Sommelet-Hauser Rearrangement of an Ammonium Ylide Derived from the HIV-1 Reverse Transcriptase Inhibitor Nevirapine

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Functionalization at the 3-position of the dipyridodiazepinone nevirapine (**1**) has been accomplished by Sommelet-Hauser rearrangement of an ylide derived from **1**. Treatment of *N*-cyanomethylpyrrolidinium salt **4** with potassium *tert*-butoxide in a mixture of dimethylsulfoxide and tetrahydrofuran at -10°, followed by acid hydrolysis, afforded a mixture of compounds **5** and **6** in a ratio of 1:1.8. Upon treatment of **4** with sodium amide in liquid ammonia, **5** and **6** were obtained in a ratio of 1.5:1 and a combined yield of 83%. Compound **5** is the desired product resulting from Sommelet-Hauser rearrangement of **4**, whereas **6** derives from competing Stevens rearrangement and intramolecular cyclization of the aldehyde produced upon hydrolysis. Baeyer-Villiger oxidation of **5** afforded the 3-hydroxy derivative **2**, a recently identified metabolite of nevirapine.

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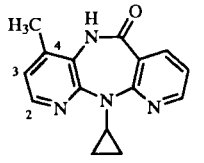
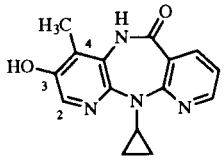
The dipyridodiazepinone nevirapine (**1**) is a potent and specific inhibitor of human immunodeficiency virus type 1 reverse transcriptase (HIV-1 RT) [1]. The compound is currently in Phase III clinical trials. As previously reported [2], the methyl substituent at position 4 of **1** contributes significantly to its potency. As part of an ongoing investigation of structure-activity relationships in the dipyridodiazepinone series, we wished to explore the effect of substitution at position 3 in combination with a 4-methyl substituent. Due to the potential complications associated with the preparation of suitably differentiated tetrasubstituted pyridine precursors, we sought methods to utilize the readily available compound **1** as an intermediate in the synthesis of the target molecules.

A particular target was the 3-hydroxy derivative **2**, a recently identified metabolite of **1**. An initial approach examined for the synthesis of **2** relied on diazotization of the corresponding 3-amino derivative, which was envisioned to be attainable by nitration of **1**, followed by reduction. In the event, however, nitration of **1** with nitronium tetrafluoroborate produced the 2-nitro derivative as the sole regioisomer. An alternative synthesis of **2** was therefore required, ideally one that would provide general access to 4-methyldipyridodiazepinones bearing substituents at the 3-position.

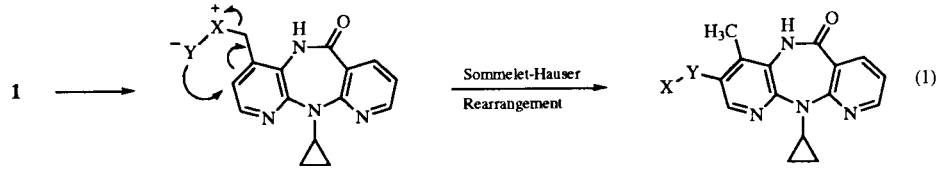
The Sommelet-Hauser rearrangement [3] of an ylide derived from **1** appeared ideally suited for this purpose, allowing the simultaneous installation of functionality at position 3 and restoration of the methyl group at position 4 of the dipyridodiazepinone (equation 1). Similar strategies for pyridine functionalization have been employed previously in syntheses of nicotine analogs [4] and of the antitumor antibiotic streptonigrin [5]. The requisite quaternary salt **4** [6] was prepared as outlined in Scheme 1. Oxidation of the dianion of **1** with oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH), as previously described [7], afforded **3** in 49% yield. Treatment of **3** with thionyl chloride, followed by prolonged heating of the resultant chloride with pyrrolidinoacetonitrile, then provided **4** in 76% yield. Ylide formation and rearrangement were first accomplished by treatment of **4** with potassium *tert*-butoxide in a mixture of dimethylsulfoxide and tetrahydrofuran at -10° (Scheme 2). Following acid hydrolysis of the resultant cyano amines, compounds **5** and **6** were



1

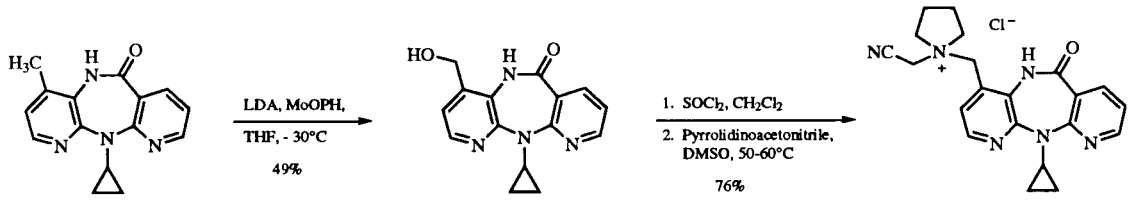


2



(1)

Scheme 1

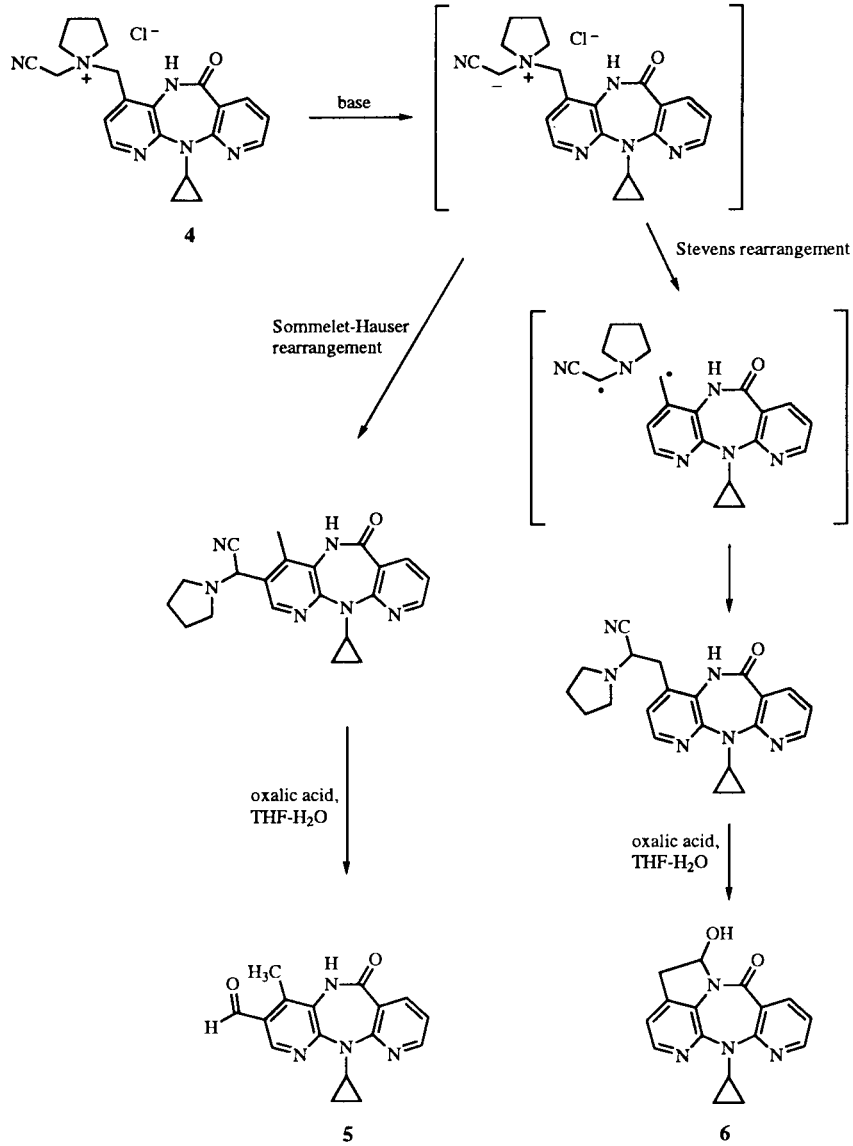


1 3 4

obtained in a combined yield of 90% and a ratio of 1:1.8. Compound **5** is the desired product resulting from Sommelet-Hauser rearrangement of **4**, whereas **6** derives from competing Stevens rearrangement [8] and intramolecular cyclization of the aldehyde produced upon hydrolysis.

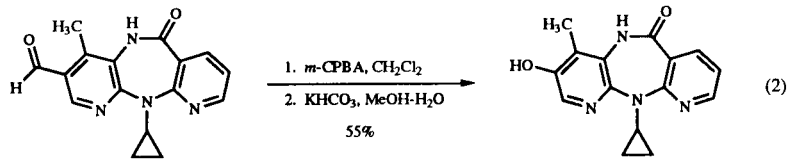
It has been reported that high concentrations of base, protic solvents, and low temperatures all favor Sommelet-Hauser rearrangement over Stevens rearrangement when the two reactions occur competitively [3]. The amount of potassium *tert*-butoxide used in the reaction of **4** was var-

Scheme 2



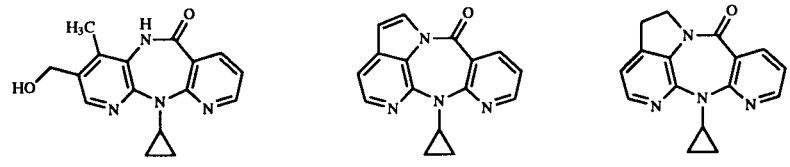
4 5 6

KO-*t*-Bu, DMSO-THF, -10 °C	32%	58%
$NaNH_2$, *l* NH_3	50%	33%



(2)

5 2



7 8 9

ied from 1 to 4 equivalents with no obvious effect on product ratio. However, upon treatment of **4** with sodium amide in liquid ammonia, **5** and **6** were obtained in 83% overall yield, this time in a ratio of 1.5:1 in favor of the Sommelet-Hauser product **5**. Baeyer-Villiger oxidation of **5**, followed by hydrolysis of the resultant formate ester, then afforded **2** in 55% yield (equation 2). Compounds **2** and **5** are useful intermediates for the synthesis of other 3,4-disubstituted dipyridodiazepinones as well, with the aldehyde and hydroxy functionalities at position 3 providing versatile handles for the introduction of a variety of substituents at this position.

Biological data is provided in Table I. Compounds **2**, **5**, and **6** are all extremely poor inhibitors of HIV-1 RT. Somewhat better potency was obtained upon reduction of aldehyde **5** to provide the hydroxymethyl derivative **7**. However, in general, 3,4-disubstituted dipyridodiazepinones exhibit disappointingly weak activity.

Table I

Inhibition of HIV-1 Reverse Transcriptase

Compound	% Inhibition at 1 μM [a]	IC_{50} (nM) [a]
2	15	ND [b]
5	39	ND
6	0	ND
7	52	1,100
8	72	162
9	88	54

[a]See Experimental . [b] ND = not determined.

Interestingly, better results were obtained with compounds derived from the Stevens rearrangement product **6**. Treatment of **6** with methanesulfonyl chloride and triethylamine afforded the elimination product **8**, which was then hydrogenated over platinum oxide to give **9**. Compounds **8** and **9** both proved to be potent inhibitors of HIV-1 RT.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Brucker WM-250 spectrometer. Elemental analyses were determined by Midwest Laboratories, Indianapolis, IN. Short path chromatography was performed over silica gel 60 (63 mesh) under air pressure.

MoOPH was purchased from Aldrich Chemical Co. and was used as received. Pyrrolidinoacetonitrile was purchased from Lancaster Synthesis.

11-Cyclopropyl-5,11-dihydro-4-(hydroxymethyl)-6*H*-dipyrido-[3,2-b:2',3'-*e*][1,4]diazepin-6-one (**3**).

To a solution of of diisopropylamine (7.0 ml, 50.0 mmoles) in 20 ml of tetrahydrofuran at -78° under argon was added 20 ml of a 2.5 *M* solution of *n*-butyllithium in hexanes. The resultant lithium diisopropylamide solution was added by cannula to a solution of **1** (2.66 g, 10.0 mmoles) in 100 ml of dry tetrahydrofuran at -30° under argon. After 5 minutes, 4.8 g (11.0 mmoles) of oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH) was added in one portion to the red reaction mixture. After 1.5 hours, the reaction was quenched by the addition of saturated aqueous ammonium chloride. The resultant mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (sodium sulfate), and concentrated. Purification by short path chromatography (elution with ethyl acetate-dichloromethane) afforded 1.39 g (49%) of **3** and 0.20 g (8%) of recovered starting material. The spectral properties of **3** matched those previously described [7].

Preparation of Quaternary Salt **4**.

To a suspension of 0.87 g (3.1 mmoles) of **3** in 35 ml of dichloromethane was added 2.2 ml (18 mmoles) of thionyl chloride, and the resultant reaction mixture was stirred at room temperature for 3.5 hours. Solvents were removed by rotary evaporation, azeotropically removing excess thionyl chloride with toluene. The residual yellow powder was dissolved in dimethyl sulfoxide (6 ml) under argon. Pyrrolidinoacetonitrile (0.9 ml) was added, and the reaction mixture was stirred at 50-60° for 4 days and at room temperature for 18 days. The reaction mixture was then diluted with ethyl acetate. The resultant precipitate was

collected by suction filtration, washed with ethyl acetate and ether, and dried in vacuo to give 1.15 g (76%) of **4** as a white powder, which contained one molar equivalent of dimethylsulfoxide, mp 160-161°; ^{1}H nmr (deuteriochloroform): δ 10.93 (s, 1 H, N*H*), 8.52 (dd, J = 2, 5, 1 H), 8.31 (d, J = 5, 1 H), 7.94 (dd, J = 2, 7.6, 1 H), 7.46 (d, J = 5, 1 H), 7.07 (dd, J = 5, 7.6, 1 H), 6.47 (br d, J = 13.5, 1 H), 5.37 (A of AB, J = 17, 1 H), 5.26 (B of AB, J = 17, 1 H), 4.95 (br d, J = 13.5, 1 H), 3.62-4.21 (m, 5 H), 2.62 (s, 6 H), 2.20-2.50 (m, 4 H), 0.89-1.08 (m, 2 H), 0.40-0.55 (m, 2 H).

Anal. Calcd. for $C_{23}H_{29}ClN_6O_2S$: C, 56.49; H, 5.98; N, 17.18. Found: C, 56.42; H, 5.89; N, 17.26.

Rearrangement of **4**. Method A.

An oven-dried 100-ml 3-necked flask, equipped with a low-temperature thermometer, rubber septum, and gas inlet adapter, was charged with 0.33g (0.68 mmoles) of **4**, 15 ml of dimethylsulfoxide, and 35 ml of tetrahydrofuran. The reaction mixture was cooled to -10°, and 0.9 ml of potassium *tert*-butoxide (1.0 *M* in *tert*-butyl alcohol 0.9 mmole) was added by syringe over 2 minutes. After 45 minutes, additional potassium *tert*-butoxide (0.37 ml, 0.37 mmole) was added. After 1 hour total reaction time, the reaction was quenched by the addition of saturated aqueous ammonium chloride. The reaction mixture was warmed to room temperature and extracted with ethyl acetate. The organic layer was concentrated, the residue was dissolved in 25 ml of tetrahydrofuran, and 5 ml of 30% aqueous oxalic acid was added. The resultant mixture was heated at reflux for 1 hour. Tetrahydrofuran was removed by rotary evaporation, and the aqueous mixture was neutralized with sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried (magnesium sulfate), and concentrated. Purification of the residue by short path chromatography (elution with 0.5-5% methanol-dichloromethane) afforded, in order of elution, 65 mg (32%) of **5**, mp 262-265° (ethyl acetate-hexanes), and 116 mg (58%) of **6**, mp 229-231° (ethyl acetate-hexanes).

The data for **5** are ^{1}H nmr (deuteriochloroform): δ 10.15 (s, 1 H), 8.62 (s, 1 H), 8.58 (dd, J = 1.9, 4.8, 1 H), 8.16 (dd, J = 1.9, 7.7, 1 H), 7.60 (br s, 1 H, N*H*), 7.14 (dd, J = 4.8, 7.7, 1 H), 3.75-3.90 (m, 1 H), 2.70 (s, 3 H), 0.95-1.10 (m, 2 H), 0.40-0.65 (m, 2 H); ms: CI m/z 295 (MH^+).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.20; H, 4.71; N, 18.96.

The data for **6** are ^{1}H nmr (deuteriochloroform): δ 8.53 (dd, J = 2, 5, 1 H), 8.19 (dd, J = 2, 7.7, 1 H), 8.14 (d, J = 5, 1 H), 7.03 (dd, J = 4.8, 7.7, 1 H), 6.91 (d, J = 5, 1 H), 6.28 (br d, J = 7, 1 H), 3.99 (br s, 1 H, O*H*), 3.48-3.58 (m, 1 H), 3.43 (dd, J = 7, 17.8, 1 H), 2.95 (dd, J = 2, 17.8, 1 H), 1.02-1.12 (m, 2 H), 0.44-0.50 (m, 2 H); ms: CI m/z 295 (MH^+).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.13, H, 4.71; N, 18.91.

Rearrangement of **4**. Method B.

An oven-dried 50-ml 3-necked flask, equipped with a dry-ice condenser, glass stopper, and gas inlet adapter, was charged with 0.25 g (0.5 mmole) of **4** and cooled to -78°. Approximately 30 ml of liquid ammonia was condensed into the flask to produce a yellow solution, and 0.68 mg (1.7 mmoles) of sodium amide was added in two portions. After 2 hours, the ammonia was evaporated, and dichloromethane and water were added. The organic layer was washed with brine, dried (magnesium sulfate), and concentrated. The residue was treated with oxalic acid as described above. Purification by short path chromatography (elution with methanol-dichloromethane) afforded 73 mg (50%) of **5** and 49 mg (33%) of **6**.

11-Cyclopropyl-5,11-dihydro-3-hydroxy-4-methyl-6*H*-dipyrido-[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**2**).

To a solution of 0.16 g (0.54 mmole) of **5** in 5 ml of dichloromethane was added 0.12 g of *meta*-chloroperbenzoic acid (80-85%, 0.56 mmole). The reaction was followed by ^{1}H nmr. When starting material had been consumed, the reaction mixture was washed with saturated aqueous sodium bicarbonate, dried (magnesium sulfate), and concentrated. The residue was dissolved in 5 ml of methanol, and 2 ml of water and 100 mg of potassium bicarbonate were added. After 20 minutes, the reaction mixture was neutralized with 2 *N* hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried (magnesium sulfate), and concentrated to give an oil. Purification by flash chromatography (elution with methanol-dichloromethane) and recrystallization (ethyl acetate-hexanes) afforded 84 mg (55%) of **2**, mp 255-258°; ^{1}H nmr (deuteriochloroform): δ 9.16 (s, 1 H, N*H*), 9.75 (br s, 1 H, O*H*), 8.47 (dd, J = 2, 4.8, 1 H), 7.97 (dd, J = 2, 7.6, 1 H), 7.76 (s, 1 H), 7.15 (dd, J = 4.8, 7.6, 1 H), 3.50-3.60 (m, 1 H), 2.13 (s, 3 H), 0.78-0.95 (m, 2 H), 0.22-0.42 (m, 2 H); ms: CI m/z 283 (MH^+).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.74; H, 5.08; N, 19.48.

11-Cyclopropyl-5,11-dihydro-3-hydroxymethyl-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one (**7**).

To a solution of 0.05 g (0.17 mmole) of **5** in 2 ml of ethanol was added excess sodium borohydride. After 2 hours, the reaction was quenched with acetone. The reaction mixture was diluted with water, and the product was extracted with ethyl acetate. The organic layer was concentrated, and the residue was dissolved in dichloromethane-methanol and passed through a short plug of silica gel. Solvent was removed and the residue was recrystallized (dichloromethane-hexanes) to afford 8 mg (16%) of the product as white crystals, mp 267-269°; ^{1}H nmr (deuteriochloroform) δ 8.54 (dd, J = 1.9, 4.8 H, 1 H), 8.19 (s, 1 H), 8.11 (dd, J = 1.9, 7.7, 1 H), 7.74 (br s, 1 H, N*H*), 7.07 (dd, J = 4.8, 7.7, 1 H), 4.70 (s, 2 H), 3.71-3.79 (m, 1 H), 2.41 (s, 3 H), 0.92-1.08 (m, 2 H), 0.38-0.59 (m, 2 H).

Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.63; H, 5.48; N, 18.72.

Dehydration of Compound **6**.

To a solution of 0.11 g (0.38 mmole) of **6** and 120 µl (0.86 mmole) of Et_3N in 5 ml of dichloromethane at 0° under argon was added 42 µl (0.54 mmole) of methanesulfonyl chloride. The reaction mixture was allowed to warm to room temperature. After 1.5 hours, the reaction mixture was concentrated, and the residue was purified by short path chromatography (elution with 20-50% ethyl acetate-hexanes) to afford 100 mg (96%) of **8**. Recrystallization (ethyl acetate-hexanes) provided 74 mg (70%) of yellow needles, mp 195.5-197°; ^{1}H nmr (deuteriochloroform): δ 8.64 (dd, J = 2, 4.7, 1 H), 8.38 (dd, J - 2, 7.8, 1 H), 8.20 (d, J = 5.4, 1 H), 8.01 (d, J = 3.6, 1 H), 7.15 (d, J = 5.4, 1 H), 7.08 (dd, J = 4.7, 7.8, 1 H), 6.72 (d, J = 3.6, 1 H), 3.55-3.65 (m, 1 H), 1.09-1.20 (m, 2 H), 0.38-0.49 (m, 2 H); ms: CI m/z 277 (MH^+).

Anal. Cacld. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.69; H, 4.40; N, 20.39.

Hydrogenation of Compound **8**.

A solution of 60 mg (0.22 mmole) of compound **8** in 2 ml of ethyl acetate was added to 5-10 mg of platinum oxide in a test tube. The test tube was placed inside a Parr bottle and pressurized to 50 psi with hydrogen. The reaction mixture was hydrogenated at room temperature with shaking for 12 hours. The reaction mixture was then filtered through Celite, added to fresh catalyst and resubjected to the reaction conditions for an additional 16 hours. The reaction mixture was filtered and concentrated, and the residue was purified by short path chromatography (elution with ethyl acetate-hexanes) to give 12 mg (19%) of **9** and 16 mg (27%) of recovered starting material. The product was recyrstallized (ethyl acetate-hexanes) to provide 11.5 mg of light yellow needles, mp 223-224°; ^{1}H nmr (deuteriochloroform): δ 8.50 (dd, J = 2, 4.7, 1 H), 8.23 (dd, J = 2, 7.7, 1 H), 8.12 (d, J = 5, 1 H), 7.03 (dd, J = 4.7, 7.7, 1 H), 6.91 (d, J = 5, 1 H), 4.30 (br s, 2 H), 3.50-3.60 (m, 1 H), 3.00-3.30 (m, 2 H), 1.00-1.12 (m, 2 H), 0.40-0.52 (m, 2 H); ms: CI m/z 279 (MH^+).

Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.99; H, 5.10; N, 19.93.

HIV-1 Reverse Transcriptase Enzyme Assay.

Reverse transcriptase was assayed by a modification of the previously described procedure [1]. The reaction mixture consisted of 50 m*M* Tris (*p*H 7.8), 50 m*M* glutamic acid, 1 m*M* dithiothreitol, 2 m*M* magnesium chloride, 0.02% CHAPS, 0.8 μg/ml poly(rC):oligo(dG) (Pharmacia), and 500 nM [^{3}H]dGTP (NEN Du Pont), adjusted to a final volume of 60 μl. The inhibitors, which were dissolved in dimethyl sulfoxide and diluted many-fold with buffer, were added as solutions, and reaction was initiated by the addition of enzyme. After 1 hour at room temperature, 50 μl each of ice-cold 10% aqueous tichloroacetic acid and 2% aqueous sodium pyrophosphate were added, and the mixture was cooled at 4° for 15 minutes. Acid-insoluble products were harvested onto No. 30 glass fiber filters (Schleicher and Schuell) by means of a Skatron cell harvester. Dried filters were counted in an LKB 1205 Betaplate liquid scintillation counter. Inhibition was determined by comparison of the amount of product in reactions run with and without test compound. Plots of percent inhbition versus log [compound] yielded the concentration at which half-maximal inhibition was observed (IC_{50}).

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