"One Pot" Synthesis of 2-Substituted 9-(2'-Hydroxy-3'-aminopropyl)-8-azahypoxanthines and 8-azaadenines (5-Substituted 3-(2'-Hydroxy-3'-aminopropyl) 7-amino and 7-hydroxy-3H-1,2,3-triazolo[4,5-*d*]pyrimidines)

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An example of the generalization of the synthesis of 8-azahypoxanthines **A** and 8-azaadenines **B**, interesting from a medicinal point of view, is presented by utilizing 1-amino-2-hydroxy-3-azidopropanes.

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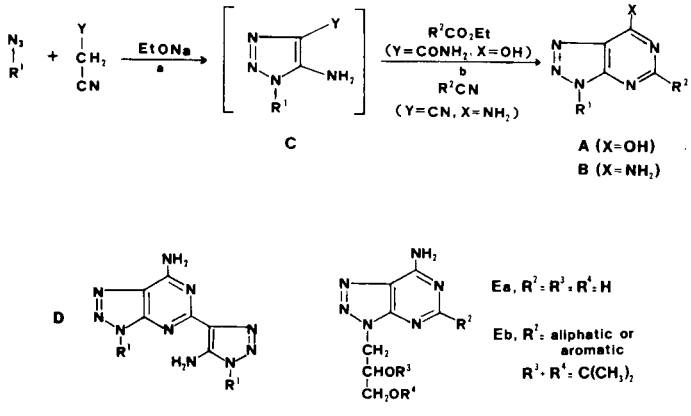
During the progress of our project regarding the preparation and the study of biological activity of new antimetabolites, we have developed a quick synthetic method for 8-azapurines, **A** and **B**, starting from simple and inexpensive products, such as cyanoacetamide or malononitrile, benzyl azide and an ester or a nitrile (Scheme 1) [1,2].

Scheme 1



After these results the generalized employment of aliphatic azides could appear to be desirable. Indeed, a profitable utilization of aliphatic azides would give a more general character to the preparative method. The preparation of several compounds of the series **A** and **B**, in which R^1 and R^2 had different and complex structures might be important in the study of the biological activity of these compounds and in the ensuing structure-activity relationships.

According to literature reports, 8-azaadenines and 8-azahypoxanthines, bearing an aliphatic substituent on N-9, were obtained by cyclizing the appropriate 4,5-diaminopyrimidine with isopentyl nitrite or nitrous acid [3a-e].

The lack of usefulness of 1,2,3-triazoles **C** as intermediates, considered to date, for the synthesis of 8-azapurines depends on the lack of 4-amino-5-carbamoyl or 5-cyano-1,2,3-triazoles with an aliphatic substituent on N-3 [4a-c]. This situation may be imputed to the hazard in the handling of low molecular weight azides [5] and to their relatively low reactivity in the base catalyzed cycloaddition, as in step a. Among azides, acyl azides were the most reactive with active methylene compounds under very mild conditions giving triazoles [6a-c] or diazo functionalized products [7a-c] in the presence of base. The triazoles obtained from malononitrile in aqueous alkali were completely unstable and were immediately converted, in the reaction vessel, into the 4-acylamino-1,2,3-triazoles by the Dimroth rearrangement [6b]. Instead 3-aryl-1,2,3-triazoles, obtained satisfactorily from aryl azides at room temperature [8a-b], gave Dimroth rearrangement at moderately high temperature [9]. In contrast the equilibrium between 3-alkyl-4-amino-5-carbamoyl-1,2,3-triazoles and the 4-alkylamino isomers was found to favour the former [10a-b]. Incidentally, the reaction with malonitrile was complicated by the formation of dimers **D** [11].

While alkyl azides reacted very slowly, in contrast with aryl azides, with phenylacetonitrile in the presence of sodium alkoxides and potassium *t*-butoxide [12], β-D-ribofuranosyl azide was reacted with cyanoacetamide at 0° for three hours in aqueous potassium hydroxide [4c].

Therefore it seems that aliphatic branched azides can also react under similar conditions of step *a*, even if they react more slowly than acyl and aryl azides for both electronic and steric factors.

On the other hand, the rate of the two steps, *a* and *b*, of the proposed method is influenced and enhanced by marked electron-with-drawing properties of groups R^1 and R^2.

As outlined previously [2], a moderately low rate in step *a* provides a more satisfactory preparation of **B**. Indeed, this event prevents the formation of dimers **D**, originating from the condensation of two molecules of the triazoles **C**, and favours the formation of **B**. If the rate of the first step is too slow, the reaction would be of little value, therefore we decided to quantify the limits of the whole process by employing aliphatic azides.

Regarding the choice of the group R^1, we considered that, after the synthesis and disclosure of antiviral proper-

ties of acyclovir [13a-b] many reports in purine chemistry have described the preparation of compounds in which a ribose fragment is present [14a-c]. Among them many efforts were devoted to the synthesis and to the biological evaluation of compounds bearing C-1'--OR fragments or their carbo and thio analogs. Some purines bonded to a C-1'--C-2'--C-3' chain on N-9 were also described, but less attention was paid to their 8-aza analogs. To our knowledge, in the 8-azapurine field, only 8 and 9-(2',3'-dihydroxypropyl) 8-azaadenines are known up to date [3e]. The 9-(2',3'-dihydroxypropyl) 8-azaadenine **Ea** was prepared both by diazotization of 4,5-diamino-6-(2',3'-dihydroxypropylamino) 1,3-pyrimidine and by alkylation of 8-azaadenine with the tosylate of 4-hydroxymethyl-1,3-dioxolane.

We have been successful with the "one pot" preparation of 2-substituted 8-azapurine **Eb** [15], starting from 4-azidomethyl-1,3-dioxolane shown in Scheme 1. A full description of these compounds will be given in a forthcoming paper. Other results, are described now, regarding the synthesis of compounds **A** and **B** [15], which seemed to be absent in literature (Scheme 2).

The presence of a hydroxy group bonded to a chiral carbon atom represents a possibility for the formation of the stable enzyme-inhibitor complex in **B** series with adenosine deaminase (ADA), as in *S*-9-(2'-hydroxypropyl)-adenine and its 1'-alkyl derivatives [16]. On the other hand, the influence of the nitrogen atom on C-3' regarding the inhibitory activity against ADA may deserve further

Scheme 2

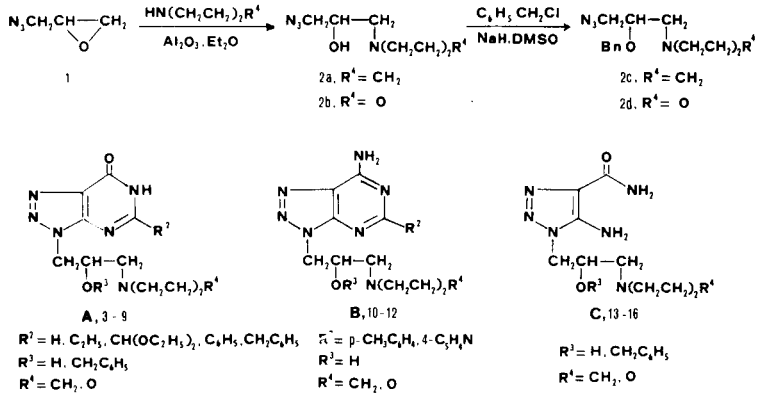


Table 1

Starting azide	Starting ester	Reaction product **A**	Reaction time (hours)	Yields (%)	Mp °C [X]	Molecular formula	Analyses % Calcd./Found C	H	N
2a	HCO_2Et	**3**	7	71	139-140 [a]	$C_{12}H_{18}N_6O_2$	51.78 51.49	6.52 6.28	30.20 29.96
2a	$(EtO)_2CHCO_2Et$	**4**	7	63	77-79 [b]	$C_{17}H_{28}N_6O_4$	53.66 53.45	7.42 7.66	22.09 21.85
2a	$C_6H_5CO_2Et$	**5**	10	61	198-200 [c] [Y]	$C_{20}H_{28}N_6O_3$	59.98 60.15	7.05 7.11	20.99 20.75
2c	$CH_3CH_2CO_2Et$	**6**	7	62	120-121 [d]	$C_{21}H_{28}N_6O_2$	63.61 63.56	7.12 6.92	21.20 21.06
2d	HCO_2Et	**7**	7	68	138-140 [b]	$C_{18}H_{22}N_6O_3$	58.36 58.06	5.99 5.75	22.69 22.49
2d	$C_6H_5CO_2Et$	**8**	10	60	182-184 [c]	$C_{24}H_{26}N_6O_3$	64.56 64.31	5.87 5.81	18.82 18.54
2d	$C_6H_5CH_2CO_2Et$	**9**	10	60	139-140 [a]	$C_{25}H_{28}N_6O_3$	65.20 65.03	6.13 5.83	18.25 17.96

[X] Crystallization solvents; [a] = chloroform-light petroleum, [b] = toluene, [c] = ethanol, [d] = toluene-light petroleum. [Y] After crystallization **5** contained one mole of this solvent as evidence by analysis and pmr.

Table 2

PMR δ (ppm) and TLC R_f (eluent) Data

3 pmr (b): 1.55 (m, CH_2, 6H), 2.69 (m, NCH_2, 6H), 4.58 (m, CHO, 1H), 4.89 (m, NCH_2, 2H), 8.26 (s, C-5-H, 1H); tlc, 0.06 (ethyl acetate/methanol 7:3)

4 pmr (b): 1.28 (t, CH_3, 6H, J = 7 Hz), 1.51 (m, CH_2, 6H), 2.47 (m, NCH_2, 6H), 3.67 (q, CH_2O, 2H), 3.70 (q, CH_2O, 2H), 4.28 (m, CHO, 1H), 4.60 (m, NCH_2, 2H), 5.35 (s, C-5-CH, 1H), 7.19 (s, NH, 1 exchangeable H); tlc, 0.22 (ethyl acetate/methanol 7:3)

5 pmr (a): 1.05 (t, CH_3, 3H, J = 7 Hz), 1.39 (m, CH_2, 6H), 2.38 (m, NCH_2, 6H), 3.42 (q, CH_2O, 2H), 4.32 (m, CHO, 1H), 4.59 (m, NCH_2, 2H), 7.54-7.63 (m, aromatic, 3H), 8.10-8.22 (m, aromatic, 2H); tlc, 0.21 (ethyl acetate/methanol 7:3)

6 pmr (b): 1.34 (t, CH_3, 3H, J = 7.5 Hz), 1.46 (m, CH_2, 6H), 2.44 (m, NCH_2, 6H), 2.84 (q, C-5-CH_2, 2H), 4.22 (m, CHO, 1H), 4.48 (q, benzylic, 2H), 4.71 (m, NCH_2, 2H), 7.00-7.36 (m, aromatic, 5H); tlc, 0.53 (ethyl acetate/methanol 7:3)

7 pmr (b): 2.45 (m, NCH_2, 6H), 3.50 (m, CH_2O, 4H), 4.10 (m, CHO, 1H), 4.43 (s, benzylic, 2H), 4.54 (m, NCH_2, 2H), 7.08-7.23 (m, aromatic, 5H), 8.00 (s, C-5-H, 1H); tlc, 0.47 (ethyl acetate/methanol 7:3)

8 pmr (b): 2.56 (m, NCH_2, 6H), 3.68 (m, CH_2O, 4H), 4.22 (m, CHO, 1H), 4.52 (q, benzylic, 2H), 4.79 (m, NCH_2, 2H), 7.11 (s, aromatic, 5H), 7.57-7.66 (m, aromatic, 3H), 8.13-8.22 (m, aromatic, 2H), 12.75 (s, NH, 1 exchangeable H); tlc, 0.23 (ethyl acetate)

9 pmr (a + b): 2.46 (m, NCH_2, 6H), 3.62 (m, OCH_2, 4H), 4.08 (s, C-5-CH_2, 2H), 4.12 (m, CHO, 1H), 4.48 (q, benzylic, 2H), 4.73 (m, NCH_2, 2H), 7.14-7.33 (m, aromatic, 10H); tlc, 0.52 (ethyl acetate/-methanol 7:3)

investigation. Furthermore, the substituent on C-2 of the nucleus constitutes the third structural element, the influence of which on the biological activity of the molecule must be considered in addition to the others.

The 2-hydroxy-3-aminopropyl azides **2** were obtained by the nucleophilic opening of the oxirane ring of the glycidyl azide **1** [17] with amines. This interesting but scarcely utilized compound **1** [18] was treated with piperidine or morpholine obtaining the adducts **2** under very mild conditions by conducting the reaction with the amine supported on alumina [19]. These conditions allowed us to avoid the presumably dangerous heating of compound **1**.

The analysis of reaction mixtures revealed that only one product was largely prevalent in this highly regioselective, practically regiospecific, process [20], so the reaction products **2** were used successively without further purification.

Regarding the synthesis of **A**, the formation of the triazoles **C**, although slower than that with benzyl azide, was accomplished in a few hours, providing an acceptable overall reaction time. The unknown compounds **C** obtained from cyanoacetamide were isolated and characterized (Tables 5 and 6).

As we have foreseen, the preparation of compounds **B** was not affected by the presence of dimeric products **D** in the reaction mixtures.

In some instances we employed the *O*-benzyl substituted azides satisfactorily.

All compounds **A** and **B** were characterized by spectroscopic and analytical methods (Tables 1, 2, 3 and 4).

These results constitute the first attempt to generalize the previously reported [1,2] preparative methods.

Our next preparative interest in this matter will be dedicated to the employment of azides similar to **2**, containing a primary or secondary amino group, trying to obtain a complete series of compounds **A** and **B**, the last of which can possibly be converted into acyclic 2-substituted 8-azapuromycin.

EXPERIMENTAL

All 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 nmr spectra were determined with a Varian CFT 20 spectrometer (pmr, DMSO-d_6 (a) or deuteriochloroform (b) as the solvent, TMS as internal standard). Reactions were monitored by tlc on Merck-Kieselgel 60 F_{254} plates. Column chromatography was performed with Merck-Kieselgel (60-230 mesh); the eluents were indicated in Tables 2, 4 and 6. In the oxirane ring opening of glycidyl azide Merck-

Table 3

Starting azide	Starting nitrile [Y]	Reaction product **B**	Reaction time (hours)	Yields (%)	Mp °C [X]	Molecular formula	Analyses % Calcd./Found C	H	N
2a	*p*-$CH_3C_6H_4CN$ [10]	**10**	4	55	90-92 [c]	$C_{19}H_{25}N_7O$	62.17 62.45	6.84 6.58	26.78 26.54
2b	*p*-$CH_3C_6H_4CN$ [10]	**11**	4	53	98-100 [b]	$C_{18}H_{23}N_7O_2$	63.32 63.41	6.79 6.63	20.52 20.31
2b	4-C_5H_4NCN [1]	**12**	2	67	245-247 [a]	$C_{16}H_{20}N_8O_2$	53.92 53.64	5.66 5.94	31.45 31.21

[Y] Nitrile/azide molar ratio. [X] Crystallization solvents; [a] = methanol, [b] = toluene-light petroleum, [c] = aqueous ethanol.

Table 4

PMR (ppm) and TLC R_f (eluent) Data

10 pmr (b): 1.48 (m, CH_2, 6H), 2.42 (m, NCH_2, 6H), 2.50 (s, CH_3, 3H), 4.38 (m, CHO, 1H), 4.74 (m, NCH_2, 2H), 6.17 (s, NH_2, 2 exchangeable H), 7.26 (d, aromatic, 2H), 8.31 (d, aromatic, 2H); tlc 0.48 (ethyl acetate/methanol 7:3)

11 pmr (b): 2.41 (s, CH_3, 3H), 2.54 (m, NCH_2, 6H), 3.70 (m, CH_2O, 4H), 4.45 (m, CHO, 1H), 4.77 (m, NCH_2, 2H), 6.25 (s, NH_2, 2 exchangeable H), 7.26 (d, aromatic, 2H), 8.28 (d, aromatic, 2H); tlc, 0.67 (ethyl acetate/methanol 7:3)

12 pmr (a): 2.45 (m, NCH_2, 6H), 3.51 (m, CH_2O, 4H), 4.28 (m, CHO, 1H), 4.66-5.11 (m, NCH_2, 2H), 8.21 (m, aromatic, 2H), 8.60 (s, NH_2, 2 exchangeable H), 8.74 (m, aromatic, 2H); tlc, 0.45 (ethyl acetate/methanol 7:3)

Aluminium oxide 90 Aktiv Neutral (70-230 mesh) was used. Distillation temperatures (°C)/pressure (mm Hg) were reported. Reaction mixtures were neutralized by Dowex-H^+ resin or acetic acid.

Reaction of Glycidyl Azide (**1**) with Amines.

a) 1-Azido-2-hydroxy-3-piperidinopropane (**2a**).

To a stirred suspension of aluminium oxide (15 g) in ethyl ether (150 ml) piperidine (0.63 g, 7.4 mmoles) was added. After ten minutes this slurry was treated with **1** (0.2 g, 2.0 mmoles) and stirring was continued for 20 hours at room temperature. Addition of methanol (150 ml) with further stirring for 3 hours, filtration on celite, and evaporation at reduced pressure afforded a yellow oil. Fractional distillation (110°/0.4) yielded 0.35 g (94%) of **2a**; ir: ν 3400 (OH), 2100 cm^{-1} (N_3); ^1H nmr (b): δ 1.53 (s, CH_2, 6H), 2.6 (m, CH_2N, 6H), 3.3 (m, CH_2N_3, 2H), 3.93 (m, CHO, 1H), 3.96 (s, OH, 1 exchangeable H).

Anal. Calcd. for $C_8H_{16}N_4O$: C, 52.15; H, 8.75; N, 30.41. Found: C, 52.41; H, 8.67; N, 30.15.

Table 5

Starting azide	Reaction product C	Yields (%)	Mp °C [X]	Molecular formula	Analyses % Calcd./Found C	H	N
2a	**13**	60	160-161 [a]	$C_{11}H_{20}N_6O_2$	49.24 49.51	7.51 7.54	31.22 31.55
2b	**14**	55	205-207 [b]	$C_{10}H_{18}N_6O_3$	44.43 44.52	6.71 6.84	31.10 31.17
2c	**15**	72	166-167 [b]	$C_{18}H_{26}N_6O_2$	60.31 60.55	7.31 7.41	23.45 23.75
2d	**16**	65	158-160 [c]	$C_{17}H_{24}N_6O_3$	56.65 56.60	6.71 6.57	23.32 23.06

[X] Crystallization solvents; [a] = chloroform/light petroleum, [b] = ethanol, [c] = methylene chloride/light petroleum.

Table 6

IR ν (cm^{-1}), PMR δ (ppm) and TLC R_f (eluent) Data

13 ir: 1660 (CO); pmr (a + b): 1.52 (m, CH_2, 6H), 2.42 (m, NCH_2, 6H), 4.27 (m, CH_2-CHO, 3H), 4.73 (s, OH, 1 exchangeable H), 6.20 (s, NH_2, 2 exchangeable H), 7.03 (s, NH_2, 2 exchangeable H); tlc, 0.06 (ethyl acetate/methanol 7:3)

14 ir: 1650 (CO); pmr (a): 2.45 (m, CH_2, 6H), 3.56 (m, CH_2O, 4H), 4.14 (m, CH_2-CHO, 3H), 5.14 (s, OH, 1 exchangeable H), 6.12 (s, NH_2, 2 exchangeable H), 7.20 (s, NH_2, 2 exchangeable H); tlc, 0.25 (ethyl acetate/methanol 7:3)

15 ir: 1650 (CO); pmr (a + b): 1.5 (m, CH_2, 6H), 2.43 (m, NCH_2, 6H), 4.00 (m, CHO, 1H), 4.37 (m, NCH_2, 2H), 4.63 (s, benzylic, 2H), 6.20 (s, NH_2, 2 exchangeable H), 6.96 (s, NH_2, 2 exchangeable H), 7.35 (s, aromatic, 5H); tlc, 0.34 (ethyl acetate/-methanol 7:3)

16 ir: 1660 (CO); pmr (b): 2.42 (m, NCH_2, 6H), 3.58 (m, CH_2O, 4H), 3.99 (m, CHO, 1H), 4.34 (m, NCH_2, 2H), 4.52 (s, benzylic, 2H), 6.23 (s, NH_2, 2 exchangeable H), 7.24 (s, aromatic, 5H), 7.27 (s, NH_2, 2 exchangeable H); tlc, 0.50 (ethyl acetate/methanol 7:3)

b) 1-Azido-2-hydroxy-3-morpholinopropane (**2b**).

This compound was obtained as described for **2a**, **2b** (87%); ir: ν 3400 (OH), 2100 cm^{-1} (N_3).

Anal. Calcd. for $C_7H_{14}N_4O_2$: C, 45.15; H, 7.58; N, 30.09. Found: C, 45.05; H, 7.63; N, 29.95.

1-Azido-2-benzyloxy-3-piperidinopropane (**2c**).

To a stirred solution obtained from sodium hydride (0.6 g, 12.5 mmoles, 50% in oil) in dimethyl sulphoxide (5 ml) were added **2a** (1.5 g, 8.15 mmoles) and, after ten minutes, benzyl chloride (3 g, 23.7 mmoles). Stirring was continued for 2 hours at room temperature. Dilution with water (100 ml), extraction with ethyl ether, drying over magnesium sulfate and evaporation afforded an oily residue. Fractional distillation (180°/0.5) yielded 1.99 g (89%) of **2c**; ir: ν 2100 cm^{-1} (N_3); ^1H nmr (b): δ 1.5 (s, CH_2, 6H), 2.4 (m, CH_2N, 6H), 3.4 (m, CH_2N_3,2H), 3.66 (m, CHO, 1H), 4.7 (s, benzylic, 2H), 7.41 (s, aromatic, 5H); tlc, R_f 0.61 (ethyl acetate/methanol 4:1).

Anal. Calcd. for $C_{15}H_{22}N_4O$: C, 65.66; H, 8.08; N, 20.42. Found: C, 65.83; H, 7.99; N, 20.15.

1-Azido-2-benzyloxy-3-morpholinopropane (**2d**).

This compound was obtained as described for **2c**, **2d** (81%); ir: ν 2100 cm^{-1} (N_3); ^1H nmr (b): δ 2.46 (m, CH_2, 6H), 3.43 (m, CH_2N_3, 2H), 3.68 (m, CHO + CH_2O, 5H), 4.7 (s, benzylic, 2H), 7.41 (s, aromatic, 5H); tlc, R_f 0.70 (ethyl acetate/methanol 4:1).

Anal. Calcd. for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.70; H, 7.30; N, 20.22.

General Procedure for the Preparation of 8-Azahypoxanthines **A**.

These compounds were prepared as described for similar compounds [1], and purified by silica gel column chromatography (Tables 1 and 2).

General Procedure for the Preparation of 8-Azaadenines **B**.

These compounds were prepared as described for similar compounds [2], and purified by silica gel column chromatography (Tables 3 and 4).

General Procedure for the Preparation of Triazoles **C**.

To an ethanolic solution of sodium ethoxide obtained by adding sodium (0.125 g, 5.4 mmoles) to ethanol (10 ml), cyanoacetamide (0.456 g, 5.4 mmoles) was added. After a few minutes the mixture was treated with the azide **2** (5.4 mmoles), and heated at reflux for 4 hours. Dilution with ethanol, neutralization, evaporation of solvent and eventual silica gel column chromatography gave the products **C** (Tables 5 and 6).

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