SYNTHESIS OF NEW CARBOCYCLIC ANALOGUES OF OXETANOCIN A AND OXETANOCIN G

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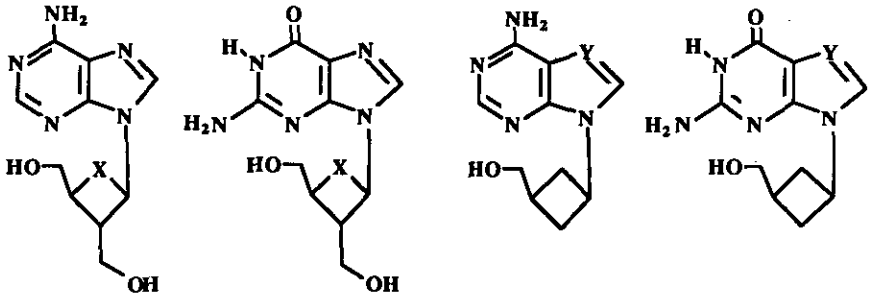
Abstract--- The synthesis of *cis*-3-amino-1-cyclobutanemethanol has been performed in six steps (59.6% yield) from *cis*-1,3-cyclobutanedicarboxylic anhydride. This allowed us to obtain two new carbocyclic analogues of oxetanocin A and oxetanocin G related to 7-deazaadenosine and 7-deazaguanosine

Cyclobut-A and cyclobut-G are carbocyclic analogues of oxetanocin A and oxetanocin G respectively, and have been found to be broad-spectrum antiviral agents, particularly potent against human immunodeficiency virus (HIV).[1] Compounds (**5**) and (**6**) have also been found to exert antiretroviral activity against HIV-1 *in vitro*.[2]

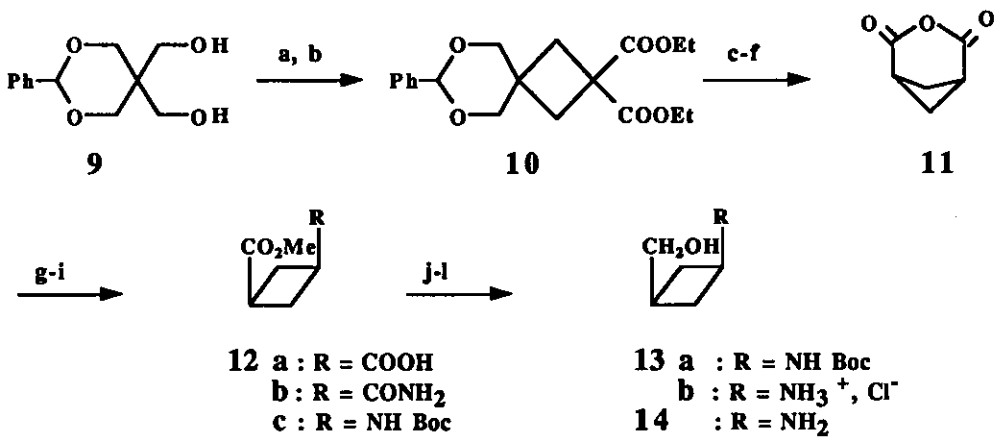


1 (Cyclobut-A): X=CH_2 **2** (Cyclobut-G): X=CH_2 **5**: Y = N **6**: Y = N
3 (Oxetanocin A): X=O **4** (Oxetanocin G): X=O **7**: Y = CH **8**: Y = CH

Therefore the analogues (**7**) and (**8**) seemed of interest, since in addition potent activity of some 7-deaza-guanosine-5'-triphosphate against the HIV reverse transcriptase has been reported.[3]

The synthesis of the disubstituted cyclobutane moieties of carbocyclic analogues of oxetanocin A and oxetanocin G was already reported. [2,4] Starting materials were either a protected 3-hydroxymethyl-cyclobutane-1-yl-methanesulfonate[4] or the mixture of stereoisomers of 3-hydroxymethylaminocyclobutanes.[2] In the later case, the *cis* and *trans* isomers of 6-chloro-9-[3-(hydroxymethyl)cyclobutyl]purine, obtained in several steps, were separated only after tritylation, with some difficulties.[2] Therefore we attempted to prepare specifically the *cis*-aminoalcohol (**14**) , considered as a useful starting material for the stereospecific preparation of **7**, **8** and related compounds.

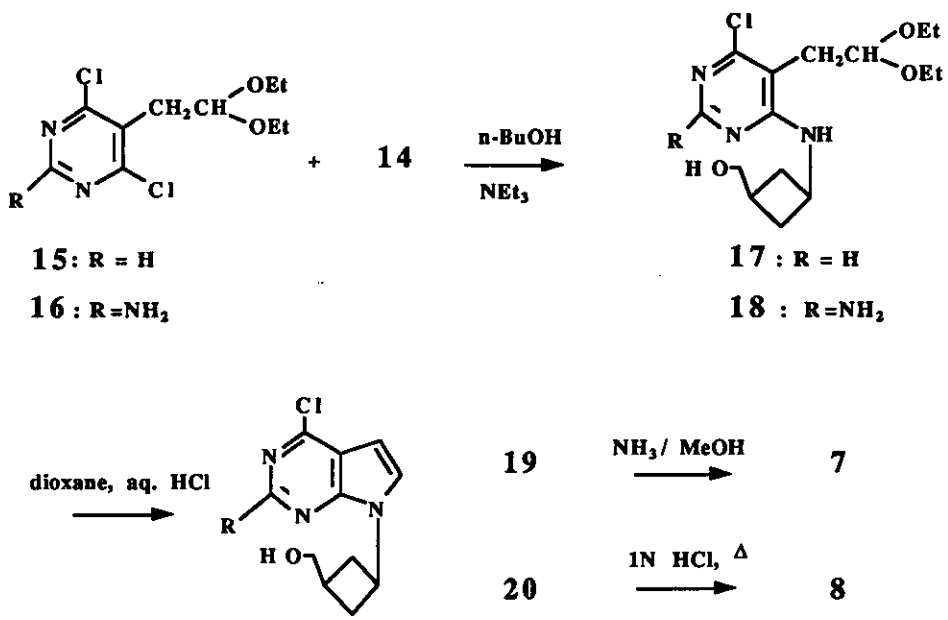
The anhydride (**11**) was obtained from pentaerythritol in 29.1 % yield (instead of 11.4 %) by using several modifications of the conditions described in reference 5. Starting from this anhydride (**11**), the six step sequence summarized in Scheme 1, led specifically to the expected *cis*-amino alcohol (**14**) in 59.6% yield.



a) 2 TsCl, Pyr; b) $CH_2(COOEt)_2$, NaH, DMF, KI; c) KOH; d) HNO_3; e) 185°C;
f) CH_3COCl; g) MeOH, Et_3N; h) ClCOOEt, Et_3N then NH_3; i) $Pb(OAc)_4$, tBuOH, Δ ;
j) $Ca(BH_4)_2$; k) HCl-MeOH; l) Dowex 50 W-X4

Scheme 1

Condensation of the pyrimidines (**15**)[6] and (**16**)[7] with amine (**14**) was performed in n-butan-1-ol at 100°C for 24 h under an inert atmosphere. Hydrolysis and cyclization of resulting **17** and **18** proceeded smoothly on treatment with 0.2N HCl in aqueous dioxane solution. Whereas chlorine aminolysis in **19** was carried out at 110°C under pressure, in methanol saturated with ammonia and led to **7**, 7-deazaguanine derivative (**8**) was obtained by hydrolysis of the chlorine atom of **20** in boiling hydrochloric acid.(Scheme 2)



Scheme 2

Compounds (**19, 20, 7** and **8**) have been tested[8] in vitro in CEM cells against human immunodeficiency virus type-1 (HIV-1) and were found inactive.

EXPERIMENTAL

Ethyl 2-phenyl-1,3-dioxaspiro[3.5]nonane-6,6-dicarboxylate **10**. A solution of **9**[9] (190 g, 0.848 mol) in pyridine (550 ml) was cooled by an ice-water bath and tosyl chloride (404 g, 2.12 mol) was added gradually to this solution with stirring . The reaction mixture was then allowed to reach room temperature. Stirring became impossible after ca. 1 h but reaction was allowed to proceed without stirring for 10 h. Afterwards ice (450 g) and 10 % aqueous HCl (400 ml) were added. The resulting mixture was stirred, the solid was separated by vacuum filtration, washed with a small amount of 10 % aqueous HCl and with iced water to provide 2-phenyl-5,5-ditosyloxymethyl-1,3-dioxacyclohexane. Yield after recrystallization (acetone) : 365 g, 81 %. mp 170-172°C. ^{1}H-Nmr (90 MHz, $CDCl_3$ + acetone-d_6) δ : 7.80-8.05 (m, 13H, H arom.) ; 5.43 (s, 1H, H-2); 4.43 (s, 2H, CH_2) ; 3.94 (m, 6H, $3CH_2$) ; 2.44 and 2.47 (2s, 6H, $2CH_3$). Anal. Calcd for $C_{26}H_{28}O_8S_2$: C, 58.63 ; H, 5.30 ; S, 12.04. Found : C, 58.90 ; H, 5.33 ; S, 12.21.

Diethyl malonate (91 g, 0.57 mol) was added dropwise at 70°C, under argon, to a stirred suspension of oil free NaH (13.44 g, 0.56 mol ; obtained from 22.4 g of 60 % mineral oil dispersion) in DMF (560 ml). After 30 min at 70°C, the reaction mixture was heated to 140°C and 2-phenyl-5,5-ditosyloxymethyl-1,3-dioxacyclohexane (151 g, 0.28 mol) and KI (4.6 g, 0.028 mol) were added quickly. After 12 h at this temperature, the mixture was cooled to room temperature and saturated NH_4Cl aqueous solution (500 ml) was added dropwise with stirring.

Extraction (4 x 400 ml of hexane then 2 x 250 ml of ether), washing (2 x 100 ml of water), drying ($MgSO_4$), evaporation and distillation (condenser at 70°C) led to **10** as a solid. Yield : 90.5 g, 93 %. bp 181-195°C, mp 64-65°C. ^{1}H Nmr (90 MHz, $CDCl_3$) δ : 7.44 (m, 5H, H arom.) ; 5.43 (s, 1H, H-7) ; 4.07-4.44 (m, 6H, $3CH_2$-O) ; 3.79 (m, 2H, 1 CH_2-O) ; 2.23 and 2.79 (2s, 2 x 2H, $2CH_2$ cyclobut.) ; 1.27 (t, J= 8.1 Hz, 3H, CH_3). Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50 ; H, 6.94. Found : C, 65.74 ; H, 6.76.

cis-1,3-Cyclobutanedicarboxylic anhydride **11**[5]. This preparation was run according to ref 5 by saponification of diester (**10**) (80 g, 0.23 mol) (yield of this saponification : 92 %), further hydrolysis of the acetal group, total oxidation into tetraacid, decarboxylation into *cis*- and *trans*-1,3-cyclobutanedicarboxylic acids and reaction with acetyl chloride to convert the *cis* isomer into the anhydride (**11**) which was isolated by distillation. The following improvements in the oxidation and decarboxylation steps led to higher yields and more reproducible results. At the end of the oxidation, water and nitric acid were removed under reduced pressure (20 Torr) until a few ml of liquid phase only remained. Water (50 ml) and NaCl (up to saturation) were then added. Continuous liquid-liquid extraction by ether (12 h), drying of this ether solution ($MgSO_4$), partial evaporation and crystallization by addition of cyclohexane led to 1,1,3,3-cyclobutanetetracarboxylic acid. Yield from the saponification product 94 % instead of 88,5 % (ref 5). Tetraacid was decarboxylated by heating (185°C) under reduced pressure (from 60 to 20 Torr). When CO_2 formation ceased (20 Torr) heating was stopped. A mixture of *cis*- and *trans*-diacids was thus obtained and it was used without further purification for preparation of anhydride (**11**). Yield from tetraacid 58 % instead of 43 % (ref 5).

cis-1,3-Cyclobutanedicarboxylic acid monomethyl ester **12a**. Dry MeOH (56 ml) and Et_3N (2.8 g, 36.4 mmol) were added at 0°C under nitrogen, with stirring to anhydride (**11**) (3.53 g, 28 mmol) in dry THF (56 ml). Reaction was allowed to proceed for 10 h at room temperature. Evaporation, addition of water (100 ml), acidification of aqueous phase to pH 3.3 with citric acid, extraction by ether (5 x 50 ml), drying of organic phases ($MgSO_4$) and evaporation led to crude **12a**[5] as an oil. Yield : 4.02 g, 91 %. ^{1}H-Nmr (90 MHz, $CDCl_3$) δ : 8.72 (br s, 1H, COOH) ; 3.73 (s, 3H, CH_3) ; 3.10 (m, 2H, 2CH) ; 2.34-2.75 (m, 4H, $2CH_2$).

cis-Methyl 3-carboxamidocyclobutanecarboxylate **12b**. Et_3N (2.6 ml) was added under nitrogen to a solution of acid ester (**12a**) (2.5 g, 15.8 mmol) in dry CH_2Cl_2 (150 ml) at 0°C, with stirring. ClCOOEt (1.8 ml, 18.7 mmol) was then added dropwise. After 30 min at 0°C, saturated solution of NH_3 in dry CH_2Cl_2 (130 ml) was added in 20 min. The reaction mixture was stirred for 1 h at 0°C and 2-3 h at room temperature (until decoloration). Filtration and removing of solvents from filtrate by evaporation led to the crude amide (**12b**) as a solid which was purified by addition of Et_2O (100 ml), stirring and filtration. Filtrate was purified by the same work up but using only 15 ml of Et_2O. The total amount of pure **12b** thus obtained was dried under reduced pressure. Yield : 2.38 g, 96 %. mp 105-107°C. ^{1}H-Nmr (90 MHz, $CDCl_3$) δ : 5.70-6.40 (br s, 2H, NH_2) ; 3.73 (s, 3H, CH_3) ; 2.80-3.23 (m, 2H, 2CH) ; 2.31-2.67 (m, 4H, $2CH_2$). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.40 ; H, 7.05 ; N, 8.90. Found : C, 53.12 ; H, 7.15 ; N, 9.12.

cis-Methyl 3-[(t-butoxycarbonyl)amino]cyclobutanecarboxylate **12c**. $Pb(OAc)_4$ (27 g, 61 mmol) was quickly added to a stirred mixture of amidoester (**12b**) (1.88 g, 11.98 mmol), tBuOH (70 ml) and DMF (35 ml) at 40°C. The reaction mixture was then heated at reflux for 20 min. Cooling, evaporation and filtration of the crude product through a column of silicagel (20 g ; eluant : 300 ml of Et_2O) led to a solution which was washed

successively with 10 % aqueous solution of NaOH (2 x 40 ml) and water (10 ml). Drying ($MgSO_4$) and evaporation led to **12c** which was used in the following step without further purification. Yield : 2.68 g, 98 %. ^{1}H-Nmr (90 MHz, $CDCl_3$) δ : 4.59-5.01 (br s, 1H, NH) ; 3.68 (s, 3H, CH_3) ; 1.86-3.08 (m, 6H, cyclobut-H) ; 1.42 (s, 9H, tBu).

cis-3-Hydroxymethyl-1-[(t-butoxycarbonyl)aminolcyclobutane **13a** and the corresponding hydrochloride **13b**. Dry $CaCl_2$ (0.43 g, 3.9 mmol) was added under nitrogen to a stirred solution of **12c** (0.35 g, 1.53 mmol) in absolute ethanol (15 ml). $NaBH_4$ (0.22 g, 5.8 mmol) was then added gradually. Reaction mixture was allowed to proceed for 12 h at room temperature and solvent was evaporated. Water (50 ml) was added. Extraction by CH_2Cl_2 (4 x 60 ml), drying ($MgSO_4$) and evaporation led to crude **13a** as an oil which crystallized on standing. Yield : 0.294 g, 96 %. mp 80-81°C. ^{1}H-Nmr (90 MHz, $CDCl_3$) δ : 4.69-5.16 (br s, 1H, NH) ; 3.61 (d, J = 6 Hz, 2H, CH_2OH) ; 1.86-2.89 (m, 6H, cyclobut. H) ; 1.45 (s, 9H, tBu). Stirring of **13a** (3.5 g, 17.32 mmol) with methanolic HCl (2M solution, 400 ml) for 4 h at room temperature followed by evaporation led to the crude hydrochloride (**13b**) as an oil. Yield : 2.15 g, 100 %.

cis-3-Amino-1-cyclobutanemethanol (**14**). A solution of **13b** (470 mg, 3.41 mmol) in ethanol (5 ml) was passed slowly through a column (30 x 2 cm) of Dowex 50W-X4 cation exchange resin (H^+ form) prepared in ethanol. The column was washed thoroughly with ethanol and the free amine was then eluted with a 2N solution of ammonium hydroxide prepared in ethanol-water (8 : 2). Evaporation of the solvents gave **14** as a pale yellow syrup which was dried *in vacuo* over pellets of potassium hydroxide for several days. Yield : 250 mg, 72.5 %.^{1}H-Nmr (200 MHz, DMSO-d_6) δ 3.32 (d, J = 6.05 Hz, 2H, CH_2OH) ; 3.08 (m, 1H, H-3) ; 2.44-2.88 (br. HDO, NH_2, OH) ; 2.18 (m, 2H, H-2, H-4) ; 1.83 (m, 1H, H-1) ; 1.33 (m, 2H, H-2, H-4).

cis-3-[[4-Chloro-5-(2,2-diethoxyethyl) pyrimidin-6-yl]aminolcyclobutanemethanol (**17**). A solution of **15**[6] (530 mg, 2 mmol), amine (**14**) (202 mg, 2 mmol), triethylamine (3 ml) in 1-butanol (30 ml) was heated under argon at 100°C for 24 h. The mixture was then cooled and evaporated to dryness. The residue was coevaporated several times with heptane before it was redissolved in chloroform (200 ml). This organic phase was washed with water (3 x 20 ml), dried ($MgSO_4$), filtered, and evaporated to dryness to give an oily residue which was subjected to silica gel column chromatography (40 x 2.5 cm) prepared in dichloromethane. The column was first washed with dichloromethane (500 ml) to eliminate the unreacted pyrimidine and some impurities and eluted then with 5 % ethanol in dichloromethane to provide a slightly colored oil which was dried *in vacuo* over potassium hydroxide. Yield 515 mg, 78 %. ^{1}H-Nmr (DMSO-d_6) δ : 8.19 (s, 1H, H-2) ; 7.07 (d, J = 7.1 Hz, 2H, NH) ; 4.65 (t, J = 5.2 Hz, 1H, CH-ethyl) ; 4.53 (t, J = 5.2 Hz, 1H, OH) ; 4.38 (m, 1H, H-3') ; 3.64 (m, 2H, CH_2-ethoxy) ; 3.49 (m, 2H, CH_2-ethoxy) ; 3.40 (m, 2H, CH_2OH) ; 2.95 (d, J = 5.3 Hz, 2H, CH_2-CH) ; 2.34 (m, 2H, H-2', H-4') ; 2.12 (m, 1H, H-1') ; 1.79 (m, 2H, H-2', H-4') ; 1.1 (t, J = 6.9 Hz, 6H, 2 x CH_3). Anal. Calcd for $C_{15}H_{24}N_3O_3Cl$: C, 54.62 ; H, 7.33 ; N, 12.74 ; Cl, 10.75. Found : C, 54.77 ; H, 7.45 ; N, 12.60 ; Cl, 10.59.

cis-3-[4-Chloro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl]cyclobutanemethanol (**19**). A solution of **17** (450 mg, 1.78 mmol) in dioxane (50 ml) and 1N HCl (10 ml) was stirred at room temperature for 48 h. Concentrated ammonium hydroxide was then added in excess to the mixture which was evaporated to dryness. The residue was dissolved in AcOEt (100 ml) and washed twice with water (10 ml portions). The organic phase was dried

($MgSO_4$), filtered and evaporated to dryness. Purification was carried out by column chromatography (silica gel) eluting with dichloromethane-ethanol (98 : 2). Yield : 275 mg, 84 %. An analytical sample was obtained by crystallization from cyclohexane. mp 102°C. ^{1}H-Nmr (DMSO-d_6) δ : 8.62 (s, 1H, H-2) ; 7.96 (d, J = 3.7 Hz, 1H, H-6) ; 6.69 (d, J = 3.7 Hz, 1H, H-5) ; 5.14 (m, 1H, H-3') ; 4.65 (t, J = 5.3 Hz, 1H, OH) ; .3.49 (t, J = 4.7 Hz, 2H, CH_2OH) ; 2.60-2.21 (m, 5H, 2 x CH_2, H-1'). Anal. Calcd for $C_{11}H_{12}N_3OCl$: C, 55.59 ; H 5,09 ; N, 17.68. Found : C, 55.66 ; H, 4.85 ; N, 18.01.

cis-3-[4-Amino-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl]cyclobutanemethanol (**7**). A solution of **19** (100 mg, 0.42 mmol) in methanol-ammonia (1-1, 100 ml) was heated at 110°C in a stainless steel vessel for 2 days. The mixture was evaporated to dryness and subjected to column chromatography on neutral alumina (Brockmann No IV grade) eluting with dichloromethane-ethanol 9 : 1. The pure fractions were combined and evaporated to a colorless oil. Yield 76 %. ^{1}H-Nmr (DMSO-d_6) δ : 8.07 (s, 1H, H-2) ; 7.36 (d, J = 3.3 Hz, 1H, H-5) ; 6.97 (s, 2H, NH_2) ; 6.58 (d, J = 3.3 Hz, 1H, H-6) ; 5.05 (m, 1H, H-3) ; 3.50 (d, J = 4.7 Hz, 2H, CH_2OH) ; 2.6-2.2 (m, 5H, 2 x CH_2, H-1'). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.53 ; H, 6.47 ; N, 25.67. Found : C, 60.18 ; H, 6.34 ; N, 25.38.

cis-3-[[2-Amino-4-chloro-5-(2,2-diethoxyethyl)pyrimidin-6-yl]amino]cyclobutanemethanol (**18**). This compound was prepared in the same manner as **17** as an oil after column chromatography. Yield 74 %. A slight contamination by the cyclized compound (**20**) was observed (nmr) in this experiment. Therefore it was engaged directly in the next step of cyclization. ^{1}H-Nmr (DMSO-d_6) δ : 6.48 (d, J = 7.6 Hz, 1H, NH) ; 6.27 (s, 2H, NH_2) ; 4.52 (m, 2H, OH, CH-ethyl) ; 4.42 (m, 1H, H-3') ; 3.66 (m, 2H, CH_2-ethoxy) ; 3.45 (m, 2H, CH_2-ethoxy) ; 2.75 (d, J = 5.2 Hz, 2H, CH_2-ethyl) ; 2.31 (m, 2H, H-2', H-4') ; 2.05 (m, 1H, H-3') ; 1.71 (m, 2H, H-2', H-4') ; 1.13 (t, J = 7 Hz, 6H, 2 x CH_3).

cis-4-[2-Amino-4-chloro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl]cyclobutanemethanol (**20**).The pyrrolo [2,3-d]-pyrimidine (**20**) was obtained as described for the preparation of **19** except that column chromatography was not necessary since **20** crystallized from toluene. Yield 85 %, mp 156°C. ^{1}H-Nmr (DMSO-d_6) δ : 7.41 (d, J = 3.7 Hz, 1H, H-5) ; 6.62 (s, 2H, NH_2) ; 6.36 (d, J = 3.7 Hz, 1H, H-6) ; 4.93 (m, 1H, H-3') ; 4.68 (t, J = 5.3 Hz, 1H, OH) ; 3.50 (m, 2H, CH_2OH) ; 2.46-2.08 (m, 5H, 2 x CH_2, H-1'). Anal. Calcd for $C_{11}H_{13}N_4OCl$: C, 52.28 ; H, 5.19 ; N, 22.17. Found : C, 52.51 ; H, 4.88 ; N, 21.86.

2-Amino-3,4-dihydro-7-[*cis*-3-(hydroxymethyl)-cyclobut-1-yl]-7*H*-pyrrolo[2,3-d]pyrimidin-4-one (**8**). A solution of **20** (200 mg, 0.86 mmol) in 1N HCl (30 ml) was stirred under reflux for 8 h. The mixture was evaporated to dryness and the residue was dissolved in hot water (1-2 ml). This solution was neutralized with a few drops of 6N NaOH and cooled. The precipitate was collected by filtration and washed with cold water. The solid was adsorbed on neutral alumina (Brockmann No IV type) and chromatographed on a column filled with the same alumina (Aldrich). Elution with dichloromethane-ethanol 1 : 1 containing 5 % (in volume) of concentrated ammonium hydroxide afforded pure **8** as an amorphous solid after evaporation and drying. Yield 38 %. mp > 260°C. ^{1}H-Nmr (DMSO-d_6) δ : 10.28 (s, 1H, NH) ; 6.95 (d, J = 3.5 Hz, 1H, H-5) ; 6.28 (d, J = 3.5 Hz, 1H, H-6) ; 6.19 (s, 2H, NH_2) ; 4.82 (m, 1H, H-1') ; 6.43 (t, J = 5.4 Hz, 1H, OH) ; 3.48 (t, J = 4.8 Hz, 2H, CH_2OH) ; 2.55-2.10 (m, 5H, 2 x CH_2, H-3'). Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40 ; H, 6.02 ; N, 23.92. Found : C, 56.25 ; H, 5.70 ; N, 23.58.

ACKNOWLEDGMENTS

The authors are indebted to Marc Lemaitre and Yvette Henin, RPR, Recherche-Developpement, 94403 Vitry sur Seine Cedex, France for performing antiviral testing. We thank the Association pour la Recherche sur le Cancer and the Agence Nationale de Recherches sur le SIDA for financial support.

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Received, 16th December, 1991