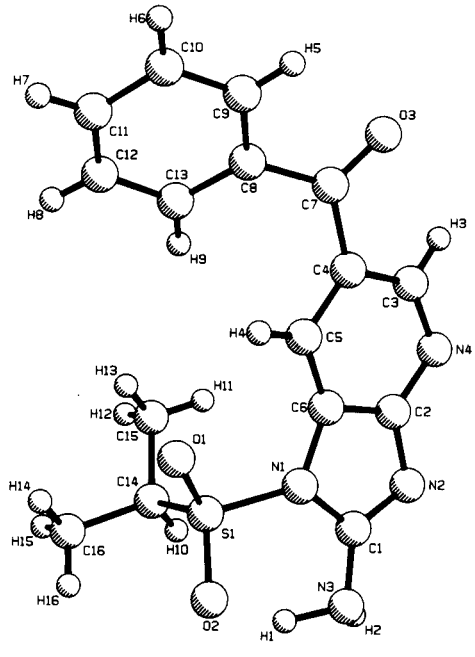


Figure 1. X-ray crystal structure of **10**.

with a coupling constant of 2.2 Hz. Unambiguous assignment of H-5 and H-7 was obtained by a 2D $^{1}H/^{13}C$ chemical shift correlation experiment [15], which showed that the proton at 8.04 ppm (H-7) was connected to the carbon at 118.6 ppm. The H-5 resonance (8.54 ppm) was correlated to a carbon at 147.9 ppm.

After the proton resonances were assigned, NOE experiments were performed to fix the position of the isopropylsulfonyl group. In both 1D NOE difference experiments and phase-sensitive 2D NOE experiments [16], a NOE was observed between the isopropyl methine proton and the pyridine H-7, which allowed unequivocal assignment of compound **10** as the N-1 isomer. To complete the chemical shift assignments of the carbon spectrum, remote (long range) proton-carbon connectivities were established *via* the 2D COLOC experiment [17]. The resulting ^{13}C and ^{1}H assignments are in the Experimental.

Compound **1** was tested for antiviral activity in the plaque reduction assay using monolayers of M-HeLa cells [18]. It was inactive against rhinovirus 1B (10% inhibition at 40 μM) and poliovirus type 1 (no effect at 20 μM) under conditions where 0.04 μM enviroxime inhibited rhinovirus 1B replication by 50 percent. These results indicate that introduction of a nitrogen atom in the 4-position of enviroxime is incompatible with antiviral activity.

EXPERIMENTAL

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian FT-80A, a XL-200, or a XL-300 spectrometer using tetramethylsilane as an external standard and DMSO-d_6 as solvent. Ultraviolet adsorption spectra were recorded on a Perkin-Elmer 571 spectrophotometer with a Digital Specialties laboratory computer used for data acquisition. Mass spectrometric analysis was performed by Oneida Research Services. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on tlc. Tlc's were developed on Whatman 200 micron MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography [19] was performed on Silica Gel 60 (40-63 μm, E. Merck No. 9385). The analytical samples gave combustion values for C, H, N within 0.4% of theoretical values. Elemental analyses were performed by Atlantic Microlab, Inc.

6-Chloro-5-nitro-3-pyridyl Phenyl Ketone **5**.

A mixture of 6-hydroxy-5-nitronicotinic acid (**3**) [13] (17.74 g, 96.37 mmoles) and phosphorus pentachloride (30.1 g, 144.62 mmoles) in dry benzene (425 ml) was refluxed for 7 hours and then stirred at ambient temperature for 18 hours while protected from moisture with a drying tube. Anhydrous aluminum chloride (34.75 g, 241.39 mmoles) was added to this solution of **4**, and the mixture was refluxed with stirring for 1.5 hours. After cooling in an ice bath, the reaction was poured into a 5% sodium bicarbonate:ice water mixture (350 ml), and rapidly extracted with dichloromethane (3 x 3000 ml). The combined extracts were washed with ice-cold 5% aqueous sodium bicarbonate (750 ml) and then filtered through a bed of Silica Gel 60 in a sintered glass funnel. The silica gel was washed with dichloromethane. The filtrate and wash were combined and spin evaporated *in vacuo* to yield 12.55 g (49%) of **5**, mp 81-85°. Recrystallization of a portion from cyclohexane gave the analytical sample, mp 98-100°; uv (*p*H 7 buffer + 9.5% ethanol): λ max 230 nm (ε 17900), 258 nm (ε 16600); ^{1}H nmr (DMSO-d_6): δ 7.5-7.9 (m, 5H, Ar), 8.85 (d, 1H, J = 2.0 Hz, pyridine H-2), 8.98 (d, 1H, J = 2.0 Hz, pyridine H-4).

Anal. Calcd. for $C_{12}H_7ClN_2O_3$: C, 54.78; H, 2.69; N, 10.67. Found: C, 54.94; H, 2.72; N, 10.63.

6-Amino-5-nitro-3-pyridyl Phenyl Ketone (**6**).

A suspension of **5** (2.92 g, 11.12 mmoles) in methanol (10 ml) and ammonium hydroxide (40 ml) was refluxed with stirring for 2.5 hours. The volatiles were removed by spin evaporation *in vacuo*. The yellow residue was dissolved in ethyl acetate:methanol and Silica Gel 60 (35 gm) was added. This mixture was spin evaporated *in vacuo*, and the residual solid was added to a column (35 mm x 150 mm) of Silica Gel 60 wetted with ethyl acetate:-hexane (1:1). The column was eluted initially with ethyl acetate:-hexane (1:1) and then with ethyl acetate using the flash chromatographic method. The appropriate fractions were combined and spin evaporated *in vacuo*. The residue was recrystallized from ethanol to give 2.26 g (83%) of **6**, mp 186-188°; uv (0.1 *N* hydrochloric acid + 9.5% ethanol): λ max 298 nm (ε 19600), 260 nm (ε 13800); (*p*H 7 buffer + 9.5% ethanol): λ max 298 nm (ε 11600), 258 nm (ε 13100); (0.1 *N* sodium hydroxide + 9.5% ethanol): λ max 298 nm (ε 20900), 258 nm (ε 12900); ^{1}H nmr (DMSO-d_6): δ 7.7-7.6 (m, 5H, Ar), 8.4 (br s, 2H, NH_2), 8.59 (d, 1H, J = 2.25 Hz, pyridine H), 8.75 (d, 1H, J = 2.25 Hz, pyridine H), 8.8 (br s, 2H, NH_2).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.20; H, 3.76; N, 17.22.

6-Benzyl-2-ethoxycarbonylamino-1*H*-imidazo[4,5-*d*]pyridine (**8**).

A mixture of **6** (0.400 g, 1.65 mmoles) and platinum oxide (30 mg) in 95% ethanol (40 ml) was shaken in the presence of hydrogen at 20-50 psi for 40 minutes. The catalyst was removed by filtration. The filtrate was acidified with 12 *N* hydrochloric acid (5 ml) and the solution was spin evaporated *in vacuo*. The residue was repeatedly diluted with toluene and spin evaporated until the air sensitive diamine **7** was obtained as a dry solid; ^{1}H nmr (DMSO-d_6): δ 7.0 (br s, 3H, NH_3^+), 7.47 (d, 1H, J = 1.75 Hz, pyridine H), 7.71 (d, 1H, J = 1.75 Hz, pyridine H), 7.5-8.0 (m, 5H, phenyl), 8.75 (br s, 2H, NH_2). This material was dissolved in acetonitrile (50 ml) and stirred magnetically under a nitrogen atmosphere. Triethylamine (0.166 g, 1.65 mmoles) was added in one portion, and the reaction was gently warmed on a steam bath to dissolve the residue. After cooling to room temperature, ethoxycarbonyl isothiocyanate (0.237 g, 1.81 mmoles) was added. The reaction was complete within 10 minutes (tlc-ethyl acetate). Dicyclohexylcarbodiimide (0.409 g, 1.98 mmole) was added to the solution, and the reaction was refluxed with stirring for 2 hours under a nitrogen atmosphere. The volatiles were removed by spin evaporation *in vacuo*. The residue was dissolved in 1 *N* sodium hydroxide (25 ml) and the solution was extracted repeatedly with dichloromethane. The sodium hydroxide solution was neutralized with acetic acid, and the product precipitated as a paste to give 0.283 g (55%) of **8** after drying; ^{1}H nmr (DMSO-d_6): δ 1.28 (t, 3H, J = 7.05 Hz, CH_3), 4.25 (q, 2H, J = 7.05 Hz, CH_2), 7.8-7.5 (m, 5H, Ar), 8.08 (d, 1H, J = 1.75 Hz, pyridine H-7), 8.58 (d, 1H, J = 1.75 Hz, pyridine H-7), 11.9 (br s, 2 H, 2 NH).

2-Amino-6-benzoyl-1*H*-imidazo[4,5-*d*]pyridine (**9**).

A mixture of **8** (3.20 g, 10.3 mmoles) and sodium hydroxide (3.20 g, 80 mmoles) in water (20 ml) was heated on a steam bath for 2 hours. The reaction was cooled to ambient temperature and neutralized with acetic acid. The product was collected and washed with water to give 0.94 g (38%) of **9**, mp 248° dec; ^{1}H nmr (DMSO-d_6): δ 7.1 (br s, 2H, NH_2), 7.5-7.8 (m, 6H, phenyl + pyridine H), 7.95 (br s, 1H, NH), 8.34 (d, 1H, J = 2.07 Hz, pyridine H).

Anal. Calcd. for $C_{13}H_{10}N_4O \cdot 0.66\ H_2O$: C, 62.42; H, 4.56; N, 22.40. Found: C, 62.50; H, 4.49; N, 22.41.

2-Amino-1-(isopropylsulfonyl)-1*H*-imidazo[4,5-*d*]pyridin-6-yl Phenyl Ketone (**10**).

Isopropylsulfonyl chloride (0.5 ml, 0.565 g, 3.96 mmoles) was added to a stirred mixture of **9** (0.94 g, 3.95 mmoles) and potassium carbonate (1.09 g, 7.9 mmoles) in dry dimethylformamide (5 ml). After 1 hour additional potassium carbonate (1.09 g, 7.9 mmoles) and isopropylsulfonyl chloride (0.5 ml, 3.96 mmoles) were added. After an additional hour, potassium carbonate (1.09 g, 7.9 mmoles) and isopropylsulfonyl chloride (0.5 ml, 3.96 mmoles) were added for a third time. The reaction was stirred for 30 minutes more and poured into ice water (100 ml). The mixture was extracted with dichloromethane (3 x 75 ml), and the combined extracts were washed with water (10 ml), dried (magnesium sulfate), and added to Silica Gel 60. This mixture was spin evaporated *in vacuo*, and the residual solids were added to a column (25 mm x 40 mm) of Silica Gel 60 wetted with dichloromethane. The column was eluted with 2% methanol in dichloromethane using the flash chromatography method. The appropriate fractions were combined and spin evaporated *in vacuo*. The residue was recrystallized from acetone-water to give 425 mg (31%) of **10** as light yellow crystals, mp 208-209° dec; uv (0.1 *N* hydrochloric acid + 9.5% ethanol): λ max 334 nm (ε 16300); (*p*H 7 buffer + 9.5% ethanol): λ max 246 nm (ε 11500); (0.1 *N* sodium hydroxide + 9.5% ethanol): λ max 353 nm (ε 10100), 256 nm (ε 18000); ^{1}H nmr (DMSO-d_6): δ 1.34 (d, 6H, J = 6.59 Hz, $CH(CH_3)_2$), 4.03 (septet, 1H, J = 6.59 Hz, $CH(CH_3)_2$), 7.61-7.53 (m, 2H, *meta* ArH), 7.71-7.64 (m, 1H, *para* ArH), 7.77-7.72 (m, 2H, *ortho* ArH), 7.91 (br s, NH_2), 8.04 (d, 1H, J = 1.80 Hz, H-4), 8.54 (d, 1H, J = 1.80 Hz, H-5); ^{13}C nmr (DMSO-d_6): 15.7 (CH_3), 56.3 (CH), 118.6 (C-7), 124.3 (C-8), 124.7 (C-6), 128.4 (Ar C-3 and C-5), 129.3 (Ar C-2 and C-6), 132.4 (Ar C-4), 137.4 (Ar C-1), 147.9 (C-5), 156.9 (C-2), 158.8 (C-9), 193.5 (C=O); ms: (CI, CH_4) m/e = 345 $(M+1)^+$.

Anal. Calcd. for $C_{16}H_{16}N_4O_3S \cdot 0.5\ H_2O$: C, 54.37; H, 4.85; N,

15.85. Found: C, 54.31; H, 4.83; N, 15.86.

2-Amino-1-(isopropylsulfonyl)-1*H*-imidazo[4,5-*b*]pyridin-6-yl Phenyl Ketone Oxime (**1**).

A mixture of **10** (0.415 g, 1.2 mmoles), hydroxyl amine•hydrochloride (1.00 g, 14 mmoles), and pyridine (1.0 g, 13 mmoles) in methanol (15 ml) was refluxed with stirring. After 4 hours the solution was concentrated by spin evaporation *in vacuo*. The residue was dissolved in water (20 ml) and extracted with dichloromethane (3 x 20 ml). The dichloromethane extracts were combined and added to 3 g of Silica Gel 60. This mixture was spin evaporated *in vacuo*, and the residual solids were added to a column (3 cm x 20 cm) of Silica Gel 60 wetted with ethyl acetate. The column was eluted with ethyl acetate, and the appropriate fractions were combined and spin evaporated *in vacuo*. The white residue was recrystallized from ethanol to give 0.130 g (30%) of **1** as a mixture of *E* and *Z* isomers (ratio 2.6 to 1 as determined by nmr), mp 230-233°; uv (0.1 *N* hydrochloric acid + 9.5% ethanol): λ max 334 nm (ε 17000); (*p*H 7 buffer + 9.5% ethanol): λ max 311 nm (ε 16300); (0.1 *N* sodium hydroxide + 9.5% ethanol): λ max 323 nm (ε 13800); ^{1}H nmr (DMSO-d_6): δ 1.29 (d, 6H, J = 6.75, CH(C*H*$_3$)$_2$), 3.93 (septet, 1H, J = 6.75 Hz, C*H*(CH$_3$)$_2$), 7.6-7.2 (m, 7H, Ar + NH$_2$), 7.74 (d, 0.28 H, J = 1.97 Hz, *syn*-oxime H-9), 7.89 (d, 0.72 H, J = 2.02 Hz, *anti*-oxime H-7), 7.96 (d, 0.72 H, J = 2.02 Hz, *anti*-oxime H-9), 8.09 (d, 0.28 H, J = 1.97 Hz, *syn*-oxime H-9), 11.33 (s, 0.72 H, *anti*-oxime NOH), 11.49 (s, 0.28 H, *syn*-oxime NOH); ms: (CI, CH_4) m/e = 360 $(M+1)^+$.

Anal. Calcd. for $C_{16}H_{17}N_5O_3S$: C, 53.47; H, 4.77; N, 19.49. Found: C, 53.21; H, 4.76; N, 19.39.

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