SYNTHESIS OF ACYCLIC ADENINE 8,N-ANHYDRONUCLEOSIDES

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9-(4-Hydroxybutyl)adenine (**10**) was obtained by reaction of adenine with 4-[(2-tetrahydropyran-2-yl)oxy]butyl chloride (**7**) in the presence of DBU. 8-Bromo-9-(4-hydroxybutyl)adenine (**13**) was prepared by bromination of **10** or by alkylation of 8-bromoadenine (**11**) with 4-bromoethyl acetate followed by methanolysis. Tosylation of compound **13** afforded the 4-tosyloxy derivative **15** which gave on heating with methylamine or cyclopropylamine 6-methyl- (**17a**) or 6-cyclopropyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17b**), while the reaction with hydrazine afforded 7,8,9,10-tetrahydro-6*H*-[1,3]diazepino-[1,2-*e*]purine-4,6-diamine (**17d**). Treatment of compound **13** with thionyl chloride gave 9-(4-chlorobutyl)-8-chloroadenine (**18**) as the main product which was transformed to **17b**, 6-propyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17c**) or 7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17e**) by reaction with cyclopropylamine, propylamine or ammonia, respectively. Compound **17e** was quite stable both in acid and alkaline solutions, at room temperature or at 90 °C. Compound **13** was converted to 9-(4-hydroxybutyl)-8-methylaminoadenine (**19**) by reaction with methylamine. Compound **19** failed to undergo intramolecular cyclization to diazepine **17a** on treatment with diphenyl carbonate, bis(4-nitrophenyl) carbonate or 1,1′-carbonyldiimidazole.

Key words: Nucleosides; Purines; Anhydronucleosides; Diazepines; Acyclic nucleoside analogues; Cyclizations.

Acyclic nucleoside analogues attract attention mainly in medicinal chemistry as a structural class comprising several important antiviral drugs (acyclovir and its congener valaciclovir, ganciclovir, buciclovir, penciclovir, femciclovir, *etc.*)[1]. Our Laboratory has been traditionally performing systematic study of acyclic nucleosides bearing centres of chirality in the side chains which replace the nucleoside sugar residues. Among these com-

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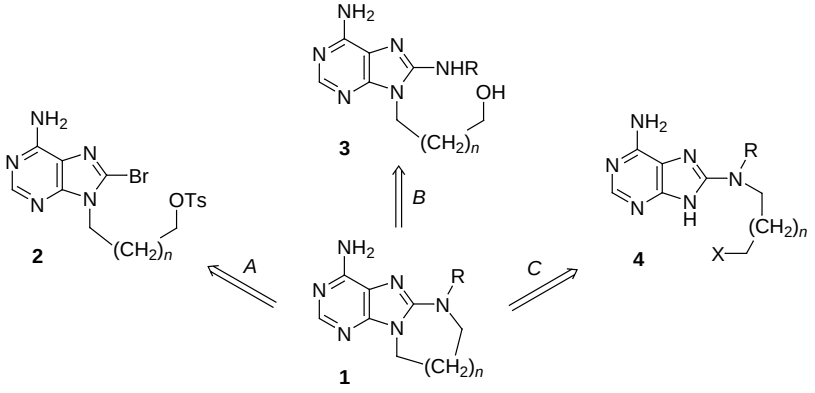
pounds, in particular (*S*)-9-(2,3-dihydroxypropyl)adenine[2] [(*S*)-DHPA] (marketed as antiherpetic Duvira gel®), structurally related 3-(adenin-2-yl)-2-hydroxypropanoic acid[3] (AHPA) and group of eritadenines[4] attract most attention. All these compounds inhibit SAH hydrolases[5] and hence exert effects on proliferative processes involving SAM-dependent methylations[6]. (*S*)-DHPA causes sequence specific hypomethylation of cytosine containing triplets in plant genomes[7]. This molecule is also parent structure of acyclic nucleoside phosphonates (ANP): its 2-phosphonomethyl ether, (*S*)-HPMPA, is a powerful antiviral[8] and also displays antiparasitic activities against *Plasmodium*, *Trypanosoma* and *Leishmania* spp.[9].

In the course of our studies on the chemistry and biological effects of acyclic adenine nucleosides, we also investigated analogues of purine cyclonucleosides ("anhydronucleosides") wherein the carbohydrate moiety of the nucleoside is covalently linked to the position 8 of the purine molecule[10]. The acyclic congeners, *i.e.*, compounds in which the aliphatic chain substituting the heterocyclic base at the position N-9 is linked simultaneously to the C-8 *via* an ether bridge, are formal analogues of the so-called 8,*O*-cyclonucleosides. Our previous papers on such compounds described their synthesis and properties[11]. Particularly intriguing properties were recorded for 4′,8-anhydro-9-(2,3-dihydroxybutyl)adenines and their 2′,3′-*O*-isopropylidene derivatives. The latter compounds exhibited CD spectra similar to 5′,8-*O*-cycloadenosine with molar ellipticity even 30% higher compared with this nucleoside[11]. The compounds are four-ring fused systems (dioxolane fused through diazepine to purine) deserving an investigation in view of diverse activities of such systems on DNA interacting enzymes. This consideration brought us to examine formation and stabilities of systems analogous to *N*-cyclonucleosides, *i.e.* compounds containing the seven-membered diazepine ring fused to the purine system. This paper describes studies on the compounds unsubstituted in the diazepine ring.

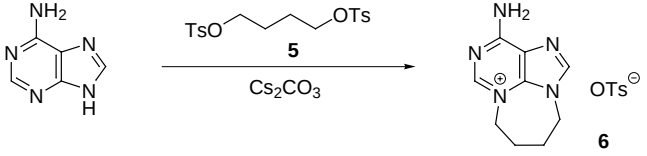
Two routes which might result in the formation of such compounds were described in nucleoside chemistry: (i) intramolecular ring closure involving double nucleophilic substitution of bromine at 8-position of adenine and *O*-tosylate situated at the 4-position of the side chain, by primary or secondary amine (**2**) (Route *A*)[12]; (ii) intramolecular ring closure between 4-hydroxy group of the side chain and 8-alkylamino group in the adenine (**3**) in the presence of suitable activation agents (Route *B*)[13]. The third method[14] which consists in (iii) introduction of the hydroxyalkylamino group at the C-8 of adenine and intramolecular alkylation at N-9 (and/or

N-7) by the action of an activating agent was used in the synthesis of acyclic nucleoside A from compound **4** (Route *C*) (Scheme 1).



SCHEME 1

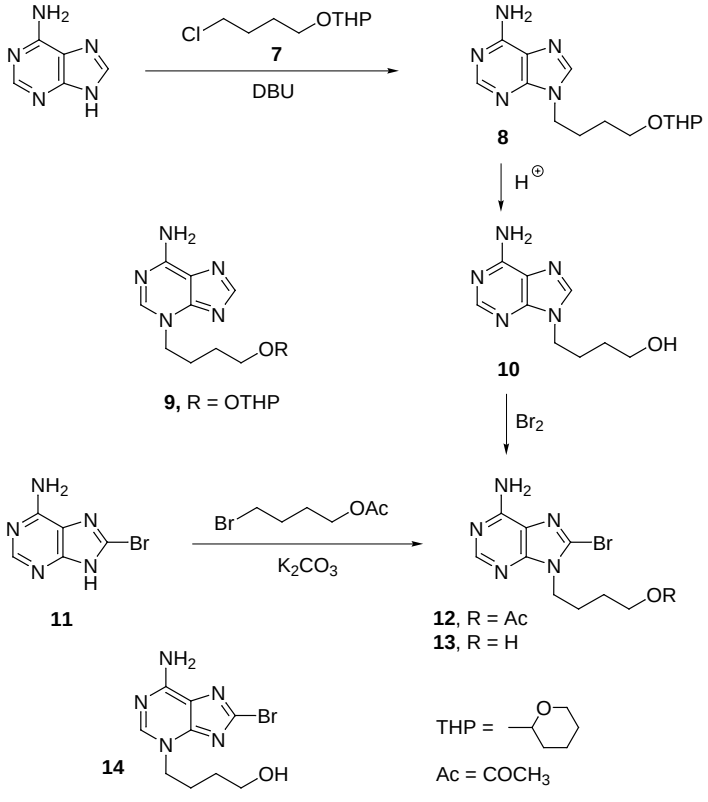
We have attempted to simplify Route *A* by direct synthesis of 9-[4-(tosyloxy)butyl]adenine by direct alkylation of adenine with butane-1,4-diyl ditosylate (**5**). However, this reaction performed in the presence of cesium carbonate at elevated temperature gave solely quaternary tosylate **6** as a product of consecutive intramolecular quaternization of the required 4-(tosyloxy)butyl intermediate in position 3 of adenine (Scheme 2).



SCHEME 2

Hence, we examined the synthesis of 8-bromo-9-(4-hydroxybutyl)-adenine (**13**) as the key compound for Route *A*. For preparation of 9-(4-hydroxybutyl)adenine (**10**) we applied the already described[11b] reaction sequence consisting in alkylation of adenine with 4-bromobutyl acetate and subsequent methanolysis of intermediary acetate. For practical reasons, we have also elaborated an alternate synthesis of compound **10**: 4-chlorobutan-1-ol was converted to its tetrahydropyran-2-yl ether **7** by an autocatalyzed reaction with dihydropyran and alkylation of adenine with this compound in the presence of DBU (ref.[15]) afforded the protected derivative **8** along with the minor quantity of the corresponding N^3-isomer **9**.

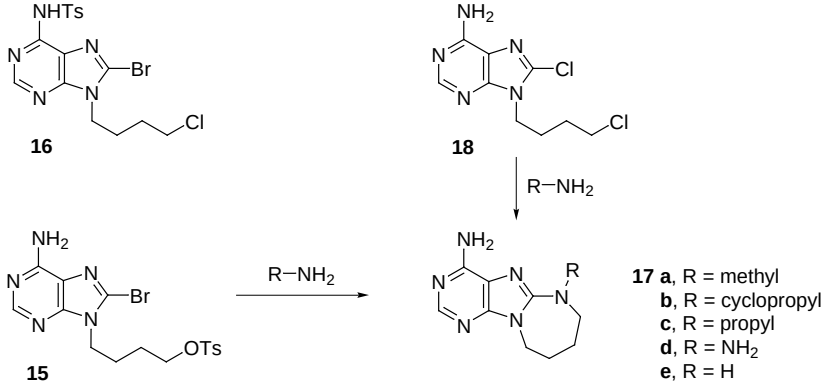
Acid hydrolysis of compound **8** gave 9-(4-hydroxybutyl)adenine (**10**). Of various variants of bromination reaction which were described for adenine nucleosides, bromination by bromine water in acetate buffer[16] (pH 4) was the method of choice. It gave the required 8-bromo derivative **13** in a good yield (Scheme 3).



SCHEME 3

An alternative procedure for the preparation of the compound **13** makes use of alkylation of 8-bromoadenine (**13**) with 4-bromobutyl acetate in the presence of potassium carbonate in DMF. The starting base was obtained by reaction of adenine with bromine without solvent (*cf.* ref.[17]). All attempts to perform the bromination in solvents such as DMF, dioxane or ethylene glycol dimethyl ether at low or elevated temperatures failed. The alkylation reaction took place only in DMF in the presence of K_2CO_3 and gave N^9-isomer **13** and N^3-isomer **14** in the ratio 2 : 1, respectively (Scheme 3). All other variants, *e.g.* reagent **7** in the presence of NaH, Cs_2CO_3 or DBU, gave

complex mixtures of products, while treatment with ditosylate **5** in the presence of Cs_2CO_3 gave a polar product, evidently an analogue of quaternary salt **6**. Tosylation of the 4-hydroxybutyl derivative **13** with tosyl chloride in pyridine gave the required *O*-tosyl derivative **15** in a low yield. Another product which was isolated from this reaction (compound **16**) arose evidently from the transformation of the originally formed **15** to the 4-chlorobutyl derivative and its subsequent *N*-tosylation (Scheme 4). Attempts to improve the yield of **15** such as by reducing excess of tosyl chloride, the presence or absence of 4-(*N*,*N*-dimethylamino)pyridine, and by decreasing the reaction temperature, failed.



SCHEME 4

Treatment of compound **15** with primary amines, such as methylamine or cyclopropylamine at elevated temperature gave the expected 6-methyl- (**17a**) and 6-cyclopropyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17b**), respectively, in high yields as the only reaction products. Also hydrazine hydrate in ethanol, in analogy to the reaction described for purine *N*-anhydronucleosides[18] gave 7,8,9,10-tetrahydro-6*H*-[1,3]diazepino-[1,2-*e*]purine-4,6-diamine (**17d**) as the main reaction product (Scheme 4).

In order to circumvent the low efficiency of this route to compounds **17** caused by the insufficient yield of the transformation **13**→**15**, we have investigated the possibility of converting the hydroxy group in compound **13** to the 4-chlorobutyl derivative by reaction with thionyl chloride. Similar conversions were described in the literature[19]. The reaction proceeded smoothly; however, the mass spectrum demonstrated that the desired reaction is accompanied by halogen exchange at C-8. The major component in the reaction product is 8-chloro-9-(4-chlorobutyl)adenine (**18**) while the expected 8-bromo analogue of compound **18** is present as a minor compo-

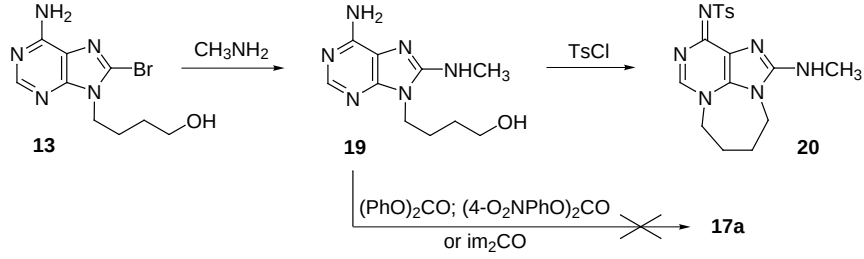
nent only. Nonetheless, crude **18** reacted as easily with methylamine or propylamine in the same manner as the tosyl derivative **15** to form the corresponding 6-alkyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amines **17a** and **17c**. Most importantly, treatment of compound **18** with methanolic ammonia at elevated temperature gave directly 7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17e**), the parent structure of the 7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine series. This facile reaction with ammonia contrasts with the situation in cyclonucleoside chemistry where indirect approaches (*e.g.*, formation of *N*-benzylamino derivative followed by hydrogenation) had to be used in order to prepare the *N*-unsubstituted 8,*N*-cyclonucleoside[20].

Compound **17e** resisted the action of 0.1 or 1 M HCl, as well of 0.1 or 1 M NaOH at room temperature or 90 °C for 20 h. This stability contrasts with the comparatively easy anhydro ring opening in structurally related acyclic 8,*O*-anhydronucleosides[11].

Another approach to compounds **17** is based on the intramolecular cyclization due to the reaction of the hydroxy group in the side chain and the R–NH substituent in the position 8 in the presence of activating agents, such as diaryl carbonates, 1,1′-carbonyldiimidazole or due to the Mitsunobu reaction. The approach has been used in nucleoside chemistry leading to satisfactory yields[20]. The starting 9-substituted 8-(methylamino)adenine derivative **19** was obtained from the 8-bromo derivative **13** by treatment with methylamine. The reaction of compound **19** with diphenyl carbonate or 1,1′-carbonyldiimidazole even at elevated temperature did not proceed at all. Replacement of diphenyl carbonate by bis(4-nitrophenyl) carbonate afforded traces of 4′-*O*-(4-nitrophenyl) carbonate only. No formation of compound **17a** was observed in any of the above experiments. It is not the first case where the reaction proceeding easily with nucleosides fails with their acyclic nucleoside counterparts. Evidently, it is a rather fixed conformation of the nucleoside molecule which strongly favours suitable mutual orientation of the substituent at C-8 of the base and a hydroxy group of the sugar moiety, which plays a very important role in intramolecular reactions leading to cyclonucleosides. Such a conformation is evidently less favoured in *N*-alkyl derivatives with sp^3 configuration of all carbon atoms of the side chain.

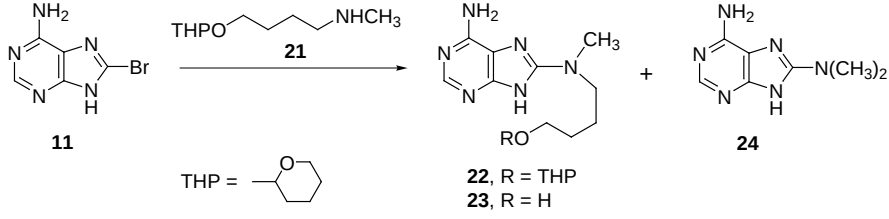
We have also tried to transform the hydroxy group in compound **19** to its tosylate with the aim to form the seven-membered ring in such a compound by the action of a strong base (*e.g.* DBU). However, compound **20** was the only product isolated from the complex tosylation mixture. It originates evidently from the expected tosylate by intramolecular alkylation

at N-3 (similar to the formation of compound **6**) and subsequent N^6-tosylation (Scheme 5).



SCHEME 5

The ultimate approach to the *N*-cyclonucleosides makes use of an appropriate 8-[*N*-(4-hydroxybutyl)-*N*-methylamino]adenine (**23**) as the key compound. This should be then converted to a reactive intermediate capable of *N*-alkylating the heterocyclic base. *N*-Methyl-*N*-[4-(tetrahydropyran-2-yl)-oxybutyl]amine (**21**) was obtained by heating 4-[(2-tetrahydropyran-2-yl)oxy]butyl chloride (**7**) with methylamine in ethanol. Treatment of 8-bromoadenine (**11**) with compound **21** on heating in DMF gave a complex mixture from which some expected 8-substituted intermediate **22** could be isolated in a very low yield. It was further processed to the 4-hydroxybutyl derivative **23**. However, the main product of this reaction is 8-dimethylaminoadenine (**24**) (Scheme 6). Thus, the reactivity of the secondary amine **21** with respect to bromine attached to the purine skeleton is very low, much lower than the reactivity of the DMF solvent.



SCHEME 6

The structures of compounds described in this paper were assigned by means of "attached proton test" and proton-coupled ^{13}C NMR spectra. Characteristic alkylation effects (upfield shift *ca* –8 ppm at C-2 and lowfield shift *ca* 12 ppm at C-8) were observed in the ^{13}C NMR spectrum of compound **14**; the splitting of C-2 doublet (δ 144.54, ^1J(C-2,H-2) = 209.0) in the proton-coupled spectrum by two H-1′ atoms (^3J(C-2,H-1′) = 4.9) evidences its

N^3-alkyl structure; in the N^9-isomer **13**, the splitting occurs at C-8 (δ 126.42). The intramolecular cycle formation in compound **17a** is characterized in the proton-coupled spectrum by doublet of triplets of C-4 (δ 150.72, ^3J(C-4,H-2) = 11.7, ^3J(C-4,H-1′) = 3.9) and by broad multiplet of C-8 (δ 156.94, W = 26 Hz); this multiplet is narrowed (C-8, δ 152.54, W = 19.5 Hz) in compound **19**, due to the absence of ^3J(C-8,H-4′). The intramolecular alkylation at N-3 in compound **20** was confirmed by the observed upfield shifts at C-2 and C-4 (*ca* –10 ppm) and by the multiplicity of carbon signals in the proton-coupled NMR spectrum. The doublet at δ 153.86 corresponds to C-6 (^3J(C-6,H-2) = 10.7), the multiplet at δ 152.59 (W = 15 Hz) to C-8, the doublet of triplets at δ 141.60 to C-2 (^1J(C-2,H-2) = 211.9, ^3J(C-2,H-4′) = 2.9), the pentet at δ 140.51 (^3J(C-4,H-1′) = ^3J(C-4,H-4′) = 3.9) to C-4 and the singlet at δ 122.23 to C-5.

The results obtained in this study demonstrate that the acyclic seven-membered *N*-cyclonucleoside analogues can be effectively prepared by concerted intramolecular reaction of 9-[(4-tosyloxy)butyl] or 9-(4-chlorobutyl) derivatives of 8-bromo- or 8-chloroadenine in the presence of ammonia or primary amines. The seven-membered system is stable both under strongly alkaline and strongly acidic conditions.

EXPERIMENTAL

Methods

Compounds were dried at 13 Pa over phosphorus pentoxide. Melting points were determined on a Kofler block and are uncorrected. TLC on silica gel was performed on Silufol UV 254 plates in the following systems: chloroform–methanol (9 : 1, S1), chloroform–methanol (85 : 15, S2), chloroform–methanol (4 : 1, S3), chloroform–methanol (3 : 7, S4), water–ethanol–acetone–ethyl acetate (1 : 1 : 1 : 4, S5), propan-2-ol–concentrated aqueous ammonia–water (7 : 1 : 2, S6). Preparative loose-layer chromatography was performed with silica gel containing UV indicator (Kavalier Votice, Czech Republic) on plates 40 × 17 × 0.4 cm. Column chromatography was done with silica gel (30 μm) obtained from the same source. Preparative RP-HPLC was performed on a Beckmann Prep 350 apparatus using 300 × 40 mm columns of Separon SGX-RPS 10μ (C18). Paper electrophoresis was performed on Whatman No. 1 paper at 20 V/cm (1 h) in 0.02 M sodium tetraborate. The mobility (E_{Up}) is related to uridylic acid. Deionisation on Dowex 50 was done with 100–150 ml columns of the resin in H^+ form prewashed with water. After application of the mixture, the column was first washed with water until the acidity of the eluate and its UV absorption (monitored by Uvicord 4 701 A, LKB, Sweden at 254 nm) dropped, and then with dilute (1 : 10) aqueous ammonia. The UV-absorbing fraction was evaporated *in vacuo*. ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian UNITY-200 (200 MHz) or Varian UNITY-500 (500 MHz) in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. ^{13}C NMR spectra (δ, ppm) were measured on Varian UNITY-500 (125.7 MHz) and chemical shifts are refer-

enced to the solvent signal ($\delta(CD_3SOCD_3)$ 39.7 ppm). UV absorption spectra were measured on a Beckman DU-65 apparatus. Mass spectra were measured on a ZAB-EQ (VG Analytical, Manchester, U.K.) mass spectrometer. Ionization was performed with FAB technique (ionization Xe, acceleration voltage 8 kV). Samples in methanol were applied to the thioglycerol–glycerol matrix (3 : 1).

Materials

Adenine, butane-1,4-diol, 4-chlorobutan-1-ol, 4-bromobutyl acetate, 4-(dimethylamino)-pyridine, methylamine and dimethylamine solution in ethanol, hydrazine hydrate, cyclopropylamine, propylamine, diphenyl carbonate, bis(4-nitrophenyl) carbonate, 1,1′-carbonyldiimidazole and DBU were purchased from Sigma–Aldrich Prague (Czech Republic); bromine, cesium carbonate, tosyl chloride, dihydropyran and thionyl chloride were products of Fluka (Germany). DMF was distilled *in vacuo* from phosphorus pentoxide and kept over molecular sieves (1A).

Butane-1,4-diyl Ditosylate (**5**)

Butane-1,4-diol (4.5 g, 50 mmol) was added dropwise under stirring to a solution of tosyl chloride (23.3 g, 122.2 mmol) in pyridine (100 ml), the mixture was kept at 0 °C for 3 h and left to stand overnight in a refrigerator. Water (20 ml) was added and the mixture was taken down in vacuum to approximately 2/3 of the original volume. Water (40 ml) was added and the mixture was extracted with ethyl acetate (four 50 ml portions). The organic layer was washed with water (50 ml), then with 1 M HCl until the extract remained acidic and finally with water. The volatiles were then evaporated *in vacuo* and the residue codistilled with toluene. Chromatography on a silica gel column (300 ml) in the system toluene–ethyl acetate followed by crystallization from methanol afforded 13.8 g (69%) of ditosylate **5**, m.p. 68 °C; ref.[20] gives m.p. 65–68 °C (methanol). For $C_{18}H_{22}O_6S_2$ (398.4) calculated: 54.25% C, 5.56% H, 16.09% S; found: 54.42% C, 5.64% H, 15.84% S.

Δ^8-4,5,6,7-Tetrahydro[1,3]diazepino[1,2,3-*cd*]purin-11-amine Tosylate (**6**)

Adenine (2.7 g, 20 mmol) and cesium carbonate (10 mmol) in DMF (70 ml) were heated at 80 °C for 1 h and tosylate **5** (10 g, 25 mmol) was added in one portion. The mixture was stirred at 100 °C under exclusion of moisture. The mixture dissolved and a crystalline material gradually precipitated. After 6 h at 100 °C, the mixture was cooled, the product was filtered off, washed successively with water, acetone and ether, and dried to afford compound **6**. Yield 2.7 g (37%), not melting below 280 °C, $E_{Up} = -0{,}55$. For $C_{16}H_{19}N_5O_3S$ (361.4) calculated: 53.17% C, 5.30% H, 19.38% N, 8.87% S; found: 52.92% C, 5.40% H, 19.33% N, 9.01% S. ^{1}H NMR: 9.20 brs, 1 H and 9.10 brs, 1 H (NH_2); 8.63 s, 1 H and 8.36, 1 H (H-2 and H-8); 7.48 d, 2 H and 7.10 d, 2 H (arom. H); 4.55 t, 2 H and 4.45 t, 2 H, $J(CH_2,CH_2) = 5.6$ (N-CH_2); 2.28 s, 3 H (arom. CH_3); 2.20 m, 2 H and 2.13 m, 2 H (C-CH_2).

4-[(2-Tetrahydropyran-2-yl)oxy]butyl chloride[21] (**7**)

4-Chlorobutan-1-ol (50 ml) in dichloromethane (270 ml) was treated at 0 °C with dihydropyran (65 ml). After the exothermic reaction has subsided, 4.5 M HCl in DMF (1.5 ml) was added and the reaction was kept at 0 °C for 30 min and at room temperature for 2 days.

A saturated $NaHCO_3$ solution (200 ml) was added, the organic phase was separated, the aqueous phase was extracted with chloroform (2 × 100 ml), the combined extracts were washed with water (2 × 50 ml), dried with anhydrous $MgSO_4$ and evaporated. The residue gave on distillation (b.p. 86–87 °C/2 kPa) 86.5 g (89.4%) of compound **7** (*ca* 90% pure by GC). For $C_9H_{17}ClO_2$ (192.7) calculated: 56.10% C, 8.89% H, 18.40% Cl; found: 56.74% C, 8.95% H, 17.66% Cl. ^{1}H NMR: 4.54 m, 1 H (O-CH-O); 3.66 t, 2 H, *J* = 6.6 (CH_2-Cl); 3.72 m and 3.42 m, 2 × 1 H (O-CH_2); 3.64 t and 3.36 t, 2 × 1 H, *J* = 6.5, 6.5, 9.8 (O-CH_2); 1.75 m and 1.63 m, 2 × 2 H and 1.48 m, 4 H (C-CH_2). MS (FAB), *m/z* (rel.%): 193 (20) $[M + H]^+$.

9-[(4-Tetrahydropyranyloxy)butyl]adenine (**8**) and 3-[(4-Tetrahydropyranyloxy)butyl]-adenine (**9**)

A mixture of adenine (6 g, 44.4 mmol) and DBU (7.1 ml) in 70 ml DMF was heated at 100 °C for 30 min and compound **7** (10 ml, 54.7 mmol) was added. The reaction mixture was stirred at 100 °C for 4 h under exclusion of moisture, DMF was evaporated *in vacuo* and codistilled with toluene (two 25 ml portions). The residue in chloroform (200 ml) was extracted with water (50 ml), the organic layer was dried with anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel in a chloroform–ethanol mixture. Yield 7.38 g (57%) of the N^9-isomer **8** and 1.42 g (11%) of the N^3-isomer **9**. Compound **8**, m.p. 58 °C, R_F 0.61 (S2). For $C_{14}H_{21}N_5O_2$ (291.4) calculated: 57.72% C, 7.26% H, 24.04% N; found: 57.61% C, 7.06% H, 23.78% N. ^{1}H NMR: 8.15 s and 8.14, 2 × 1 H (H-2 and H-8); 7.20 brs, 2 H (NH_2); 4.50 m, 1 H (O-CH-O); 4.17 t, 2 H, *J*(1′,2′) = 7.1 (H-1′); 3.69 m, 1 H and 3.62 m, 1 H and 3.39 m, 1 H and 3.33 m, 1 H (O-CH); 1.86 m, 2 H and 1.68 m, 1 H and 1.58 m, 1 H and 1.52–1.40 m, 6 H (C-CH). ^{13}C NMR: 156.17 (C-6); 152.57 (C-2); 149.77 (C-4); 141.05 (C-8); 118.97 (C-5); 98.16 (O-C-O); 61.47 (C-4′); 42.96 (C-1′); 30.45 (C-3′); 26.70 (C-2′); 66.26, 26.57, 25.21 and 19.35 [CH_2(THP)]. MS (FAB), *m/z* (rel.%): 292.2 (65) $[M + H]^+$. Compound **9**, m.p. 154 °C, R_F 0.42 (S2). For $C_{14}H_{21}N_5O_2$ (291.4) calculated: 57.72% C, 7.26% H, 24.04% N; found: 57.44% C, 7.29% H, 23.54% N. ^{1}H NMR: 8.35 s, 1 H (H-8); 7.96 brs, 1 H and 7.82 brs, 1 H (NH_2); 7.75 s, 1 H (H-2); 4.50 m, 1 H (O-CH-O); 4.32 t, 2 H, *J*(1′,2′) = 7.1 (H-1′); 3.69 m, 1 H and 3.61 m, 1 H and 3.38 m, 1 H and 3.33 m, 1 H (O-CH_2); 1.95 m, 2 H and 1.67 m, 1 H and 1.57 m, 1 H and 1.52–1.40 m, 6 H (C-CH_2). ^{13}C NMR: 155.13 (C-6); 152.67 (C-8); 149.88 (C-4); 143.45 (C-2); 120.72 (C-5); 98.15 (O-C-O); 61.45 (C-4′); 43.36 (C-1′); 30.43 (C-3′); 25.98 (C-2′); 66.31, 26.41, 25.19 and 19.34 [CH_2(THP)]. MS (FAB), *m/z* (rel.%): 292.2 (100) $[M + H]^+$.

9-(4-Hydroxybutyl)adenine (**10**)

Compound **8** (7 g, 24.0 mmol) was refluxed under stirring for 30 min in 20% aqueous methanol (450 ml) with Dowex 50 (H^+-cycle) (30 ml). The suspension was filtered, washed successively with methanol and with *ca* 3% methanolic ammonia solution, the combined filtrates were evaporated and the residue was crystallized from ethanol. Yield 4.53 g (91%) of compound **10**. M.p. 198–200 °C, R_F = 0.37 (S5). For $C_9H_{13}N_5O$ (207.2) calculated: 52.16% C, 6.32% H, 33.79% N; found: 51.94% C, 6.29% H, 33.63% N. ^{1}H NMR: 8.145 s, 1 H and 8.14 s, 1 H (H-2 and H-8); 7.23 brs, 2 H (NH_2); 4.46 t, 1 H, *J*(OH,4′) = 4.9 (OH); 4.14 t, 2 H, *J*(1′,2′) = 7.1 (H-1′); 3.39 dt, 2 H, *J*(4′,3′) = 6.6 (H-4′); 1.82 m, 2 H (H-2′); 1.37 m, 2 H (H-3′). MS (FAB), *m/z* (rel.%): 208 (100) $[M + H]^+$.

8-Bromoadenine (**11**)

Bromine (30 ml, 0.59 mol) was cautiously poured onto adenine (10 g, 74 mmol) in 500 ml flask (*CAUTION! Vigorous reaction!*) and the mixture was left to stand 3 h in a stoppered flask. The excess bromine was then left to evaporate in the hood. The residue was stirred in water (≈100 ml), alkalized with concentrated aqueous ammonia to dissolution and the alkaline solution was neutralized by addition of acetic acid. The precipitated crude product was filtered off, washed with water and boiled under stirring with water (250 ml). This suspension was filtered while hot, the precipitate was washed with water, acetone and ether, and dried *in vacuo*. Yield 9.5 g (59.7%) of compound **13**, m.p. >250 °C, R_F 0.40 (S2). For $C_5H_4BrN_5$ (214.0) calculated: 28.06% C, 1.88% H, 37.33% Br, 32.72% N; found: 27.79% C, 1.95% H, 36.68% Br, 32.27% N. ^{1}H NMR: 13.70 br, 1 H (NH); 8.10 s, 1 H (H-2); 7.44 brs, 2 H (NH_2). MS (FAB), *m/z* (rel.%): 215.1 (8) $[M + H]^+$.

8-Bromo-9-(4-hydroxybutyl)adenine (**13**)

Method A: By bromination of 9-(4-hydroxybutyl)adenine. 4-(Hydroxybutyl)adenine (**10**; 10 g, 48.4 mmol) was dissolved by slight heating in water (200 ml), an equal volume of 0.5 M CH_3COONa/acetic acid buffer (pH 4) was added and saturated aqueous bromine (5 ml, 96.6 mmol bromine) solution was added dropwise under stirring. The stirring was continued at room temperature for 6 h, a saturated $NaHSO_3$ solution was added until the discoloration disappeared and the pH of the mixture was set to 6–7 with concentrated NaOH solution. The mixture was evaporated, codistilled with ethanol and the residue was extracted with chloroform in a Soxhlet apparatus for 16 h. The crude extract was purified by silica gel chromatography and crystallized from water. Yield 10 g (72%) of a slightly yellow product **13**, m.p. 208 °C, R_F 0.50 (S2). For $C_9H_{12}BrN_5O$ (286.1) calculated: 37.78% C, 4.34% H, 27.93% Br, 24.48% N; found: 37.43% C, 4.25% H, 27.93% Br, 23.99% N. ^{1}H NMR: 8.13 s, 1 H (H-2); 7.38 brs, 2 H (NH_2); 4.44 t, 2 H, J(OH,H) = 5.1 (OH); 4.13 t, 2 H, J(1′,2′) = 7.3 (H-1′); 3.39 t, 2 H (H-4′); 1.78 m, 2 H and 1.40 m, 2 H (H-3′ and H-2′). ^{13}C NMR: 154.92 (C-6); 152.96 (C-2); 150.93 (C-4); 126.42 (C-8); 119.16 (C-5); 60.29 (C-4′); 43.86 (C-1′); 29.64 (C-3′); 25.91 (C-2′). MS (FAB), *m/z* (rel.%): 288 (90) $[M + H]^+$.

Method B: By alkylation of 8-bromoadenine with 4-bromobutyl acetate. 8-Bromoadenine (**11**; 0.5 g, 2.32 mmol) and potassium carbonate (0.64 g, 4.6 mmol) in DMF (5 ml) was stirred at 135 °C for 30 min. 4-Bromobutyl acetate (0.68 g, 3.50 mmol) was added and the mixture heated at this temperature for another 8 h. The solvent was stripped *in vacuo* and the residue was codistilled with toluene. The crude product was extracted with methanol, the filtrate evaporated *in vacuo* and the residue was separated by loose-layer TLC. The bands were eluted with methanol, evaporated and the residues treated with 0.1 M sodium methanolate in methanol (1 h); after neutralization with Dowex 50, the mixtures were evaporated *in vacuo*. Subsequent crystallization of the products from ethanol gave 0.3 g (44.8%) of N^9-isomer **13** (identical with the product obtained by method *A*) and 0.15 g (22.4%) of the N^3-isomer **14**, m.p. 208 °C, R_F 0.50 (S2), respectively. ^{1}H NMR: 8.40 s, 1 H (H-2); 8.17 brs, 2 H (NH_2); 4.26 t, 2 H, J(1′,2′) = 7.1 (H-1′); 3.40 t, 2 H, J(4′,3′) = 7.4 (H-4′); 1.88 m, 2 H and 1.40 m, 2 H (H-3′ and H-2′). ^{13}C NMR: 153.67 (C-6); 149.52 (C-4); 144.54 (C-2); 138.22 (C-8); 120.90 (C-5); 60.30 (C-4′); 49.60 (C-1′); 29.38 (C-3′); 25.70 (C-2′).

Tosylation of 8-Bromo-9-(4-hydroxybutyl)adenine (**13**)

Crystalline tosyl chloride (18.6 g, 97.6 mmol) was added under stirring to an ice-cool solution of compound **13** (14 g, 48.9 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (100 mg) in pyridine (170 ml), the solution was stirred at 0 °C for 3 h and left to stand overnight in a refrigerator. Water (200 ml) was added and the solution was left in refrigerator for additional 3 h. The precipitate was filtered off, washed with ether and dried *in vacuo*. Yield 2.37 g (11%) of 8-bromo-9-[4-(tosyloxy)butyl]adenine (**15**), m.p. 149 °C, R_F 0.81 (S2). For $C_{16}H_{19}BrN_5O_3S$ (441.2) calculated: 43.65% C, 4.12% H, 18.15% Br, 15.91% N, 7.28% S; found: 42.02% C, 4.06% H, 18.65% Br, 15.62% N, 7.42% S. ^{1}H NMR: 8.10 s, 1 H (H-2); 7.74 d and 7.44 d, 2 × 2 H (arom. H); 7.39 brs, 2 H (NH_2); 4.06 t, 2 H, J = 7.0 and 4.04 t, 2 H, J = 6.3 (H-1′and H-4′); 2.40 s, 3 H (CH_3-arom.); 1.71 m and 1.55 m, 2 × 2 H (H-2′ and H-3′). MS (FAB), *m/z* (rel.%): 441.9 (100) $[M + H]^+$.

The filtrate was evaporated and the residue codistilled with water. The residue in water (100 ml) was repeatedly extracted with chloroform and ethyl acetate. The combined extracts were dried with anhydrous $MgSO_4$, filtered, and the solvents were taken down *in vacuo*. The residue afforded 8-bromo-9-(4-chlorobutyl)-6-(tosylamino)purine (**16**) (0.24 g; 15.1%), m.p. 176 °C, R_F 0.96 (S2). For $C_{16}H_{17}BrClN_5O_2S$ (458.8) calculated: 41.89% C, 3.73% H, 17.42% Br, 7.73% Cl, 15.27% N, 6.99% S; found: 41.81% C, 3.89% H, 18.20% Br, 7.92% Cl, 14.93% N, 6.72% S. ^{1}H NMR: 12.80 br, 1 H (NH); 8.35 brs, 1 H (H-2); 7.86 m, 2 H and 7.37 d, 2 H (arom. H); 4.19 t, 2 H, J(1′,2′) = 6.8 (H-1′); 3.64 t, 2 H, J(4′,3′) = 6.3 (H-4′); 2.36 s, 3 H (CH_3-arom.); 1.87 m, 2 H and 1.70 m, 2 H (H-2′ and H-3′). MS (FAB), *m/z* (rel.%): 460 (30) $[M + H]^+$.

8-Chloro-9-(4-chlorobutyl)adenine (**18**)

Compound **13** (2.15 g, 7.5 mmol) in chloroform (25 ml) was treated under stirring with DMF (0.25 ml) and $SOCl_2$ (13 ml, 21.2 g, 0.18 mol). The resulting solution was refluxed for 3 h, taken down *in vacuo*, the residue was dissolved in methanol, neutralized with aqueous ammonia and evaporated. The residue was triturated with ether, filtered off, dried (5.2 g) and used without purification for further reactions with amines. MS (FAB), *m/z* (rel.%): 260 (100) [M + H] [$C_9H_{12}{}^{35}Cl_2N_5$ (260.1)]; 170 (25) [BH].

6-Methyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17a**)

Method A: Compound **15** (1.4 g, 3.17 mmol) in 30% ethanolic methylamine (50 ml) was heated in an autoclave at 100 °C for 2 days. The reaction mixture was evaporated, the residue was dissolved in chloroform and extracted with water. The chloroform layer was dried with anhydrous $MgSO_4$, filtered and evaporated. Crystallization from ethanol afforded the title compound **17a** (0.67 g; 97%), m.p. 262–263 °C, R_F 0.39 (S2). For $C_{10}H_{14}N_6$ (218.3) calculated: 55.03% C, 6.47% H, 38.50% N; found: 55.23% C, 6.33% H, 38.80 N. ^{1}H NMR: 7.98 s, 1 H (H-2); 6.63 brs, 2 H (NH_2); 4.01 m and 3.13 m, 2 × 2 H (H-1′ and H-4′); 3.01 s, 3 H (N-CH_3); 1.89 m, 2 H and 1.77 m, 2 H (H-2′ and H-3′). ^{13}C NMR (APT): 156.94 (C-8); 153.32 (C-6); 150.72 (C-4); 149.91 (C-2); 116.445 (C-5); 53.96 (C-4′); 42.76 (C-1′); 41.215 (CH_3); 29.47 and 26.34 (C-2′ and C-3′). UV (methanol), λ_{max} (ε_{max}): 277.5 (18 305). MS (FAB), *m/z* (rel.%): 219.1 (100) $[M + H]^+$.

Method B. The dried crude 4-chlorobutyl derivative **18** (1.5 g) was heated in 30% ethanolic methylamine (50 ml) in an autoclave at 100 °C for 10 h. The solution was evapo-

rated and the residue was deionized on Dowex 50 (H^+-form) (100 ml) and the ammonia eluate was evaporated *in vacuo*. The residue, on purification by silica gel column chromatography in chloroform–methanol, gave compound **17a**. Yield 0.22 g (46.5%).

6-Cyclopropyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17b**)

A mixture of 8-bromo-9-[4-(tosyloxy)butyl]adenine (**15**; 0.250 g, 0.57 mmol), ethanol (20 ml) and cyclopropylamine (0.5 ml, 7.1 mmol) was heated in an autoclave at 100 °C for 2 days. After evaporation and codistillation of the residue with ethanol, the crude product was purified on silica gel column (100 ml) in the system chloroform–methanol. Yield 0.087 g (63%) of compound **17b**, m.p. 250 °C, R_F 0.58 (S4). For $C_{12}H_{16}N_6$ (244.3) calculated: 59.00% C, 6.60% H, 34.40% N; found: 47.14% C, 6.05% H, 22.98% N. ^{1}H NMR: 7.99 s, 1 H (H-2); 6.70 brs, 2 H (NH_2); 3.94 m, 2 H (H-1′); 3.24 m, 2 H (H-4′); 2.86 m, 1 H (N-CH); 1.80 m and 1.70 m, 2 × 2 H (H-2′ and H-3′); 0. 72 m and 0.48 m, 2 × 2 H (C-CH_2). MS (FAB), *m/z* (rel.%): 245.18 (100) $[M + H]^+$.

6-Propyl-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17c**)

The dried crude 4-chlorobutyl derivative **18** (0.4 g) in an ethanol–propylamine mixture (1 : 1, 40 ml) was heated in an autoclave at 100 °C for 2 days, evaporated and codistilled with ethanol. After desalting on Dowex 50 (H^+-form), purification of the residue by silica gel column chromatography in chloroform–methanol and crystallization from chloroform, compound **17c** (41 mg, 28.8%) was isolated. M.p. 181–182 °C, R_F 0.54 (S2). For $C_{12}H_{18}N_6$ (246.3) calculated: 58.52% C, 7.37% H, 34.12% N; found: 55.83% C, 7.33% H, 32.37% N. ^{1}H NMR: 7.96 s, 1 H (H-2); 6.54 brs, 2 H (NH_2); 4.01 m, 2 H (H-1′); 3.40 t, 2 H, J(1″,2″) = 7.3 (H-1″); 3.22 m, 2 H (H-4′); 1.83 m, 4 H (H-2′ and H-3′); 1.65 sext, 2 H, J(2″,1″) = J(2″,3″) = 7.3 (H-2″); 0.90 t, 3 H, J(3″,2″) = 7.3 (H-3″). MS (FAB), *m/z* (rel.%): 247.1 (100) $[M + H]^+$.

6-Amino-7,8,9,10-tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purine-4,6-diamine (**17d**)

Hydrazine hydrate (3 ml, 103 mmol; 98%) was added to a suspension of 8-bromo-9-[4-(tosyloxy)butyl]adenine (**15**; 300 mg, 0.68 mmol) in ethanol (15 ml) and the mixture was stirred at room temperature for 3 days until the starting compound disappeared (the reaction course was followed by TLC in S5). The heterogeneous reaction mixture was evaporated to dryness and excess hydrazine was removed by codistillation with ethanol. The resulting mixture was desalted on Dowex 50 (H^+-cycle) and the product purified by preparative reverse phase chromatography. Yield of compound **17d**, 52 mg (35%; after crystallization from ethanol). M.p. 242 °C, R_F 0.28 (S1). For $C_9H_{13}N_7 \cdot 2H_2O$ (255.3) calculated: 42.35% C, 6.71% H, 38.41% N; found: 42.54% C, 6.31% H, 37.64% N. ^{1}H NMR: 8.01 s, 1 H (H-2); 6.76 brs and 4.92 brs, 2 × 2 H (NH_2); 4.00 m, 2 H (H-1′); 3.29 m, 2 H (H-4′); 1.91 m and 1.72 m, 2 × 2 H (H-2′ and H-3′). MS (FAB), *m/z* (rel.%): 220.1 (100) $[M + H]^+$.

7,8,9,10-Tetrahydro-6*H*-[1,3]diazepino[1,2-*e*]purin-4-amine (**17e**)

The dried crude 4-chlorobutyl derivative **18** (2.5 g) was heated at 120 °C with saturated methanolic ammonia (50 ml) in an autoclave for 3 days. After evaporation and codistillation with ethanol the crude reaction product was desalted on Dowex 50 (H^+-form), adsorbed from methanolic solution on silica gel and purified by column chromatography on

the same sorbent in chloroform–methanol. Crystallization from methanol afforded compound **17e** (0.41 g; 55.6%), m.p. 237 °C, R_F 0.27 (S1), 0.47 (S2). For $C_9H_{12}N_6$ (204.2) calculated: 52.93% C, 5.92% H, 41.15% N; found: 52.50% C, 5.76% H, 40.85% N. ^{1}H NMR: 7.96 s, 1 H (H-2); 6.61 t, 1 H, *J*(NH,4′) = 3.4 (NH); 6.53 brs, 2 H (NH_2); 3.98 brt, 2 H, *J*(1′,2′) = 5.0 (H-1′); 3.06 brtd, 2 H, *J*(4′,NH) = 3.4, *J*(4′,3′) = 5.0 (H-4′); 1.80 m, 4 H (H-2′ and H-3′). MS (FAB), *m/z* (rel.%): 205.2 (100) $[M + H]^+$.

Stability of Compound **17e** in Acid and Alkali

The stability was studied in 0.1 and 1 M solutions of HCl or NaOH, respectively. The mixtures were kept at room temperature overnight and/or heated at 90 °C. Samples were taken after 1, 4 and 20 h and analyzed by TLC in the system S2. No formation of ring-opening products was observed under any of the above conditions.

9-(4-Hydroxybutyl)-8-(methylamino)adenine (**19**)

8-Bromo-9-(4-hydroxybutyl)adenine (**13**) (1.0 g, 3.5 mmol) in 30% methylamine solution in ethanol (50 ml) was heated at 100 °C in an autoclave for 3 days. The mixture was evaporated, the residue deionized on a column (50 ml) with Dowex 50 (H^+-form) and finally purified by column (150 ml) chromatography on siliga gel in chloroform–methanol. Yield 0.57 g (69%) of compound **19**, m.p. 205 °C, R_F 0.30 (S3). For $C_{10}H_{16}N_6O$ (236.3) calculated: 50.83% C, 6.83% H, 35.57% N; found: 50.13% C, 6.94% H, 34.40% N. ^{1}H NMR: 7.89 s, 1 H (H-2); 6.66 q, 1 H, *J*(NH,CH_3) = 4.6 (NH); 6.36 brs, 2 H (NH_2); 4.43 t, 1 H, *J*(OH,4′) = 5.1 (OH); 3.91 t, 2 H, *J*(1′,2′) = 7.2 (H-1′); 3.38 td, 2 H, *J*(4′,OH) = 5.1, *J*(4′,3′) = 6.5 (H-4′); 2.90 d, 3 H, *J*(CH_3,NH) = 4.6 (N-CH_3); 1.64 m, 2 H and 1.38 m, 2 H (H-2′ and H-3′). ^{13}C NMR (APT): 152.54 (C-8); 152.08 (C-6); 150.51 (C-4); 148.81 (C-2); 116.99 (C-5); 60.55 (C-4′); 40.32 (C-1′); 29.72 (C-2′); 29.27 (CH_3); 25.40 (C-3′). MS (FAB), *m/z* (rel.%): 237.1 (100) $[M + H]^+$.

Attempts on Cyclization of 9-(4-Hydroxybutyl)-8-(methylamino)adenine (**19**) (*cf.* ref.[22])

a) *With diphenyl carbonate*: A mixture of compound **19** (23.6 mg, 0.1 mmol), diphenyl carbonate (32.1 mg, 0.15 mmol) and triethylamine (90.6 µl, 65.8 mg, 0.65 mmol) in DMF (1.5 ml) was stirred at 135 °C for 24 h. TLC in S3 did not detect any change of compound **19** under these conditions.

b) *With bis(4-nitrophenyl) carbonate and triethylamine*: A mixture of compound **19** (23.6 mg, 0.1 mmol), bis(4-nitrophenyl) carbonate (45.6 mg, 0.15 mmol) and triethylamine (83.6 µl, 60.7 mg, 0.60 mmol) in DMF (1.5 ml) was stirred at 135 °C for 24 h. TLC in S3 detected 4′-*O*-(4-nitrophenyl) ester (giving a yellow spot in ammonia vapour); no formation of compound **17a** was observed.

c) *With bis(4-nitrophenyl) carbonate and DBU*: A mixture of compound **19** (23.6 mg, 0.1 mmol), bis(4-nitrophenyl) carbonate (45.6 mg, 0.15 mmol) and DBU (0.60 mmol) in DMF (1.5 ml) was stirred at 135 °C for 16 h. TLC in S3 did not detect formation of compound **17a**. Minor formation of a 4′-*O*-(4-nitrophenyl) ester (giving a yellow spot in ammonia vapour) was observed by TLC analysis. Major part of compound **19** remained unchanged.

d) *With 1,1′-carbonyldiimidazole*: A mixture of compound **19** (23.6 mg, 0.1 mmol), 1,1-carbonyldiimidazole (24.3 mg, 0.15 mmol) in DMF (0.6 ml) was stirred at 135 °C for 20 h. TLC in S3 did not detect formation of compound **17a**, nor other change of compound **19**.

N-Methyl-11-(tosylimino)-4,5,6,7-tetrahydro-11*H*-[1,3]diazepino[1,2,3-*cd*]purin-2-amine (**20**)

Tosyl chloride (0.81 g, 4.23 mmol) was added in one portion under stirring at 0 °C to a solution of compound **19** (0.5 g, 2.12 mmol) and 4-(dimethylamino)pyridine (26 mg, 0.212 mmol) in pyridine (20 ml). The mixture was stirred at 0 °C for additional 3 h and left overnight in a refrigerator. Water (20 ml) was then added, the reaction mixture was taken down nearly to dryness *in vacuo* and codistilled with toluene (3 portions). The residue was deionized on a column (100 ml) of Dowex 50 (H^+-form) and then purified by preparative HPLC in water to afford white crystalline compound **20** (0.095 g; 12%), m.p. >250 °C, R_F 0.64 (S6). For $C_{17}H_{20}N_6O_2S{\cdot}2H_2O$ (408.5) calculated: 49.99% C, 5.92% H, 20,57% N, 7.85% S; found: 49.44% C, 5.92% H, 20.85% N, 8.12% S. ^{1}H NMR: 8.05 s, 1 H (H-2); 7.72 d, 2 H and 7.21 d, 2 H (arom. H); 6.95 brq, 1 H, J(NH,CH_3) = 4.5 (NH); 4.35 m, 2 H (H-1′); 4.01 m, 2 H (H-4′); 2.87 d, 3 H, J(CH_3,NH) = 4.5 (N-CH_3); 2.31 s, 3 H (CH_3-Ts); 2.09 m and 2.03 m, 2 × 2 H (H-2′ and H-3′). ^{13}C NMR (APT): 153.86 (C-6); 152.59 (C-8); 142.86 (C-arom.); 141.595 (C-2); 140.51 (C-4); 140.13, 128.43 and 127.09 (C-arom.); 122.23 (C-5); 51.58 (C-4′); 44.19 (C-1′); 29.41 (N-CH_3); 25.32 and 25.24 (C-2′ and C-3′); 21.10 (CH_3). UV (methanol), λ_{max} (ε_{max}): 319.5 (16 028). MS (FAB), *m/z* (rel.%): 373.2 (100) $[M + H]^+$.

N-Methyl-*N*-[4-(tetrahydropyran-2-yloxy)butyl]amine (**21**)

Compound **7** (25 g, 0.13 mol) in ethanolic methylamine solution (8 M, 70 ml, 0.56 mol) was heated in an autoclave at 100°C for 6 h. The mixture was cooled to 0 °C, filtered and washed with ether; the filtrate was evaporated *in vacuo*. Triethylamine (1 ml) was added to the crude residue and distilled *in vacuo* to afford 19.6 g (80.8%) of colourless **21**, b.p. 86–90 °C/20 Pa. ^{1}H NMR: 4.51 m, 1 H (O-CH-O); 3.72 m and 3.41 m, 2 × 1 H (OCH_2); 3.60 br, 1 H (NH); 3.60 dt and 3.31 dt, 2 × 1 H, J = 6.5, 6.5, 9.6 (O-CH_2); 2.43 t, 2 H, J = 6.9 (N-CH_2); 2.24 s, 3 H (N-CH_3); 1.70 m and 1.58 m, 2 × 1 H and 1.55–1.40 m, 6 H (C-CH_2). MS (FAB), *m/z* (rel.%): 188 (100) $[M + H]^+$.

Reaction of 8-Bromoadenine (**11**) with Compound **21**

8-Bromoadenine (**11**; 1 g, 4.67 mmol) was dissolved by heating in DMF (25 ml) at 110 °C and compound **21** (2.174 g, 11.68 mmol) was added. The mixture was stirred at 125 °C for 2 days until the starting material disappeared and then stripped *in vacuo*. The residue was codistilled with toluene (2 × 25 ml). Chromatography on loose-layer of silica gel in methanol–chloroform (1 : 3) system gave two fractions which were further purified on silica gel columns in chloroform–methanol. The less polar, orange colored oil gave by precipitation with ether from a minimum of ethanol 284 mg (19%) of amorphous 8-[*N*-methyl-*N*-(4-tetrahydropyranyloxy)butylamino]adenine (**22**), R_F 0.93 (S2). ^{1}H NMR: 8.12 s, 1 H (H-2); 6.92 brs, 2 H (NH_2); 4.53 dd, 1 H, J = 2.8 and 4.6 (O-CH-O); 3.71 m and 3.40 m, 2 × 1 H (O-CH_2); 3.64 dt and 3.36 dt, 2 × 1 H, J = 6.5 and 6.5 and 9.8 (O-CH_2); 3.40 t, 2 H, J = 7.1 and 7.1 (N-CH_2); 3.07 s, 3 H (N-CH_3); 1.73–1.35 m, 8 H (C-CH_2). MS (FAB), *m/z* (rel.%): 321.4 (40) $[M + H]^+$, 237.3 (100) $[M - THP + H]^+$. HR MS (FAB) for $C_{15}H_{25}N_6O_2$ (MH) calculated: 321.2039, found: 321.1990.

On passing of an aqueous solution of compound **22** (190 mg, 593 μmol) through a Dowex 50 column (H^+-form, 20 ml) and evaporation of the UV-absorbing eluate gave 8-[*N*-methyl-*N*-(4-hydroxybutylamino)adenine] (**23**; 130 mg; 93%), m.p. 191–192 °C, R_F 0.64 (S2). For $C_{10}H_{16}N_6O{\cdot}H_2O$ (254.3) calculated: 47.23% C, 7.13% H, 33.03% N; found:

46.99% C, 7.12% H, 30.70% N. ^{1}H NMR: 11.80 br, 1 H (NH); 7.92 s, 1 H (H-2); 6.21 brs, 2 H (NH_2); 4.45 brs, 1 H (OH); 3.45 t, 2 H and 3.43 t, 2 H, J = 6.4 (N-CH_2 and O-CH_2); 3.02 s, 3 H (N-CH_3); 1.59 m and 1.42 m, 2 × 2 H (C-CH_2). MS (FAB), *m/z* (rel.%): 237.3 (100) $[M + H]^+$.

Purification of the main reaction product obtained from loose-layer plate chromatography on silica gel column followed by crystallization from methanol gave 8-(*N*,*N*-dimethylamino)-adenine (**24**), 520 mg (62.6%), m.p. >250 °C, R_F 0.80 (S2). For $C_7H_{10}N_6$ (178.2) calculated: 47.18% C, 5.66% H, 47.16% N; found: 46.19% C, 5.67% H, 45.80% N. ^{1}H NMR: 12.0 br, 1 H (NH); 8.14 s, 1 H (H-2); 6.98 brs, 2 H (NH_2); 3.09 s, 6 H (2 × CH_3). MS (FAB), *m/z* (rel.%): 179.5 (100) $[M + H]^+$.

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