SYNTHESIS OF RING-ENLARGED CYCLOBUT-A AND CYCLOBUT-G ANALOGUES AS HIV INHIBITORS. PART 4[1]

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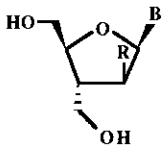
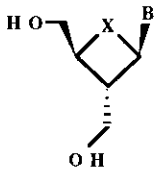
Abstract ----- Two ring-expanded analogues (compounds **13** and **14**) of the anti-HIV agents Cyclobut-A and Cyclobut-G are described. They were synthesized from *trans*-3,4-bis-(hydroxymethyl)cyclobutylamine which was obtained from *threo*-3,4-bis(methoxycarbonyl)-hexane dioic acid. Neither compound (**13**, **14**) was able to provide protection to CEM cells against HIV-1 infection.

Various examples of nucleoside analogues branched with a hydroxymethyl group in the position 1',[2] 2',[3] 3'[4-6] or 4'[7,8] of their sugar portion are already known. Some of them have shown interesting antiviral activities. Thus among the 3'-branched nucleoside analogues (**1-8**), uracil derivative (**4**) has been shown to inhibit varicella zoster virus (VZV)[5] while a profile of antiviral activity against human immunodeficiency virus (HIV) similar to that of oxetanocin A (**9**) has been described for the adenine derivative **8**.[3] In addition, oxetanocin G (**10**) has been found to be a potent and selective inhibitor of the replication of human cytomegalovirus (HCMV)[9] whereas cyclobut-A (**11**) and cyclobut-G (**12**) have been identified as broad spectrum antiviral agents.[10] Particularly noticeable is the activity of cyclobut-G which appeared to be comparable to that of AZT against HIV in ATH8 cells *in vitro*.[10] All these data prompted us to synthesize the related compounds (**13**) and (**14**) which are ring-expanded analogues of **11** and **12**.





1 : B = Uracil ; R = OH

2 : B = Thymine ; R = OH

3 : B = 5-Iodouracil ; R = OH

4 : B = (E)-5-(2-Bromovinyl)uracil ; R = OH

5 : B = Uracil ; R = H

6 : B = 5-Iodouracil ; R = H

7 : B = Thioguanine ; R = H

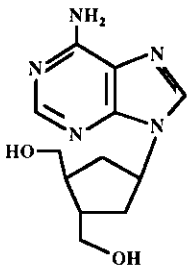
8 : B = Adenine ; R = H

9 (Oxetanocin A) : B = Adenine ; X = O

10 (Oxetanocin G) : B = Guanine ; X = O

11 (Cyclobut- A) : B = Adenine ; X = CH_2

12 (Cyclobut- G) : B = Guanine ; X = CH_2



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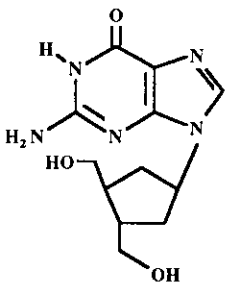
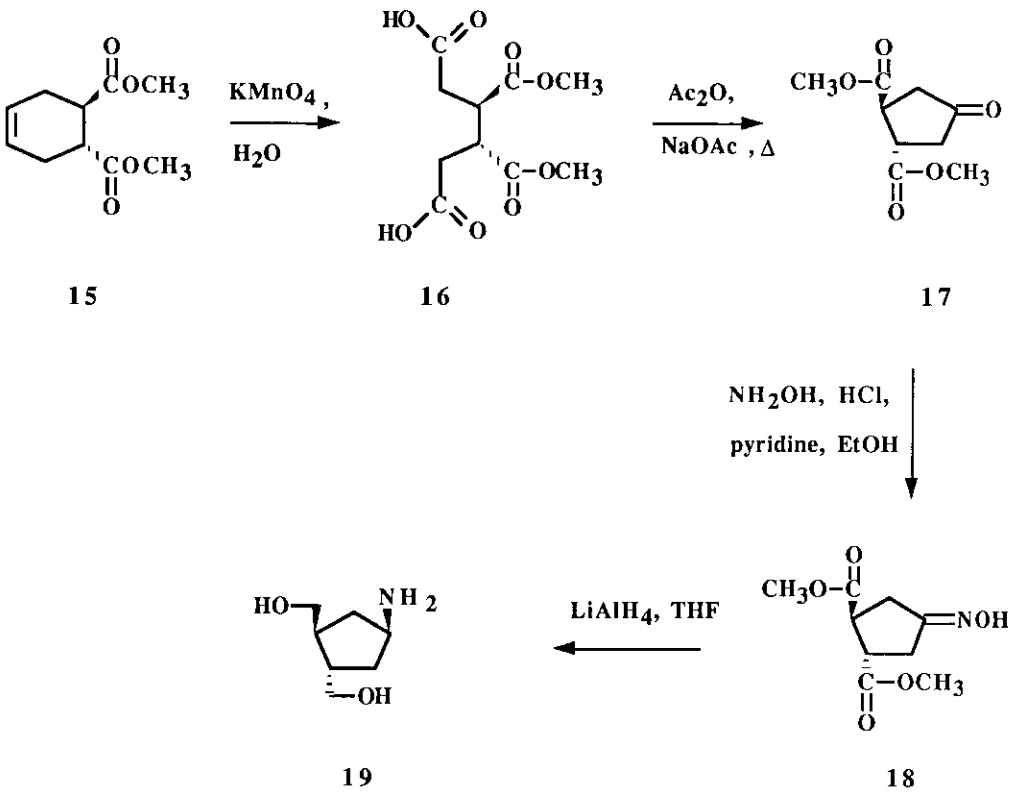


14

The *trans*-3,4-dimethoxycarbonylcyclopentanone (**17**) was already prepared by isomerization of the mixture of cis and trans isomers obtained by Dolby's method.[11] It was used as an intermediate in the synthesis of prostaglandins[12,13] but only the (-)diester obtained as the degradation product of brefeldin A was characterized by Sigg in 1964.[14]

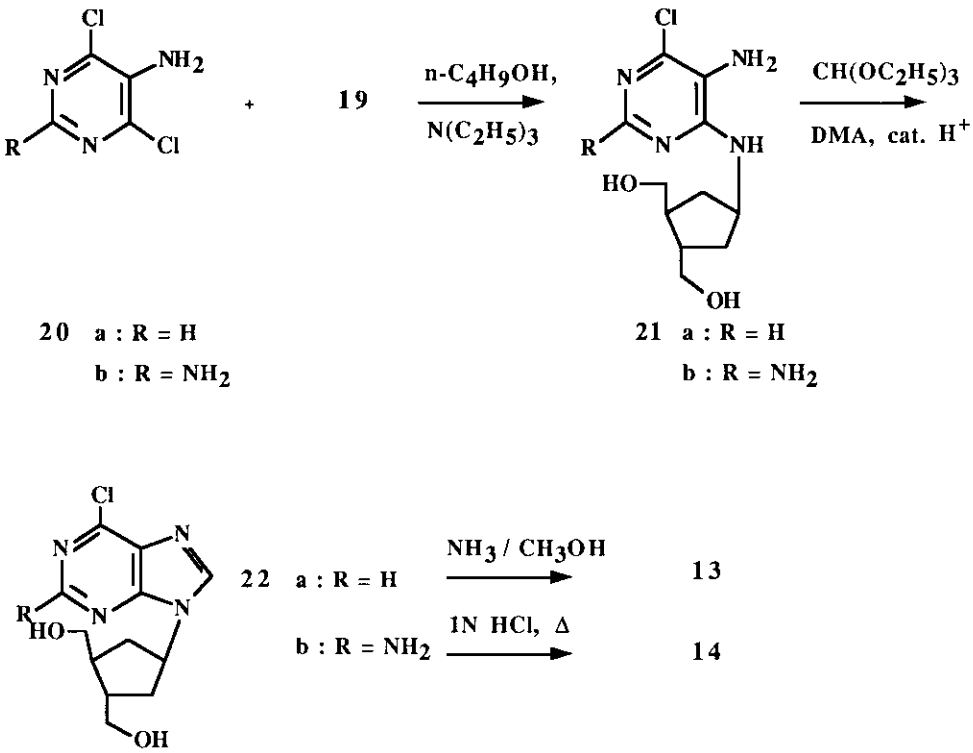
As we needed this intermediate on a large scale we started with the *trans*-cyclohexene diester (**15**) readily available in one step from butadiene and dimethyl fumarate.[15] Oxidative cleavage of the double bond in **15** with potassium permanganate in water gave a 75 % yield of *threo* -diacid (**16**). Decarboxylative cyclization of **16** in acetic anhydride with sodium acetate led to **17** in 72 % yield. The corresponding oxime was obtained in mild conditions. Complete reduction of oxime and diester functions in **18** was then achieved in one pot by lithium aluminum hydride ($LiAlH_4$) giving the (±) *trans*-3,4-bis(hydroxymethyl) cyclopentylamine (**19**) (Scheme 1).

Scheme 1



Adenine and guanine precursors (**22a**) and (**22b**) were then elaborated from **20a**[16] and **20b**[17] respectively by a known two step sequence[18] (Scheme 2). The oxidizable triaminopyrimidine (**21b**) was obtained in one step from the requisite 2,5-diamino-4,6-dichloropyrimidine (**20b**) itself obtained by chlorination of 2,5-diamino-4,6-dihydroxypyrimidine.[17] Cyclization of the key intermediates (**21a**) and (**21b**) with triethyl orthoformate in the presence of a catalytic amount of concentrated hydrochloric acid provided the 6-chloropurine derivatives (**22a**) and (**22b**). Whereas the 6-chloro atom in **22a** was displaced with ammonia to provide **13** it was hydrolyzed in **22b** by refluxing in dilute hydrochloric acid to give **14**.

Scheme 2



Compounds (**13**) and (**14**) have been tested *in vitro*[19] in CEM cells against human immunodeficiency virus type I (HIV-1) . They were found inactive.

EXPERIMENTAL

All melting points are uncorrected. The elemental analyses were performed at the ICSN, CNRS 91198 Gif sur Yvette. Preparative low pressure liquid chromatographies (10-20 bars) were carried out in glass columns packed with silica gel (230-400 mesh, Merck). ^{1}H-Nmr spectra were recorded on a Bruker AC 200 spectrometer (200 MHz). Mass spectrum (ms) of **19** was obtained with a Ribermag spectrometer, ICMO Université de Paris XI, 91405 Orsay.

threo-3,4-Bis(methoxycarbonyl)hexanedioic acid (**16**). To a well-stirred solution of $KMnO_4$ (25 g, 0.158 mol) in water (400 ml) was slowly added at 0°C, cyclohexene (**15**) (10 g, 0.05 mol). An ice-NaCl cooling bath was used to maintain the temperature below 5°C. After being stirred for 3-4 h at room temperature, water (200 ml) was added and the pH was adjusted to 10 with 10% aqueous NaOH. The solid was filtered over celite and washed with water. The filtrate was acidified to pH 2 by the addition of concentrated HCl and extracted with four portions (1 l) of ether. The combined extracts were dried with $MgSO_4$ and concentrated in a rotary evaporator. The solid

residue was recrystallized from EtOAc/n-hexane (dissolution in hot EtOAc and addition of n-hexane until a turbidity appeared) to give **16** (9.9 g, 75 %) as colorless crystals. mp 171°C . ^{1}H-Nmr ($CDCl_3$) δ 2.64 (m, 2H, CH_2), 2.96 (m, 2H, CH_2), 3.74 (s, 6H, 2 x CH_3), 4.35 (br s, 2H, 2 x COOH), 4.84 (m, 2H, 2 x CH). Anal. Calcd for $C_{10}H_{14}O_8$: C, 45.80 ; H, 5.34. Found : C, 45.76 ; H, 5.32.

(±)-*trans*-4-Oxo-1,2-cyclopentanedicarboxylic acid bis(methyl ester) (**17**). A well stirred suspension of dicarboxylic acid (**16**) (10 g, 38.1 mmol) and anhydrous NaOAc (2.7 g, 32.9 mmol) in acetic anhydride (50 ml) was heated under reflux for 1.5 h. The reaction mixture was then cooled and stored for 4 h at 5°C. Precipitated NaOAc was filtered off and acetic anhydride was removed under reduced pressure (oil pump). The oily residue was distilled (118°C, 0.02 mm Hg). The semi-crystalline material thus obtained was recrystallized from ether to give 5.5 g of **17** (72 %). mp 62°C. ^{1}H-Nmr ($CDCl_3$) δ 2.46-2.54 (m, 2H, H-3, H-5), 2.62-2.69 (m, 2H, H-3, H-5), 3.35-3.42 (m, 2H, H-1, H-2), 3.74 (s, 6H, 2 x CH_3). Anal. Calcd for $C_9H_{12}O_5$: C, 54.00 ; H, 6.00. Found : C, 54.05 ; H, 5.97.

(±)-*trans*-4-Hydroxyimino-1,2-cyclopentanedicarboxylic acid bis(methyl ester) **18**. A mixture of 17 (5 g, 25 mmol) and hydroxylamine hydrochloride (17.5 g, 251 mmol) in pyridine and ethanol (1 : 1, 100 ml) was stirred for 15 min at room temperature. The mixture was then partitioned between brine (300 ml) and AcOEt (300 ml). The aqueous phase was extracted three times with AcOEt (100 ml). The combined organic phases were washed with 1N HCl, dried ($MgSO_4$) and evaporated to dryness to give an oily residue which crystallized on standing. Recrystallization from ether gave **18** (4.21 g, 78 %) ; mp 85°C. ^{1}H-Nmr ($CDCl_3$) δ 2.62-3.00 (m, 4H, H-3, H-5), 3.20-3.30 (m, 2H, H-1, H-2), 3.74 (s, 6H, 2 x CH_3). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23 ; H, 6.04 ; N, 6.51. Found : C, 50.19 ; H, 6.23 ; N, 6.41.

(±)- (1β,3α,4β)-3,4-Bis(hydroxymethyl)-1-cyclobutylamine **19**. A solution of **18** (2.29 g, 10.6 mmol) in THF (30 ml) was added dropwise to a well stirred suspension of lithium aluminum hydride (1.011 g, 26.5 mmol) in THF (50 ml). The mixture was stirred for 2 h at 0°C, overnight at room temperature, refluxed for 4 h, cooled and treated with 15 % NaOH (2 ml). The mixture was diluted with THF (100 ml), filtered and dried ($MgSO_4$) to give a syrup (1.15 g). Amine (**19**) was passed slowly through a column of Dowex 50W-X4 cation exchange resin (H^+ form) in methanol. The column was washed with methanol-water (9 : 1, 1000 ml) and eluted with 2N NH_4OH in methanol to afford 617 mg of **19** as a yellowish oil; yield 40 %. ^{1}H-Nmr (DMSO-d_6) δ 1.40-2.10 (m, 6H, 2 x CH_2, H-3, H-4), 3.20-3.52 (m, 9H, 2 x CH_2OH, 2 x OH, H-1, NH_2). Cims (NH_3) m/z : 146 (MH^+, 100 %).

(±)-5-Amino-4-chloro-6-[[(1β,3α,4β)-3,4-bis(hydroxymethyl)cyclopentan-1-yl]amino]pyrimidine **21a**. A solution of **20a** (677 mg, 4.13 mmol), **19** (0.5 g, 3.4 mmol), triethylamine (5 ml, 35 mmol) in n-butan-1-ol (40 ml) was stirred at 100°C for 2 days under argon. The mixture was cooled, evaporated to dryness and adsorbed on silica gel before column chromatography. Elution with dichloromethane-ethanol (95 : 5) afforded **21a** (contaminated with triethylamine) which crystallized from ethyl acetate-methanol (98 : 2), yield 539 mg (48 %); mp 172°C. ^{1}H-Nmr (DMSO-d_6) δ 1.50-2.45 (m, 6H, 2 x CH_2, H-3, H-4), 3.42 (m, 4H, 2 x CH_2OH), 4.32 (m, 1H, H-1'), 4.73 (m, 2H, 2 x OH), 5.10 (br s, 2H, NH_2), 6.71 (unresolved d, 1H, NH), 7.74 (s, 1H, H-2).

(±)-6-Chloro-9-[(1β,3α,4β)-3,4-bis(hydroxymethyl)cyclopentan-1-yl]-*9H*-purine **22a**. To a solution of **21a** (250 mg, 0.91 mmol) in freshly distilled N,N-dimethylacetamide (10 ml) and freshly distilled triethyl orthoformate (10 ml, 60 mmol) was added at 0°C 0.5 ml of concentrated HCl. The reaction mixture was stirred for 24 h at room temperature and evaporated to dryness (oil pump). The oily residue was stirred at room temperature for 4 h in 50 % acetic acid (20 ml) and then concentrated *in vacuo*. The residue was evaporated several times in the presence of methanol. The resulting syrup in 20 ml of 28% ammonium hydroxide-methanol (10 : 90) was stirred at room temperature for 4 h and concentrated in vacuo. The residue was adsorbed on silica gel and chromatographed on a silica gel column eluting with dichloromethane-ethanol (95 : 5) to afford 88 mg (34 %) of **22a** as a solid ; mp 132-133°C (and 70 mg (29 %) of **13**). ^{1}H-Nmr of **22a** (DMSO-d_6) δ 2.00-2.50 (m, 6H, 2 x CH_2, H-3', H-4'), 3.37-3.53 (m, 4H, 2 x CH_2OH), 4.75 (m, 2H, 2 x CH_2OH), 5.00 (m, 1H, H-1'), 8.81 (s, 1H, H-8), 8.86 (s, 1H, H-2). Anal. Calcd for $C_{12}H_{15}N_4O_2Cl$: C, 50.97 ; H, 5.30 ; N, 19.82. Found : C, 50.92 ; H, 5.31 ; N, 19.58.

(±)-6-Amino-9-[(1β,3α,4β)-3,4-bis(hydroxymethyl)cyclopentan-1-yl]-*9H*-purine **13**. A solution of **22a** (100 mg, 0.35 mmol) in liquid ammonia (50 ml) was stirred at room temperature in a sealed vessel for 24 h. The vessel was chilled, opened and the ammonia was evaporated with a current of nitrogen. The residue was dissolved in methanol, adsorbed on silica gel and chromatographed on a silica gel column eluting with dichloromethane-ethanol (9 : 1) ; crystallization occurred in ethanol. yield 89 mg (95 %) ; mp 182-183°C. ^{1}H-Nmr (DMSO-d_6) δ 1.88-2.27 (m, 6H, 2 x CH_2, H-3', H-4') ; 3.34-3.47 (m, 4H, 2 x CH_2OH), 4.71 (br s, 2H, 2 x CH_2OH), 4.81 (m, 1H, H-1'), 7.20 (s, 2H, NH_2), 8.13 (s, 1H, H-8), 8.24 (s, 1H, H-2). Anal. Calcd for $C_{12}H_{17}N_5O_2$. 1/2H_2O: C, 52.94 ; H, 6.61 ; N, 25.73. Found : C, 53.21 ; H, 6.41 ; N, 25.83.

(±)-4-Chloro-2,5-diamino-6-[[(1β,3α,4β)-3,4-bis(hydroxymethyl)cyclopentan-1-yl]amino]pyrimidine **21b**. A solution of **19** (810 mg, 5.2 mmol), **20b** (1 g, 5.6 mmol), triethylamine (10 ml, 71.7 mmol) in n-butan-1-ol (70 ml) was stirred at 100°C under argon for 48 h. The reaction mixture was cooled, evaporated to dryness, adsorbed on silica gel and chromatographed on a silica gel column eluting with dichloromethane-ethanol (92 : 8). The crude syrup thus obtained (703 mg, 47 %) was used in the next step. ^{1}H-Nmr (DMSO-d_6) δ 1.66-1.97 (m, 2H, 2 x CH_2, H-3', H-4'), 4.22-4.29 (m, 4H, 2 x CH_2OH), 4.69 (m, 3H, H-1', 2 x CH_2OH), 5.60 (br s, 2H, NH_2), 6.40 (d, J = 7.1 Hz, 1H, NH), 10.13 (br s, 2H, NH_2).

(±)-2-Amino-6-chloro-9-[(1β,3α,4β)-3,4-bis(hydroxymethyl)cyclopentan-1-yl]-*9H*-purine **22b**. To a mixture of pyrimidine (**21b**) (500 mg, 0.17 mmol), freshly distilled N,N-dimethylacetamide (10 ml), and redistilled triethyl orthoformate (10 ml, 60 mmol) at 0-5°C was added 0.5 ml of 12N hydrochloric acid. The mixture was stirred at room temperature overnight, evaporated to dryness and coevaporated several times with water. The residue was stirred for 4 h in 50 % acetic acid, evaporated to dryness and coevaporated several time with methanol. The residue was stirred for 4 h in methanol-28% ammonium hydroxide (90 : 10), evaporated to dryness and adsorbed on silica gel. Elution with dichloromethane-ethanol (92 : 8) afforded 460 mg (90 %) of **22b** as colorless crystals from ethanol, mp 196°C. ^{1}H-Nmr (DMSO-d_6) δ 1.82-2.32 (m, 6H, 2 x CH_2, H-3', H-4'), 3.44 (m, 4H, 2 x

$C\underline{H_2}OH$), 4.74 (m, 3H, 2 x $CH_2O\underline{H}$, H-1'), 6.93 (s, 2H, NH_2), 8.31 (s, 1H, H-8). Anal. Calcd for $C_{12}H_{16}N_5O_2Cl$. 1/3 H_2O : C, 47.44 ; H, 5.46 ; N, 23.06. Found : C, 47.71 ; H, 5.51 ; N, 22.73.

(±)-2-Amino-9-[(1β,3α,4β)-3,4-bis(hydroxymethyl)cyclopentan-1-yl]-1,9-dihydro-6*H*-purin-6-one **14**. A solution of **22b** (200 mg, 0.67 mmol) in 1N hydrochloric acid (10 ml) was refluxed for 6 h with stirring. The mixture was evaporated to dryness, redissolved in water (3 ml) and neutralized with a few drops of 6N sodium hydroxide. A first crop of **14** precipitated and was washed with water (51 mg, 27.1 %). A second crop of **14** was obtained after column chromatography on silica gel (dichloromethanol-ethanol 90 : 10) and recrystallization from ethanol to yield 92 mg. Total yield 143 mg (76 %). mp 244°C. ^{1}H-Nmr (DMSO-d_6) δ 1.74-2.27 (m, 6H, 2 x CH_2, H-3', H-4'), 3.40-3.52 (m, 4H, 2 x $C\underline{H_2}OH$), 4.62 (m, 1H, H-1'), 4.71 (t, J = 5 Hz, 2H, 2 x $CH_2O\underline{H}$), 6.45 (br s, 2H, NH_2), 7.85 (s, 1H, H-8), 10.54 (s, 1H, NH). Anal. Calcd for $C_{12}H_{17}N_5O_3$. 1/3H_2O : C, 50.52 ; H, 6.19 ; N, 24.56. Found : C, 50.55 ; H, 5.87 ; N, 24.83.

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