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Synthesis of Carbocyclic Adenosine Analogs: 9-(2′,3′,4′,5′-Tetrahydroxycyclopentyl)adenines[1)]

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The synthesis of five 9-(2′,3′,4′,5′-tetrahydroxycyclopentyl)adenines with 1,2,4/3,5- (**2a**), 1,2,3/4,5- (**2b**), 1,4,5/2,3- (**2c**), 1,4/2,3,5- (**2e**) and all-*cis* configuration (**2d**) are described, by amination of 4-amino-5-nitro-6-chloropyrimidine with the respective 5-aminocyclopentanetetrols (**3a**—**e**), followed by reduction of the nitro group and cyclization with formamide.

Preliminary antifungal properties are reported.

Nucleoside analogs, in which the ribofuranosyl moiety is replaced by the hydrolytically and enzymatically more stable cyclopentane ring, have attained much interest in the past decade[1,3–8)], its main stimulus stemming from their possible function as antimetabolites or nucleoside substitutes in nucleic acid metabolism. This allurement was enhanced by the isolation of aristeromycin (**1**), with promising antibacterial and antifungal properties, from natural sources,[5)] which, nevertheless, was preceded by a chemical synthesis of the DL-form of **1**.[4)]

Since it has been demonstrated in the case of a carbocyclic puromycin analog, that the lack of the ring-*O*-function and the hydroxymethyl group in the ribofuranosyl moiety are not detrimental for bioactivity,[8)] it appeared of interest to biologically evaluate adenosine analogs of type **2**, in which the ribofuranose portion is replaced by a tetrahydroxycyclopentane system.

The present report describes the synthesis of five of these 9-(2′,3′,4′,5′-tetrahydroxycyclopentyl)adenines (**2a**—**e**), *i. e.* products that—with respect to the C–2′ and C–3′ arrangement of the OH–groups in adenosine–resemble the *ribo*-configuration (**2a** and **2b**), as well as the *xylo*-(**2a**, **2e**), *lyxo*- (**2d**) and *arabino*-forms (**2b**, **2c**), the latter being conceivably of main interest in view of the antiviral activity of 9-(β-D-arabinofura-

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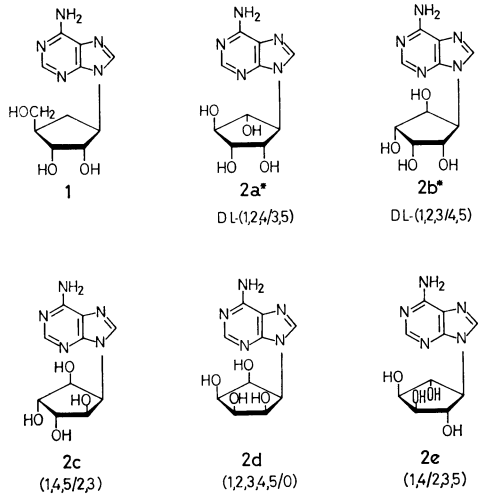

Scheme 1.

*) Formulae **2a** and **2b** depict only one enantiomer of the respective racemate.

nosyl)adenine.[9]

Since methods are available for the stepwise *de novo* construction of the purine base from a cycloalkylamino function,[1,6-8] the principal problem was the preparation of the respective 5-aminocyclopentanetetrols. All ten theoretically possible isomers being known now in the form of their pentaacetyl derivatives,[10] the more readily accessible compounds **3a**—**e**[10-12] were subjected to complete deacetylation with hydrochloric acid to afford the respective aminotetrols **4a**—**e** (Table 1). By condensation with 4-amino-5-nitro-6-chloropyrimidine, they were converted into the corresponding 6-tetrahydroxycyclopentylamino derivatives **5a**—**e**, each obtained in crystalline form and quite acceptable yields (Table 2). The next step, reduction of the nitro group, was carried out by using zinc dust as the reductant in boiling water, affording the crude

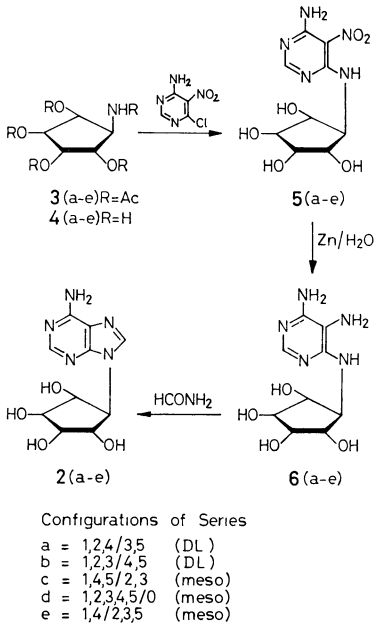

Table 1. Aminotetrols, **4a**—**e**

Compd.	Mp (°C)	Yield (%) of crude product	Anal (%) C 40.26	H 7.43	N 9.39[a]
4a	185—186 (dec)	89	40.51	7.19	9.19
4b	sirup	95	—	—	—
4c	114—118	54	40.24	7.29	9.27
4d	sirup	93	—	—	—
4e	159—161	77	40.59	7.25	9.38

a) Calcd for $C_5H_{11}NO_4$

Table 2. Tetrahydroxycyclopentylamino derivatives, **5a**—**e**

Compd.	Mp (°C) (dec)	Yield (%) of crude product	Anal (%) C 37.63	H 4.56	N 24.20[a]
5a	266—271	61	37.73	4.42	24.20
5b	247—248	94	37.89	4.41	24.45
5c	263—264	77	37.56	4.61	24.01
5d	240—243	81	37.76	4.45	24.47
5e	250—253	80	37.60	4.31	24.75

a) Calcd for $C_9H_{13}N_5O_6$

Table 3. Tetrahydroxycyclopentyladenines, **2a**—**e**

Compd.	Configuration	Mp (°C)	Yield (%)	Anal (%) C 44.94	H 4.90	N 26.21[a]	λ_{max} in nm ($\varepsilon \times 10^3$) pH 1 (0.1M HCl)	pH 7 (H_2O)	pH 13 (0.5% NaOH)
2a	1,2,4/3,5	268—270 (dec)	39	45.01	4.85	26.10	259 (23)	261 (21)	261 (19)
2b	1,2,3/4,5	263—264 (dec)	36	44.70	4.71	25.88	259 (9)	260 (17)	263 (16)
2c	1,4,5/2,3	330	30	45.02	4.69	25.98	260 (7)	260 (7)	260 (11)
2d	1,2,3,4,5/0	263—267 (dec)	11	45.10	4.86	26.00	261 (12)	260 (14)	260 (14)
2e	1,4/2,3,5	270—275 (dec)	22	45.24	4.84	25.96	259 (15)	261 (15)	261 (15)

a) Calcd for $C_{10}H_{13}N_5O_4$

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triaminopyrimidines **6a—e** in yields above 70%. Without further purification, they were cyclized by refluxing in formamide to give the title compounds, adenine analogs **2a—e** (Table 3), featuring the UV absorption characteristics at pH 1, 7 and 13, required for 9-substituted adenine derivatives.[13]

The antiviral properties of compounds **2a—e** are being evaluated. With respect to antifungal activity, **2e** showed an inhibition value of 34% against *piricularia oryzae* (strain Kita No. 373), whilst the pentahydroxycyclohexyl-adenines of *scyllo* and *myo*-2 configuration[1] exhibited values of 30 and 41% respectively, in this systems.

Experimental[14]

Melting points were determined in capillary tubes and uncorrected. UV spectral measurements were effected with a Hitachi EPS-2 instrument. Since preparative procedures employed varied only slightly within the different stereoisomers (a—e series, respectively), general procedures are given exclusively.

*5-Amino-1,2,3,4-cyclopentanetetrols (**4a—e**) by Deacetylation of Their Pentaacetates.* The respective tetra-*O*-acetyl-5-acetamido-1,2,3,4-cyclopentanetetrol (**3a**,[10] **3b**,[10] **3c**,[11] **3d**[11] and **3e**,[12] 1.0—1.3 g portions) was refluxed in 6 M hydrochloric acid (10 ml) for 1.5—2.0 h and subsequently evaporated *in vacuo*. The residue was taken up in water and triturated with Amberlite IRA-400 for removal of chloride ions. Charcoal treatment and evaporation to dryness yielded a crystalline residue in the case of **4a**, **4c** and **4e**, which was filtered with ethanol to give the crude products, that were directly used for the ensuing reaction. For analytical samples, small amounts were recrystallized from ethanol giving the data in Table 1. The aminotetrols **4b** and **4d** resisted crystallization from the usual solvents. Their sirups were used for further reactions.

*4-Amino-5-nitro-6-(2′,3′,4′,5′-tetrahydroxycyclopentyl)aminopyrimidines (**5a—e**).* The crude aminotetrols (**4a—e**), as obtained above (500 mg portions), and 4-amino-5-nitro-6-chloropyrimidine[15] (590 mg, 1.05 mol) were refluxed for 8 h in 2-menthoxyethanol (50 ml) containing 3 ml of triethylamine. On allowing the reaction mixture to cool to ambient temperature, crystallization occurred in the case of **5a**, **5d** and **5e**. The crystals were filtered off to give the crude products used for further experiments. In the cases (**5b** and **5c**), the reaction mixture was evaporated *in vacuo*, followed by crystallization of the residue with a small amount of water (**5b**) or by extraction with ethyl acetate (**5c**), to give the crude products. Small samples of each were recrystallized from water to give the data in Table 2.

*4,5-Diamino-6-(2′,3′,4′,5′-tetrahydroxycyclopentyl)aminopyrimidines (**6a—e**).* The respective nitropyrimidines **5a—e**, as obtained above (600—700 mg portions), were added to a boiling suspension of 15 g of zinc powder in 150 ml of water with vigorous stirring, and the heating was continued for 8 h. The reaction mixture was filtered whilst still hot. On cooling to ambient temperature, crystallization occurred in all cases except **6b**, which required prior concentration to a small volume. Filtration and drying *in vacuo* gave the crude products, used for the subsequent cyclization, as pale yellow crystals except for **6d**, obtained as an amorphous solid; **6a** (mp 255—258 °C, dec; 85%), **6b** (mp 181—187 °C, dec; 72%), **6c** (mp 151—155 °C; 89%), **6d** (mp 200—210 °C, dec; 98%) and **6e** (mp 260—265 °C, dec; 74%).

*9-(2′,3′,4′,5′-Tetrahydroxycyclopentyl)adenines (**2a—e**).* The respective triaminopyrimidines **6a—e** (400—500 mg portions) were refluxed in formamide (10—20 ml) for 30—60 min, whereafter the mixture was taken to dryness *in vacuo*. The residue was triturated with water or ethanol to give the crude product, which was recrystallized from water, involving charcoal treatment, to give the analytically pure products of Table 3.

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