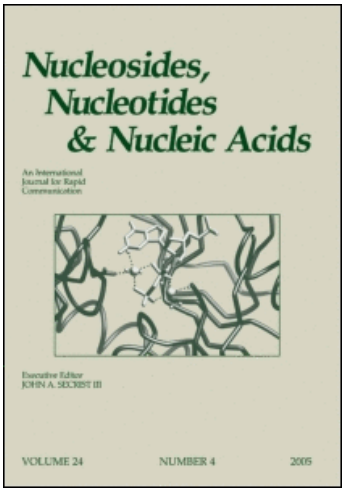


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Studies Toward Synthesis of C2-Substituted Adenosines: An Efficient Synthesis of 2-(Phenylamino)Adenosine [CV-1808]

Bharat K. Trivedi[a]
[a] Department of Chemistry, Parke-Davis Pharmaceutical Research Warner/Lambert Company, Ann Arbor, Michigan

To cite this Article Trivedi, Bharat K.(1988) 'Studies Toward Synthesis of C2-Substituted Adenosines: An Efficient Synthesis of 2-(Phenylamino)Adenosine [CV-1808]', Nucleosides, Nucleotides and Nucleic Acids, 7: 3, 393 — 402
To link to this Article: DOI: 10.1080/07328318808068719
URL: http://dx.doi.org/10.1080/07328318808068719

NUCLEOSIDES & NUCLEOTIDES, 7(3), 393-402 (1988)

STUDIES TOWARD SYNTHESIS OF C2-SUBSTITUTED ADENOSINES: AN EFFICIENT SYNTHESIS OF 2-(PHENYLAMINO)ADENOSINE [CV-1808]

Bharat K. Trivedi
Parke-Davis Pharmaceutical Research
Warner/Lambert Company
Department of Chemistry
Ann Arbor, Michigan 48105

Abstract: In this paper we report general and highly efficient synthetic routes to certain C2,N6-disubstituted adenosines including an efficient synthesis of 2-(phenylamino)adenosine [CV-1808, a highly A2 receptor selective adenosine agonist] originally developed as an antianginal agent.

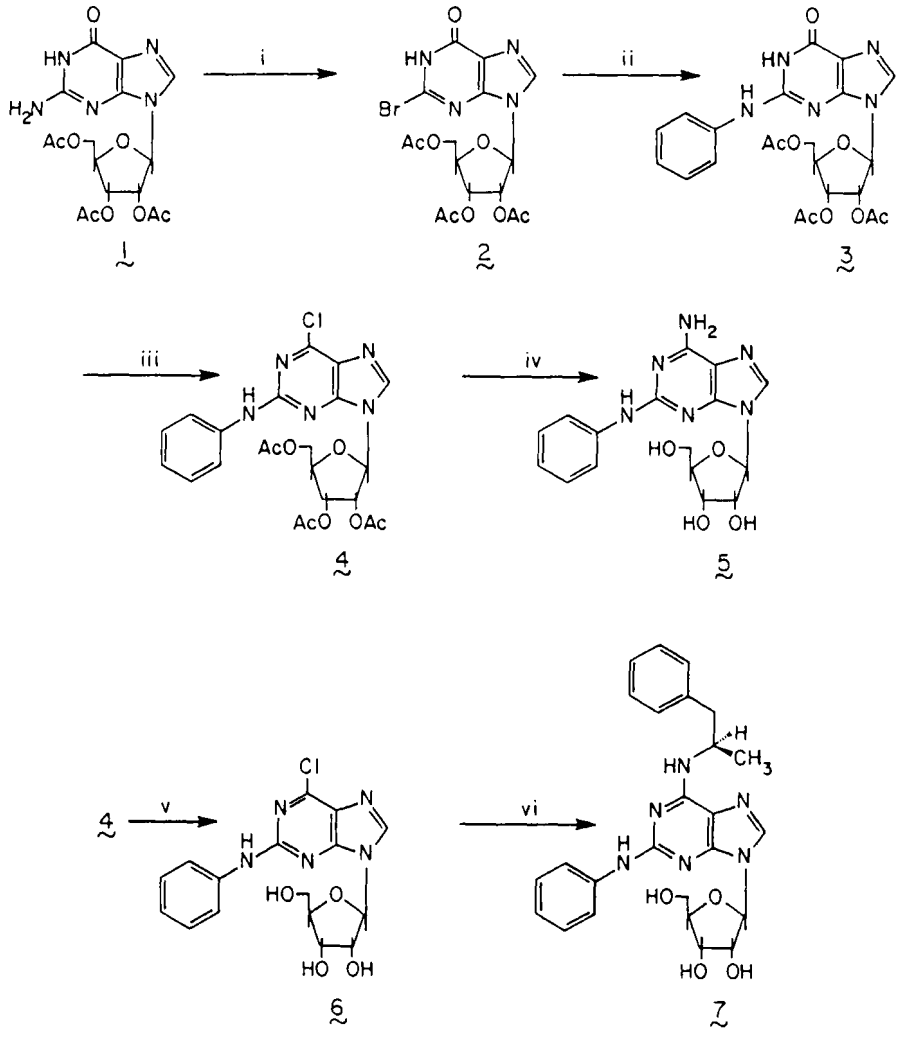
A large number of substituted adenosines have been reported in the literature as modulators of extracellular adenosine receptors designated as A1 (mediating inhibition of adenylate cyclase) and A2 (mediating stimulation of adenylate cyclase).[1] A significant number of A1-selective agonists have been thoroughly investigated for their pharmacological profile. However, it is only recently that Bruns et al.[2] have identified 2-(phenylamino)adenosine (CV-1808) as an A2 selective agonist in the rat brain preparation. We were interested in the synthesis of CV-1808 and its analogues. 2-(Phenylamino)adenosine (CV-1808) (5) was originally synthesized by R. Marumoto et al. and was developed as an antianginal agent.[3,4] Each of the syntheses reported starts with 5-amino-1-(β-D-ribofuranosyl)-1H-imidazole-4-carboxamide (AICA-R). Unfortunately, this compound's sole source is a costly fermentation. We began investigating the chemistry of C-2 modified inosines with the aim of developing a simple and economical synthesis of CV-1808. Halogenation of guanosine 2',3',5'-triacetate (1) using a modification of Nair's procedure[5] gave 2-bromoinosine 2',3',5'-triacetate (2) in 35% yield.[6] Nucleophilic displacement with aniline in refluxing methanol afforded N-phenylguanosine 2',3',5'-triacetate (3) in 69% yield. Halogenation of 3 under standard Vilsmeier conditions (DMF-$POCl_3$) afforded 6-chloro-N-phenyl-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purin-2-amine (4) in moderate yield (50-60%). The yield of 4 can be improved to 90% by using

Robins' procedure[7] which employs phosphorous oxychloride/N,N-dimethylaniline in acetonitrile. Reaction of 4 with saturated methanolic-ammonia at 120°C for four h gave 2-(phenylamino)adenosine (CV-1808) (5) in 75% yield. This represents the first highly efficient and inexpensive synthesis of 2-(phenylamino)adenosine (CV-1808) (5) starting from commercially available guanosine. Additionally, selective deprotection of the triacetate 4 using methanolic-ammonia at room temperature afforded 6-chloro-N-phenyl-9-β-D-ribofuranosyl-9H-purin-2-amine (6) in 91% yield. The later compound serves as a key intermediate for the preparation of a wide variety of N^6-substituted 2-(phenylamino) adenosines. For example, compound 7, a representative of this class of compounds was synthesized in 64% yield by reacting 6 with (R)-1-phenyl-2-propanamine in refluxing ethanol.

Simultaneously, we were also interested in the preparation of 2-(phenylthio)adenosine and its derivatives. A wide variety of 2-alkylthioadenosines has been synthesized by (1) condensation of 2-alkylthioadenines with appropriate ribose derivatives[8-11] (2) amination of 2-alkylthio-6-chloropurine ribosides,[10] and (3) alkylation of 2-thioadenosines[12,13] and (4) photoinduced alkylthiolation of halogenated nucleosides.[14] However, most of these procedures are all long sequences and are not readily accessible routes for the synthesis of a variety of 2-phenylthio, N^6-substituted adenosines. Therefore, we investigated the possibility of introducing the phenylthio functionality directly at the C-2-position of a purine riboside (as shown in Scheme I).

Reaction of 6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purin-2-amine (8) with diphenyl disulfide and i-amylnitrite in refluxing acetonitrile afforded 6-chloro-2-(phenylthio)-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (9) in 45% yield. Treatment of 9 with saturated methanolic-ammonia at 100°C for 12 h gave a 44% yield of 2-(phenylthio)adenosine (10).[15] Compound 9 serves as an important intermediate which allows one to introduce under mild conditions a variety of substituted amines at the C-6 position, followed by standard deprotection of the acetate to yield C-2, N^6-disubstituted nucleosides (Scheme II). As an example of the use of 9 in this manner, the 2-phenylthio analog (11) of the standard reference agonist (R)-PIA was prepared in 48% yield by reaction of 9 with (R)-1-phenyl-2-propanamine in dimethoxyethane at room temperature, followed by deprotection using methanolic ammonia at room temperature. The synthetic schemes described above clearly demonstrate a very facile entry into a wide range of C-2, N^6-disubstituted nucleosides of biological interest.

Scheme I[a]



[a](i) $CHBr_3$, n-amyl nitrite, Δ;

(ii) $PhNH_2$, MeOH, Δ;

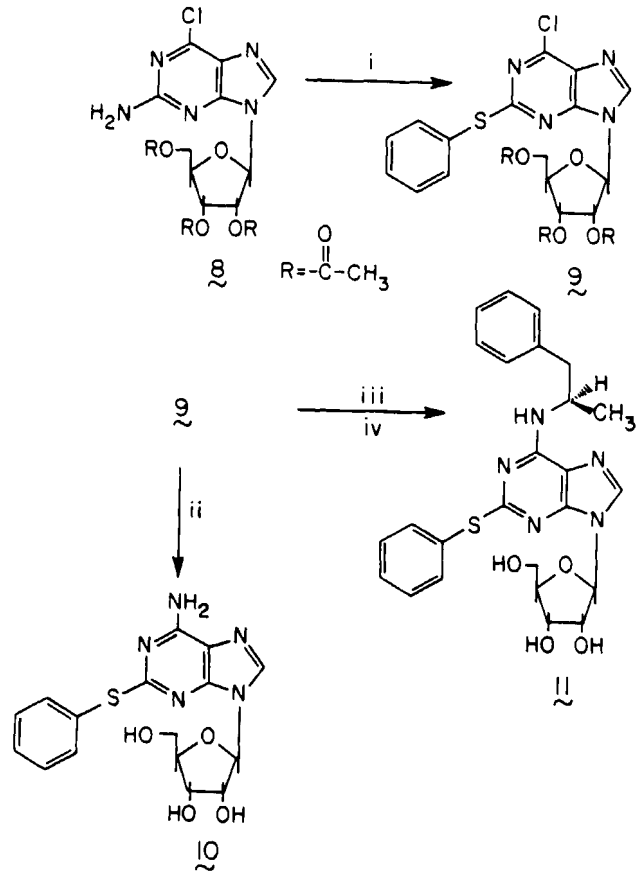
(iii) $POCl_3$, N,N-dimethylaniline, Et_4NCl, CH_3CN, Δ;

(iv) NH_3-MeOH, Δ;

(v) MeOH-NH_3, R.T.;

(vi) $PhCH_2CHCH_3NH_2$, Et_3N, EtOH, Δ.

Scheme II[a]



[a] (i) PhSSPh, i-amylnitrite, CH_3CN, Δ;

(ii) MeOH-NH_3, 100°C, 12 hr;

(iii) $PhCH_2CHCH_3NH_2$, DME, Et_3N, R.T.;

(iv) MeOH-NH_3, R.T.

EXPERIMENTAL SECTION

Melting points are uncorrected. Analytical thin layer chromatography (TLC) was done with precoated glass plates (EM reagents silica gel 60 F-254). Flash column chromatography was performed on silica gel 60 (230-400 mesh). ^1H NMR spectra were obtained on Varian EM-390 or Varian XL-200 spectrometer. Mass spectra were recorded on a Finnegan 4500 mass spectrometer with an INCOS data system or a VG 7070 E/HR mass spectrometer with an 11/250 data system. Solvents and reagents were commercially available unless otherwise noted and were used directly. Elemental analyses were determined at Warner-Lambert/Parke-Davis.

2-Bromoinosine 2',3',5'-triacetate (2). Guanosine 2',3',5'-triacetate[7] (1) (20 g, 48.8 mmol), n-amyl nitrite (40 mL) and bromoform (50 mL) were heated at 90°C for 0.5 h.[16] Volatiles were evaporated under reduced pressure and the residue was purified on silica gel by flash chromatography using chloroform. Evaporation of solvent yielded 5.5 g of 2-bromoinosine 2',3',5'-triacetate (R_f = 0.33, 5% MeOH-$CHCl_3$). An additional 2.78 g (total yield, 35%) of the product was obtained after chromatographic purification of the crude fractions. ^1H NMR ($CDCl_3$): δ 2.03, 2.06, 2.12 (3 x 3H, -$COCH_3$), 4.23-4.4 (m, 3H, H_4 and 2H'$_5$), 5.56 (t, 1H, 3H'), 5.82 (t, 1H, 2H'), 6.15 (d, 1H, 1H'), and 13.5 (bs, 1H, -NH).

N -Phenylguanosine 2',3',5'-triacetate (3). To a solution of 2-bromoinosine 2',3',5'-triacetate (2) (5.5 g, 11.6 mmol) in methanol (50 mL), aniline (7 mL) was added and the reaction mixture was refluxed at 95°C for three h. Volatiles were removed under reduced pressure, and the dark-brown residue was dissolved in 20 mL of methanol. Upon standing at room temperature, a light-yellow crystalline solid was obtained (R_f = 0.08, 5% MeOH-$CHCl_3$) which was filtered and dried yielding 3.9 g (69%) of N-phenylguanosine 2',3',5'-triacetate: mp 222-225°C.
[Lit[4] mp = 231-233°C]
Anal. Calcd. for $C_{22}H_{23}N_5O_8$: C, 54.43; H, 4.77; N, 14.42;
Found: C, 54.50; H, 4.84; N, 14.52.
^1H NMR (DMSO-d_6): δ 1.9 (3H, -$COCH_3$), 2.06 (3H, -$COCH_3$), 2.12 (3H, -$COCH_3$), 4.06-4.31 (m, 3H, H'$_4$ and 2H'$_5$), 5.37 (t, 1H, H'$_3$), 5.98 (t, 1H, H'$_2$), 6.08 (d, 1H, H'$_1$), 7.07-7.56 (m, 5H, phenyl), 8.02 (s, 1H, H_8), 8.86 (s, 1H, NH-C_6H_5), 10.8 (bs, 1H, NH), mass spectrum m/z (relative intensity) 486 (100, m + 1).

6-Chloro-N -phenyl-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purin-2-amine (4). To a solution of N-phenylguanosine 2',3',5'-triacetate (3) (1.0 g, 2 mmol) in dry acetonitrile (10 mL), tetraethylammonium/chloride (dried over P_2O_5) (0.8 g) followed by N,N-dimethylaniline (0.35 mL) and phosphorous oxychloride (1.4 mL) was added. The reaction was kept in an oil bath preheated at 100°C for ten min under nitrogen. The volatiles were evaporated under reduced pressure, and the residue was dissolved in 50 mL of chloroform. The organic solution was added to ice water, and the layers were separated. The aqueous layer was extracted with chloroform (2 x 50 mL) and the combined organic extract was washed with 10% $NaHCO_3$ (3 x 25 mL) and water (2 x 25 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was evaporated to yield 0.99 g of solid which was purified on silica gel by flash chromatography using chloroform. Evaporation of solvent from pure fractions (R_f = 0.62, 5% MeOH-$CHCl_3$) afforded 0.88 g (85%) of 6-chloro-N-phenyl-9-(2,3,5-tri-O-acetyl-β-D- ribofuranosyl)-9H-purin-2-amine: mp 80-85°C.
Anal. Calcd. for $C_{22}H_{22}N_5O_7Cl$: C, 52.44; H, 4.40; N, 13.89; Cl, 7.02; Found: C, 52.24; H, 4.67, N, 13.69; C, 7.27.
^1H NMR (DMSO-d_6): δ 1.91 (s, 3H, -$COCH_3$), 2.06 (s, 3H, -$COCH_3$), 2.13 (s, 3H, -$COCH_3$), 4.2-4.37 (m, 3H, 1H'$_4$ and 2H'$_5$), 5.49 (t, 1H, H'$_3$), 6.05 (t, 1H, H'$_2$); 6.22 (d, 1H, H'$_1$), 7.02 (t, 1H, phenyl), 7.33 (t, 2H, phenyl), 7.71 (d, 2H, phenyl), 8.5 (s, 1H, H_8), and 10.07 (s, 1H, -NH-C_6H_5), mass spectrum m/z (relative intensity) 504 (100, m+).

2-(Phenylamino)adenosine (5). A mixture of 6-chloro-N-phenyl-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purin-2-amine (0.85 g, 1.68 mmol) and saturated methanolic-ammonia (50 mL) was heated at 120°C for four h in an autoclave. Upon cooling, the volatiles were evaporated from the colored solution and the residue was purified on silica gel by flash chromatography using 5% MeOH-$CHCl_3$ as eluent. Evaporation of the solvents from the pure fractions (R_f = 0.33, 20% MeOH-$CHCl_3$) yielded 0.45 g (75%) of 2-(phenylamino)adenosine (1): mp 240-242°C. [Lit[4] mp = 244-245°C] Anal. Calcd. for $C_{18}H_{18}N_6O_4 \cdot 0.05\ CHCl_3$: C, 52.91; H, 4.99; N, 23.06; Found: C, 52.61; H, 5.10; N, 22.81.
^1H NMR (DMSO-d_6): δ 3.51-3.70 (m, 2H, H'$_5$), 3.9 (m, 1H, H'$_4$), 4.14 (m, 1H, H'$_3$), 4.58 (q, 1H, H'$_2$), 5.01 (t, 1H, 5'-OH), 5.16 (d, 1H, 3'-OH), 5.44 (d, 1H, 2'-OH), 5.84 (d, 1H, H'$_1$), 6.86 (t, 1H, phenyl), 6.9 (s, 2H, -N^6H_2), 7.23 (t, 2H, phenyl), 7.83 (d, 2H, phenyl), 8.11 (s, 1H, H_8), 8.90 (s, 1H, -NH-C_6H_5).

6-Chloro-N-phenyl-9-β-D-ribofuranosyl-9H-purin-2-amine (6). A mixture of 6-chloro-N-phenyl-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purin-2-amine (2.5 g, 4.96 mmol) and saturated methanolic-ammonia (50 mL) was stirred at room temperature for 8.5 h. The volatiles were evaporated, and the residue upon treatment with 50 mL of chloroform precipitated a solid which was filtered and dried affording 1.7 g (91%) of 6-chloro-N-phenyl-9-β-D-ribofuranosyl-9H-purin-2-amine ^{1}H NMR (DMSO-d_6): δ 3.6 (dq, 2H, 2H'$_5$), 3.95 (q, 1H, H'$_4$), 4.16 (t, 1H, H'$_3$), 4.59 (t, 1H, H'$_2$), 4.8-5.7 (br, 3H, 5', 3', 2'-OH), 7.0-7.8 (m, 5H, phenyl), 8.32 (s, 1H, H_8), and 10 (s, 1H, NH-C_6H_5), mass spectrum m/z (relative intensity) 377 (28), 245 (100), 210 (35).

(R)-N-(1-Methyl-2-phenylethyl)-2-(phenylamino)adenosine (7). A mixture of 6-chloro-N-phenyl-9-β-D-ribofuranosyl-9H-purin-2-amine (0.25 g, 0.66 mmol), (R)-1-phenyl-2-propanamine (0.13 g, 0.99 mmol) and triethylamine (0.1 g, 0.99 mmol) in absolute ethanol (15 mL) was refluxed under nitrogen for 20 h. Upon cooling, volatiles were removed under reduced pressure, and the residue was treated with cold water. The precipitated solid was filtered and purified by flash column chromatography on silica-gel using 2% methanol-chloroform as the eluent. Evaporation of the solvent from the pure fractions gave solid material which upon crystallization from ethylacetate-hexane afforded 0.2 g (64%) of (R)-N-(1-methyl-2-phenylethyl)-2-(phenylamino)adenosine: mp 148-150°C.
Anal. Calcd. for $C_{25}H_{28}N_6O_4$: C, 63.01; H, 5.92; N, 17.63
Found: C, 63.07; H, 5.81; N, 17.42.
^{1}H NMR (DMSO-d_6); δ 1.19 (d, 3H, CH_3), 2.75 (dd, 1H, -CH_2Ph), 3.05 (dd, 1H, -CH_2Ph), 3.5 (m, 2H, H'$_5$), 3.9 (d, 1H, H'$_4$), 4.14 (brs, 1H, H'$_3$), 4.56 (brs, 2H, H'$_2$, C$\underline{H}$$CH_3$), 5.0-5.5 (br, 3H, 5',3',2'-O$\underline{H}$), 5.85 (d, 1H, H'$_1$), 7.0-7.8 (m, 11H, phenyl and N$\underline{H}$), 8.1 (s, 1H, H_8), and 8.9 (s, 1H, N$\underline{H}$$C_6H_5$), mass spectrum (FAB) m/z (relative intensity) 477 (100), 345 (76).

6-Chloro-2-(phenylthio)-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (9). A mixture of 6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purin-2-amine (8)[6] (4.0 g, 9.3 mmol), diphenyl disulfide (10 g, 46 mmol), and i-amyl nitrite (10.84 g, 93 mmol) in acetonitrile (100 mL) was refluxed at 100°C for three hours. The volatiles were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using chloroform as an eluent. Evaporation of the solvent from pure fractions afforded 2.2 g

(45%) of 6-chloro-2-(phenylthio)-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine. ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 3.84-3.87 (m, 2H, H'$_5$), 4.24 (m, 1H, H'$_4$), 5.02 (t, 1H, H'$_3$), 5.88 (m, 2H, H'$_2$ and H'$_1$), 7.47 (m, 3H, phenyl), 7.66 (m, 2H, phenyl), and 8.02 (s, 1H, H_8).

2-(Phenylthio)adenosine (10). A solution of 6-chloro-2-(phenylthio)-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (9) (2.0 g, 3.83 mmol) in saturated methanolic-ammonia (100 mL), was heated at 100°C for 12 h. Upon cooling, the volatiles were removed under reduced pressure, and the residual solid was purified by flash column chromatography on silica gel using 5% methanol-chloroform as the eluent. Evaporation of the solvent from the pure fractions (R_f = 0.34, 20% MeOH-$CHCl_3$) afforded 0.65 g (44%) of 2-(phenylthio)adenosine: mp 113-117°C.
Anal Calcd. for $C_{16}H_{17}N_5O_4S \cdot 0.5H_2O$: C, 49.99; H, 4.71; N, 18.21; S, 8.34; Found: C, 49.52; H, 4.41; N, 18.02; S, 8.18.
^{1}H NMR (DMSO-d_6): δ 3.3 (m, 2H, H'$_5$), 3.76-3.86 (m, 2H, H'$_3$ and H'$_4$), 4.52 (q, 1H, H'$_2$), 4.84 (t, 1H, 5'-OH), 5.02 (d, 1H, 3'-OH), 5.33 (d, 1H, 2'-OH), 5.63 (d, 1H, H'$_1$), 7.38-7.60 (m, 7H, $-NH_2$ and phenyl), and 8.2 (s, 1H, H_8); mass spectrum m/z (relative intensity) 375 (28), 286 (26), 272 (40), 242 (85).

(R)-N-(1-Methyl-2-phenylethyl)-2-(phenylthio)adenosine (11) A mixture of 6-chloro-2-(phenylthio)-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine (9) (1.0 g, 2.0 mmol), (R)-1-phenyl-2-propanamine (0.32 g, 2.4 mmol), and triethylamine (0.26 g, 2.6 mmol) in dry dimethoxyethane (15 mL) was stirred at room temperature for 16 h. The precipitated solid ($Et_4N^+HCl^-$) was filtered, washed with DME and the volatiles were evaporated. The residue was dissolved in 50 mL of saturated methanolic-ammonia and stirred at room temperature for five h. The volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 5% MeOH-$CHCl_3$. Evaporation of the solvent from the pure fractions afforded 0.45 g (48%) of (R)-N-(1-methyl-2-phenylethyl)-2-(phenylthio)adenosine (11): mp 118-120°C.
Anal Calcd. for $C_{25}H_{27}N_5O_4S$: C, 60.83; H, 5.51; N, 14.18; S, 6.49; Found: C, 60.66; H, 5.30; N, 14.24; S, 6.32.
^{1}H NMR (DMSO-d_6): δ 0.97 (d, J=6.9 Hz, 3H, CH_3), 2.5-2.78 (m, 2H, CH_2), 3.42-3.49 (m, 2H, 5'CH_2), 3.86 (m, 1H, H'$_4$), 3.97 (bs, 1H, H'$_3$), 4.11 (m, 1H, CH-CH_3), 4.52 (t, 1H, H'$_2$); 4.5-5.3 (bs, 3H, -OH), 5.72 (d, 1H, H'$_1$), 6.9-7.58 (m, phenyl), 7.86 (d, 1H, -NH), and 8.2 (s, 1H, H_8); mass spectrum m/z (relative intensity) 493 (16), 402 (84), 270 (100).

ACKNOWLEDGEMENTS

We are grateful to the Analytical Service Group at Warner-Lambert/ Parke-Davis for supplying the analytical data. We thank D. R. Johnson for performing the high-pressure reactions. Finally, we thank J. Bristol and A. Bridges for helpful discussions.

REFERENCES

1. For reviews in this area see: a) Daly, J. W., J. Med. Chem. 1982, 25, 197; b) Kusachi, S., Thompson, R. D., Bugni, W. J., Yamada, N., Olsson, R. A., J. Med. Chem. 1985, 28, 1636; c) Olsson, R. A., Kusachi, S., Thompson, R. D., Ukena, D., Padgett, W., Daly, J. W., J. Med. Chem. 1986, 29, 1683.

2. Bruns, R. F., Lu, G. H., Pugsley, T. A., Mol. Pharmacol., 1986, 29, 331.

3. Marumoto, R., Yoshikoto, Y., Honjo, M., Kawazoe, K., US Patent 3 936 439, 1976.

4. a) Marumoto, R., Yoshikoto, Y., Miyashita, O., Shima, S., Imai, K., Kawazoe, K., Honjo, M., Chem. Pharm. Bull. 1975, 23(4), 759; b) Omura, K., Marumoto, R., Furukawa, Y., Chem. Pharm. Bull. 1981, 29(7), 1870.

5. a) Richardson, S. G., Nair, V., Synthesis, 1982, 670; b) Nair, V., Young, D., DeSilvia, R., J. Org. Chem., 1987, 52, 1344; c) Nair, V., Chamberlain, S., J. Org. Chem., 1985, 50, 5069.

6. Several attempts to prepare 2-bromoinosine according to the procedure of R. Marumoto, et al. [Chem. Pharm. Bull., 1974, 22(2), 342 and 1971, 19(3), 576] in which AICA-riboside was first converted to the potassium salt of a 2-thioinosine followed by bromination to afford 2-bromoinosine, were unsuccessful.

7. Robins, M. J., Uznanski, B., Can. J. Chem., 1981, 59, 2601.

8. Davoll, J., Lowy, B., J. Am. Chem. Soc., 1952, 74, 1563.

9. Ishido, Y., Kikuchi, Y., Sato, T., Nippon Kagaku Zasshi, 1965, 86, 126.

10. Maguire, M., Nobbs, D., Einstein, R., Middleton, J., J. Med. Chem. 1971, 14, 415.

11. Burrows, W., Armstrong, D., Skoog, F., Hecht, S., Boyle, J. T., Leonard, N., Occolowitz, J., Science 1968, 161, 691.

12. Kikugawa, K., Suehiro, H., Ichino, M., J. Med. Chem. 1973, 16, 1381.

13. Kikugawa, K., Suehiro, H., Aoki, A., Chem. Pharm. Bull. 1977, 25(10), 2624.

14. Nair, V. Young, D., Synthesis, 1986, 450.

15. 2-(Phenylthio)adenosine has been prepared by direct arylation of 2-thioadenosine with iodobenzene in a very poor (<10%) yield. See Ref. 13.

16. Nair et al, (Ref. 5a) have used a large excess of bromoform (10 mL/0.385 mmole of the substrate) in their preparation of 2-bromo-6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine. This makes it highly expensive and inconvenient procedure for a large-scale preparation. After several runs at different concentrations, we found the optimum amounts of the respective reactants as reported in the experimental procedure. Recently, Nair et al (Ref 5b and 5c) have modified their experimental conditions specifically for iodination reaction in which quantity of iodoform is reduced and acetonitrile is used as a solvent.

Received September 29, 1987