A Method for the Synthesis of Racemic and Optically Active 2-Substituted 9-(2',3'-Dihydroxypropyl)-8-azahypoxanthines and 8-azaadenines [1]

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Several 9-(2',3'-*O*-isopropylidene)- and 9-(2',3'-dihydroxypropyl)-8-azahypoxanthines and 8-azaadenines were synthesized by a "one pot" method starting from the acetonide of racemic or (*S*)-1-azido-2,3-dihydroxypropane, obtained from D-mannitol. 9-(2',3'-Dihydroxypropyl)-8-azapurines were tested as adenosine deaminase inhibitors.

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During the last few years we have been interested in the chemical and biological properties of purine analogs. Special attention was devoted to devise general synthetic methods which would allow one to prepare a large series of derivatives of the same heterocycle. Therefore, we have identified the azapurine nucleus as the pharmacophoric heterocycle which can be readily synthesized with substituents whose structure could be changed to permit SAR studies. In this manner we have obtained 8-azahypoxanthines [2,4] and 8-azaadenines [3,4], bearing different substituents in the 2 and 9 positions, and we have studied their biological inhibitory activities against catabolic enzymes [5] and the binding affinity to adenosine A_1 and A_2 receptors [6].

Schaeffer and co-workers showed in 1967 the stereoselective formation of the Enzyme-Inhibitor complex in the interaction between adenosine deaminase and (*S*)-9-(2'-hydroxy-1'-propyl)adenine [7].

Subsequently these authors prepared some *erythro* 9-(2'-hydroxy-3'-alkyl)adenines [8] which were more potent inhibitors of adenosine deaminase than their corresponding *threo* diastereoisomers.

The steric requirement of adenosine deaminase regarding the substituent on N^9 as with other enzymes such as *S*-adenosyl-L-homocysteine hydrolase [9] have demonstrated the importance of a chiral group at this position, with a configuration favorable for assuring the greatest biological activity.

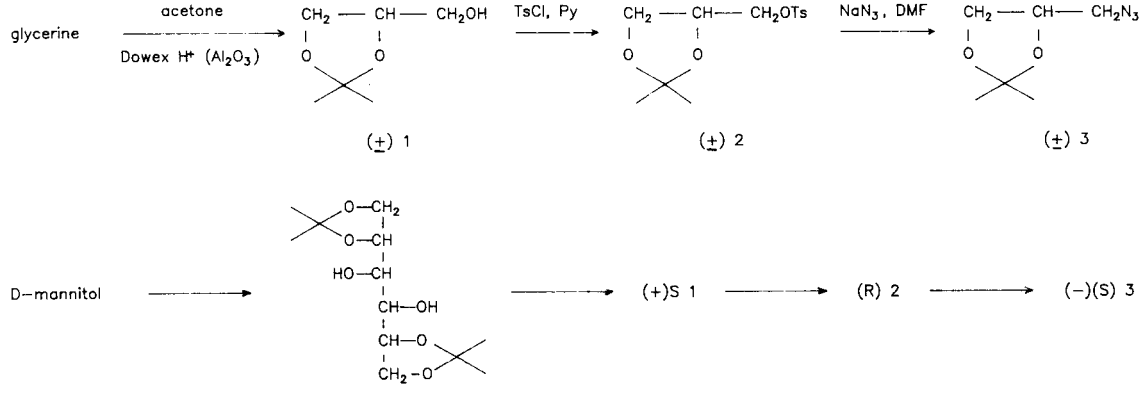
In the hope of obtaining an asymmetrical compound we sought to prepare an optically active azide with a short chain bearing the chiral carbon on C2 with respect to the azide group. The acetonide of racemic 1-azido-2,3-dihydroxypropane was employed to find the best reaction conditions which could be employed with the optically active products.

The racemic and optically active azides were prepared according to Scheme I.

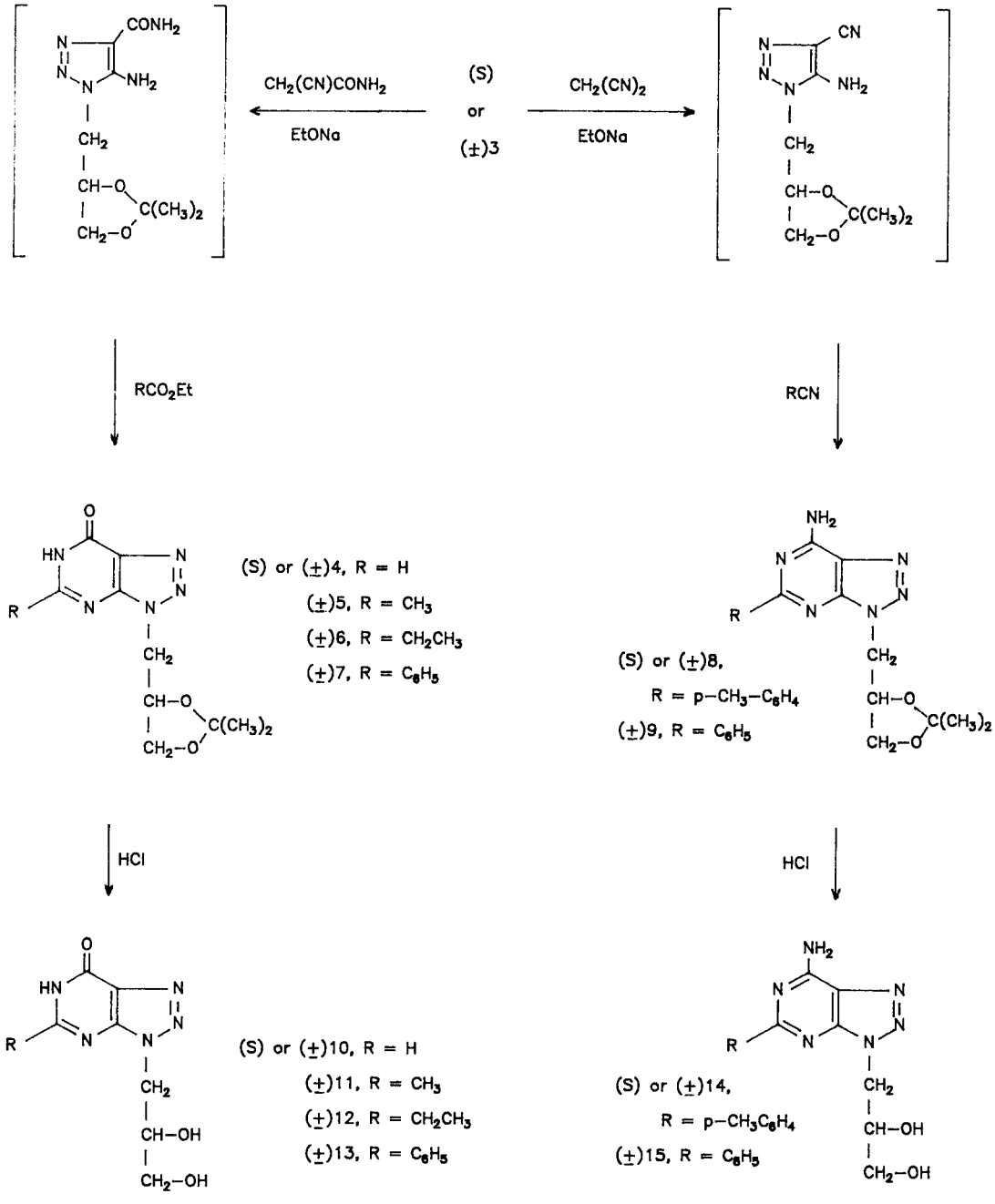
The racemic 4-hydroxymethyl-2,3-dimethyl-1,3-dioxolane was obtained from glycerol and acetone by employing aluminium oxide as a drying agent [10] and the azide *via* a nucleophilic substitution of the tosylate group.

The optically active azide was obtained as a chiral fragment from D-mannitol according to the classical method based on the preparation of the 1,2:5,6-di-*O*-isopropyli-

Scheme I



Scheme II



dene-D-mannitol [11]. The preparation of the 1,2:5,6-di-*O*-isopropylidene-D-mannitol had been tried by several scientists but a systematic study in this matter was accomplished by J. Kuszmann *et al.* [12].

Further, the cleavage of the diacetonide of D-mannitol, followed by the reduction of the intermediate aldehyde which gave, without racemization, the (*S*)-glycerol 1,2-acetonide and the preparation of the tosylate (*R*)-3-tosyloxypropane-1,2-diol was carried out according to Baldwin *et al.* [13].

Mild heating of compound **2** in DMF in the presence of a nearly stoichiometric amount of sodium azide provided (*S*)-4-azidomethyl-2,2-dimethyl-1,3-dioxolane.

Both the racemic and chiral azide were employed to prepare 8-azahypoxanthines and 8-azaadenines (Scheme II). The sodium salt of cyanoacetamide or malononitrile was

reacted with the azide in a 1,3-dipolar cycloaddition [14-15] and afforded the intermediate triazoles which were converted directly to the 8-azapurines by treating with a suitable ester [2,16] or nitrile [3]. The percentage of racemization determined by the nmr method on the diastereomer complexes with Europium shift reagent ($Eu(tfc)_3$) [17], showed less than 2% racemized product [18].

9-(2',3'-Dihydroxy)-8-azapurines, obtained from the isopropylidene derivatives with dilute hydrochloric acid [19], were tested as adenosine deaminase inhibitors (IC_{50}) [20]. The IC_{50} values showed that the 8-azaadenines were more active than 8-azahypoxanthines.

EXPERIMENTAL

Melting points were taken on a Kofler apparatus and are uncorrected. The ir spectra were determined in nujol mulls with a Perkin-Elmer 197 spectrometer. The nuclear magnetic resonance (^1H nmr) spectra were determined at 60 MHz with a Varian A 360 spectrometer and at 200 MHz with a Bruker AC 200 spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to tetramethylsilane as the internal standard. Elemental analyses were performed with a Carlo Erba Elemental Analyzer Model 1106 apparatus. Thin layer chromatography (tlc) was run on silica gel 60 F_{254} Merck plates. E. Merck silica gel (210-400 mesh) was used for flash column chromatography. The reactions were monitored by tlc analysis. When cited, the reaction mixtures were neutralized with Dowex H^+ form resin and were evaporated at reduced pressure (20-25 mm Hg) with a Buchi Rotavapor RE 111. Distillations were performed in a Buchi GKR-50 tubular oven. Analytical and preparative high performance liquid chromatographies were performed by a chromatographic system consisting of a Waters Associates liquid chromatograph equipped with U6 K injector, 6000A solvent delivery system, UV detector Model 480.

Enzyme inhibition assay was performed according to a modified procedure of the method described by Colowick and Kaplan [20]. It involves measuring the rate of disappearance of the absorption band of adenosine at 265 nm. All reactions were run in 0.05 *M* Tris buffer at *p*H 7.00 at 25°. The stock solutions of all reagents were prepared by dissolving the compounds in dimethyl sulfoxide and diluting the solutions with 0.05 *M* Tris buffer at *p*H 7.00. Substrate concentrations in the cuvette were 0.064 mmoles/liter.

(±)-2,2-Dimethyl-1,3-dioxolan-4-ylmethanol (**1**).

A mixture of glycerin (30 ml), acetone (100 ml), light petroleum ether (150 ml) and Dowex H^+ form resin (5 g) was refluxed trapping the moisture with anhydrous aluminium oxide (150 g) as filtering material of the condensed vapors. Reflux was prolonged for 12 hours until the disappearance of the two phases. Filtration and evaporation of the volatile fractions gave an oily residue which was distillated. The collected fractions, bp 91-93°/20 mm Hz, 26 g (65%) were identified as **1** by ir and ^1H nmr; ir (pure liquid): 3420 (OH), 2980, 2940, 2880, 1375, 1260, 1215, 1160, 1075, 1050, 845 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.20 (s, 1H, OH, deuterium oxide-exchangeable), 3.60 (m, 2H, CH_2OH), 3.70-4.40 (m, 3H, CH_2-CH).

(+)(*S*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethanol (**1**).

This compound was prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol [12] according to the experimental method described by Baldwin [13]. The obtained alcohol **1** (45%) showed bp 60°/0.3 mm Hg and $[\alpha]_D^{22} = 11.6$ (c 5.15, chloroform), $[\alpha]_D^{20} = 11.55$ (c 4.7, methanol).

(*R*) and (±)-3-Tosyloxy-1,2-isopropylidene-1,2-dihydroxypropane (**2**).

This compound, liquid at room temperature solidified on standing at 0-5°, was prepared in 70% yield according the method of Baldwin [13], and was used without further purification.

(−)(*S*) and (±)-2,2-Dimethyl-1,3-dioxolan-4-ylmethanazide (**3**) [21].

A solution of 3-tosyloxy-1,2-isopropylidene-1,2-dihydroxypropane (**2**) (7.05 g, 24.6 mmoles), and sodium azide (1.9 g, 29.2 mmoles) in dimethylformamide (30 ml) was heated at 60° for 12 hours. After cooling, the reaction mixture was diluted with water (70 ml) and extracted repeatedly with dichloromethane. The organic layer washed with water, dried with magnesium sulphate, filtered and evaporated at reduced pressure, gave an oily residue which was distilled collecting the fractions with bp 50°/0.5 mm Hg, 1.6 g (38%); ir (pure liquid): 2100 cm^{-1}; tlc: R_f 0.6 (acetone-chloroform 5:4 v/v); hplc: single peak at 6.84 minutes (retention time), eluting with a methanol-water mixture 6:4 v/v and a 1.5 ml/min flux on a steel column filled with Lichrosorb RP 18 (5 micrometer).

From (*R*)-3-Tosyloxy-1,2-isopropylidene-1,2-dihydroxypropane (**2**).

Compound (−)(*S*)-**3** was obtained (40%); this product could be purified from the reaction mixture by eluting on a silica gel column with ethyl acetate/petroleum ether 3:10 v/v: bp 40°/0.2 mm Hg, $[\alpha]_D^{20} = -56.7$ (c 2.8, $CHCl_3$).

General Procedure for the Preparation of (±)-7-Hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines Starting from (±) **3**.

A solution obtained from sodium (0.069 g, 3 mmoles) in dry ethanol (3 ml) was heated with cyanoacetamide (0.084 g, 1 mmole). After a few minutes the azide **3** (0.157 g, 1 mmole) was added and the mixture was refluxed until the disappearance of the azide as monitored by tlc. A suitable ester (ethyl formate for **4**; ethyl acetate for **5**; ethyl propionate for **6**; ethyl benzoate for **7**) (5-10 mmoles), previously dried with aluminum oxide, was added and the heating was continued until the disappearance of the intermediate triazole (tlc). At the end, dilution with ethanol (20 ml), neutralization and filtration afforded a solution which was evaporated at reduced pressure. The residue was crystallized from a suitable solvent to yield **4**, **5**, **6** or **7**.

(±)-3-2',3'-*O*-Isopropylidene-2',3'-dihydroxypropyl-7-hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**4**).

This compound was prepared according to the described general procedure, reaction time, 2 hours, **4** was crystallized from chloroform-petroleum ether (80%), mp 210-211°; ^1H nmr (deuteriochloroform): δ 1.33 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.99-4.20 (m, 2H, CH_2O), 4.64-4.78 (m, 3H, CHO + CH_2N), 7.40 (s, 1H, C5-H); tlc: R_f 0.27 (ethyl acetate), 0.22 (chloroform-methanol 95:5 v/v).

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.73; H, 5.02; N, 27.57.

(−)(*S*)-3-2′,3′-*O*-Isopropylidene-2′,3′-dihydroxypropyl-7-hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**4**).

This product was prepared by the same method used for the racemic compound; it was crystallized from ethanol to give **4** (75%), mp 199-201°, $[\alpha]_D^{1.5} = -30.8$ (c 2.83, DMF), R_f 0.22 (chloroform-methanol 95:5 v/v). Proton magnetic resonance spectrum was identical with that of the racemic compound. The portionwise addition of Europium shift reagent, $Eu(tfc)_3$ [14], to racemic and (−)(*S*)-**4** caused the shift and splitting of many signals. Particularly, the effect was more evident for the singlet at higher magnetic field, attributed to a methyl group of the isopropylidene bridge. The splitting effect reached 0.039 ppm which showed that the product (*S*)-**4** had an optical purity higher than 96%.

(±)-3-2′,3′-*O*-Isopropylidene-2′,3′-dihydroxypropyl-5-methyl-7-hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**5**).

This compound was obtained according to the described general procedure, reaction time, 3 hours, **5** was crystallized from ethanol (62%), mp 156-158°; ^{1}H nmr (deuteriochloroform): δ 1.23 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.22 (s, 3H, C5-CH_3), 3.93 (m, 2H, CH_2O), 4.42 (m, 3H, CHO + CH_2N); tlc: 0.37 (ethyl acetate), 0.24 (chloroform-methanol 95:5 v/v).

Anal. Calcd. for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 50.03; H, 5.31; N, 26.09.

(±)-3-2′,3′-*O*-Isopropylidene-2′,3′-dihydroxypropyl-5-ethyl-7-hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**6**).

This compound was obtained according to the described general procedure, reaction time, 5 hours, **6** was crystallized from ethanol (67%), mp 171-173° ^{1}H nmr (deuteriochloroform): δ 1.21 (s, 3H, CH_3), 1.23 (t, 3H, CH_3), 1.25 (s, 3H, CH_3), 2.69 (q, 2H, C5-CH_2), 4.01 (m, 2H, CH_2O), 4.56 (m, 3H, CHO + CH_2N), 11.25 (s, 1H, NH); tlc: R_f 0.50 (ethyl acetate), 0.27 (chloroform-methanol 95:5 v/v).

Anal. Calcd. for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.14; N, 25.08. Found: C, 51.40; H, 6.26; N, 25.38.

(±)-3-2′,3′-*O*-Isopropylidene-2′,3′-dihydroxypropyl-5-phenyl-7-hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**7**).

This compound was prepared according to the described general procedure, reaction time, 3 hours, **7** was crystallized from ethanol (65%), mp 174-175°; ^{1}H nmr (deuteriochloroform): 1.30 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 3.86-3.94 (m, 1H, ½ CH_2O), 4.12-4.20 (m, 1H, ½ CH_2O), 4.58-4.63 (m, 1H, CHO), 4.80, 4.83 (d, 2H, CH_2N), 7.48-7.64 (m, 3H, phenyl protons), 7.96-8.01 (m, 2H, phenyl protons), 9.98 (s, 1H, NH); tlc: R_f 0.69 (ethyl acetate), 0.38 (chloroform-methanol 95:5 v/v).

Anal. Calcd. for $C_{16}H_{17}N_5O_3$: C, 58.70; H, 5.23; N, 21.40. Found: C, 58.60; H, 5.35; N, 21.25.

(±)-3-2′,3′-*O*-Isopropylidene-2′,3′-dihydroxypropyl-5-*p*-tolyl-7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**8**).

A solution of sodium (0.028 g, 1.2 mmoles) in dry ethanol (3 ml) was treated with malononitrile (0.066 g, 1 mmole) and heated at 80° for 10 minutes then to the mixture was added a solution of azide (±)-**3** (0.157 g, 1 mmole) and *p*-toluonitrile (1.17 g, 10 mmoles). Heating was prolonged until the disappearance of the azide (tlc). After cooling the solution, it was diluted with ethanol (20 ml), neutralized and filtered and finally evaporated to an oily residue from which excess of the nitrile was distilled, bp 100°/0.5 mm Hg. The residue was chromatographed on a silica gel column, using chloroform/petroleum ether 1:1 v/v as eluent, to give **8**, 0.214 g (63%), mp 155-157°; ir: 3350, 3150 (NH_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.34 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.12 (m, 2H, OCH_2), 4.75 (m, 3H, NCH_2 + CHO), 6.25 (s, 2H, NH_2), 7.27 (d, 2H, phenyl protons), 8.34 (d, 2H, phenyl protons); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.22 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.06 (m, 2H, OCH_2), 4.67 (m, 3H, NCH_2 + CHO), 7.30 (d, 2H, phenyl protons), 8.30 (s, 2H, NH_2), 8.34 (d, 2H, phenyl protons); tlc: R_f 0.90 (ethyl acetate), 0.62 (chloroform-methanol 95:5 v/v).

Anal. Calcd. for $C_{17}H_{20}N_6O_2$: C, 59.98; H, 5.92; N, 24.70. Found: C, 60.15; H, 5.92; N, 24.51.

(+)(*S*)-**8**.

This compound (40%) was prepared according to the method used for the racemic product and was purified with an hplc apparatus (254 nm) eluting with ethyl acetate-hexane 1:1 v/v on a steel column filled with Merck-Kieselgel 60, mp 160-161°, $[\alpha]_D^{22} = 4.5$ (c 1.38, chloroform), tlc: R_f 0.62 (chloroform-methanol 95:5 v/v).

(±)-3-2′,3′-*O*-Isopropylidene-2′,3′-dihydroxypropyl-5-phenyl-7-amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**9**).

This compound was prepared with the procedure described for **8**. Benzonitrile was employed and the reaction time was 3 hours; **9** was crystallized from chloroform-petroleum ether (55%), mp 154-155°; ^{1}H nmr (dimethyl sulfoxide-d_6-deuteriochloroform): δ 1.36 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 4.18 (m, 2H, CH_2O), 4.80 (m, 3H, CH-CH_2N), 7.33 (s, 2H, NH_2, deuterium oxide-exchangeable), 7.60 (m, 3H, 3′, 4′, 5′ phenyl protons), 8.60 (m, 2H, 2′, 6′ phenyl protons); tlc: R_f 0.58 (chloroform-methanol 95:5 v/v).

Anal. Calcd. for $C_{16}H_{18}N_6O_2$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.80; H, 5.66; N, 25.80.

General Procedure for the Hydrolysis of Isopropylidene Derivatives [19].

The protected compounds, except **5**, (70 mg, 0.205-0.278 mmole) were suspended in 1 *M* hydrochloric acid (3 ml) at 60° for 15 minutes and the mixtures were successively evaporated at reduced pressure keeping the temperature below 40°. Evaporation and drying over phosphorus pentoxide gave a pure solid in 100% yield.

(±)-3-2′,3′-Dihydroxypropyl-7-hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidine (**10**).

This product was prepared according to the general procedure, mp 192-193°, R_f 0.23 (chloroform-methanol 80:20 v/v), IC_{50} 187 10^{-6} *M*.

Anal. Calcd. for $C_7H_9N_5O_3$: C, 39.81; H, 4.30; N, 33.17. Found: C, 39.65; H, 4.50; N, 32.95.

(−)(*S*)-3-2′,3′-Dihydroxypropyl-7-hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidine (**10**).

This product was prepared by the same method used for the racemic compound, mp 176-178°, R_f 0.23 (chloroform-methanol 80:20 v/v), $[\alpha]_D^{18} = -16.2$ (c 1.0, methanol), IC_{50} 152 10^{-6} *M*.

Anal. Calcd. for $C_7H_9N_5O_3$: C, 39.81; H, 4.30; N, 33.17. Found: C, 39.70; H, 4.45; N, 33.05.

(±)-3-2′,3′-Dihydroxypropyl-5-methyl-7-hydroxy-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine (**11**).

This compound was obtained by treating **5** (30 mg, 0.108

mmole) with a saturated solultion (2 ml) of hydrogen chloride in methanol for 15 minutes and evaporating the solution at room temperature. The solid residue showed mp 219-221°, R_f 0.31 (chloroform-methanol 80:20 v/v), IC_{50} >200 10^{-6} *M*.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.66; H, 4.92; N, 31.10. Found: C, 42.50; H, 4.75; N, 29.95.

(±)-3-2',3'-Dihydroxypropyl-5-ethyl-7-hydroxy-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine (**12**).

This compound was obtained according to the general procedure, mp 184-185°, R_f 0.44 (chloroform-methanol 80:20 v/v), IC_{50} >200 10^{-6} *M*.

Anal. Calcd. for $C_9H_{13}N_5O_3$: C, 45.18; H, 5.48; N, 29.28. Found: C, 45.05; H, 5.60; N, 29.10.

(±)-3-2',3'-Dihydroxypropyl-5-phenyl-7-hydroxy-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine (**13**).

This compound was prepared according to the general procedure, mp 161-163°, R_f 0.49 (chloroform-methanol 80:20 v/v), IC_{50} not evaluable as **13** is scarcely soluble.

Anal. Calcd. for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.25; H, 4.70; N, 24.20.

(±)-3-2',3'-Dihydroxypropyl-5-*p*-tolyl-7-amino-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine (**14**).

This compound was prepared according to the general procedure, mp 219-221°, R_f 0.36 (chloroform-methanol 90:10 v/v), IC_{50} 23.6 10^{-6} *M*.

Anal. Calcd. for $C_{14}H_{16}N_6O_2$: C, 55.99; H, 5.37; N, 27.99. Found: C, 55.75; H, 5.50; N, 27.85.

(−)(*S*)-3-2',3'-Dihydroxypropyl-5-*p*-tolyl-7-amino-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine (**14**).

This compound was prepared according to the general procedure, mp 210-211°, $[\alpha]_D^{18} = -27.3$ (c 0.84, dimethyl sulfoxide), R_f 0.36 (chloroform-methanol 90:10 v/v), IC_{50} 19.2 10^{-6} *M*.

Anal. Calcd. for $C_{14}H_{16}N_6O_2$: C, 55.99; H, 5.37; N, 27.99. Found: C, 55.80; H, 5.45; N, 27.80.

(±)-3-2',3'-Dihydroxypropyl-5-phenyl-7-amino-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine (**15**).

This compound was prepared according to the general procedure, mp 199-200°, R_f 0.32 (chloroform-methanol 90:10 v/v), IC_{50} 15.6 10^{-6} *M*.

Anal. Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.36. Found: C, 54.35; H, 5.05; N, 29.20.

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