Table I. Monoamine Oxidase Inhibitory Activity of Cyclopropyltryptamines (Tryptamine as a Substrate)

Compd	% inhibn at given concn, mol/l. 10^{-4}	10^{-5}	10^{-6}	10^{-7}
3a	100	93	81	67
3a[a]	100	93	74	56
3b	92	68	32	
3c	81			
5	5			
Pargyline	100	81	65	41

[a]Tyramine as the substrate. All bioassays were done at least twice. Values given are averages with no more than ±3% variation.

min at 0°, the yellow solid which formed was filtered and a suspension of this solid in 100 ml of CH_2Cl_2 was added to a cold solution of 30 g (0.202 mol) of *N*-benzylcyclopropylamine[7] and 18 g (0.18 mol) of Et_3N. After stirring 30 min at 25°, the solution was extracted with dilute HCl and then dilute Na_2CO_3 and concentrated to get 41.5 g (77%) of the amide 1a, mp 158–160°. *Anal.* ($C_{20}H_{18}N_2O_2$) C, H, N.

By the same procedure 5-methoxyindole was converted into **1b**, mp 165–167°, in 78% yield. *Anal.* ($C_{21}H_{20}N_2O_3$) C, H, N.

7-Methoxyindole[8] was converted into 1c, mp 150–152°, in 90% yield. *Anal.* ($C_{21}H_{20}N_2O_3$) C, H, N.

Indole and cyclopropylmethylamine[9] were converted into **4**, mp 186–187°, in 59% yield. *Anal.* ($C_{14}H_{14}N_2O_2$) C, H, N.

***N*-Benzyl-*N*-cyclopropyltryptamine Hydrochloride (2a).** Amide 1a (8.0 g, 25.2 mmol) in 125 ml of tetrahydrofuran was treated with 7.0 g (0.184 mol) of $LiAlH_4$ and refluxed 4 hr. The excess $LiAlH_4$ was decomposed with EtOAc and the mixture worked up with 8 ml of H_2O and 15 ml of 15% NaOH solution. The base was acidified with HCl in *i*-PrOH to give **2a** · HCl salt: mp 200–201°; 6.20 g (76%). *Anal.* ($C_{20}H_{22}N_2$ · HCl) C, H, N.

Synthesized by the same procedure were **2b**, mp 190–192°, in 48% yield [*Anal.* ($C_{14}H_{18}N_2O$ · HCl) C, H, N]; **2c**, mp 203–205°, in 82% yield [*Anal.* ($C_{14}H_{18}N_2O$ · HCl) C, H, N]; and **4**, mp 177–178° (note: EtOAc not used in work-up), in 54% yield [*Anal.* ($C_{14}H_{18}N_2$ · HCl) C, H, N].

***N*-Cyclopropyltryptamine (3a).** Compound **2a** (19.6 g, 62.5 mmol) was dissolved in 150 ml of H_2O, 150 ml of EtOH, and 500 ml of MeOH and hydrogenated with 4.0 g of 5% Pd/C catalyst. After uptake was complete, the catalyst was filtered, the solution concentrated, and the residue crystallized from *i*-PrOH to give 11.5 g (82% yield) of **3a**, mp 180–182°. *Anal.* ($C_{13}H_{16}N_2$ · HCl) C, H, N.

Synthesized by the same procedure were **3b**, mp 173–175°, in 82% yield [*Anal.* ($C_{14}H_{18}N_2O$ · HCl) C, H, N] and 3c, mp 208–210°, in 90% yield [*Anal.* ($C_{14}H_{18}N_2O$ · HCl) C, H, N].

Pharmacology. MAO inhibitory activity was determined with MAO from mouse brains by the method of Wurtman and Axlerod.[11]

5-Hydroxytryptophan Potentiation. Three mice were first pretreated with pargyline (40 mg/kg ip), followed by the drug (oral), and then challenged with 5-HTP 4 hr later. Effects observed are tremors, head movements, abducted limbs, and irritability.

Acknowledgments. The microanalyses were done by Ms. J. Hood, nmr spectra under the direction of Dr. R. Egan, and ir spectra under Mr. W. Washburn. Pharmacological testing was done by Mr. F. Will and Ms. Fely Alix.

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Synthesis of 8-(3′-Deoxy-α-D-*threo*-pentofuranosyl)adenine and 9-(3′-Deoxy-α-D-*threo*-pentofuranosyl)adenine†

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3-Deoxy-2,5-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosyl bromide (1) reacted with mercuric cyanide to give 2,5-anhydro-4-deoxy-D-*lyxo*-hexononitrile (2) which upon acid hydrolysis of the CN group gave acid 3. Saponification of the protecting groups gave 2,5-anhydro-4-deoxy-D-*lyxo*-hexonic acid (4) which reacted with 4,5,6-triaminopyrimidine forming an amide (5) that was pyrolized to give 8-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (6). Reaction of bromide 1 with 6-(benzamido)chloromercuriopurine followed by saponification yielded 9-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (8). 8-(β-D-Ribofuranosyl)adenine, 8-(β-D-arabinofuranosyl)adenine, and 8-(3′-deoxy-β-D-*erythro*-pentofuranosyl)adenine, as well as compound 6, showed no antimalarial activity.

The antibiotic, cordycepin (3′-deoxyadenosine), which has shown some antiplasmodial activity, is deactivated by hydrolases and by adenosine deaminase.[1] In an attempt to overcome the deactivation by hydrolases, we synthesized 8-(3-deoxy-β-D-*erythro*-pentofuranosyl)adenine[2] and 8-(β-D-arabinofuranosyl)adenine,[3] as well as various 8-hydroxyalkyladenines[4] in which the hydrolyzable *N*-glycosidic bond was replaced by a more stable C–C bond.

In this paper we describe the synthesis of 8-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (6) and 9-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (8) and discuss some preliminary screening results of the antiplasmodial activity of various 8-substituted adenine C-nucleosides.

The starting material for the synthesis of 8-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (6) and 9-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (8) was 3-deoxy-2,5-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosyl bromide (1)[5]

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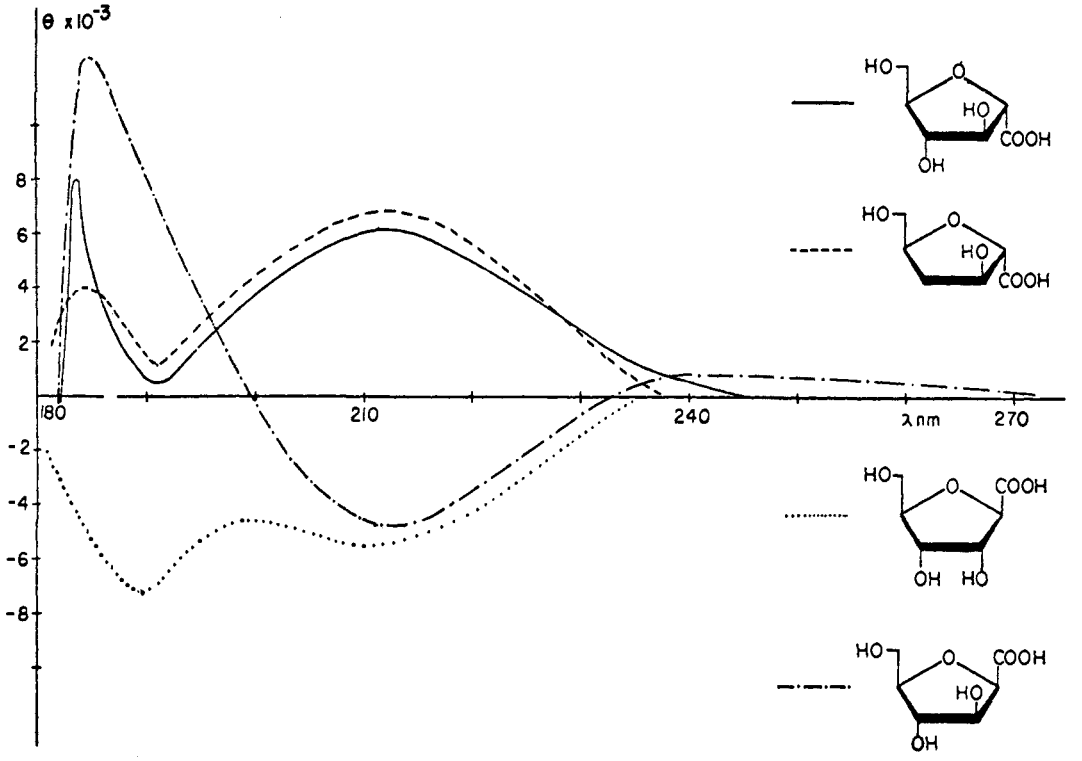


Figure 1.

which was allowed to react with mercuric cyanide in nitromethane to afford a crystalline 2,5-anhydro-4-deoxy-3,6-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexononitrile (**2**). The configuration of the nitrile group attached to C-2, which later decides the anomeric configuration of the C-nucleoside, was determined by studying the CD spectrum of the 2,5-anhydro-3-deoxyhexonic acid (**4**) obtained upon hydrolysis and saponification of nitrile **2**. The spectrum (see Figure 1) showed a positive Cotton effect at 210 nm. A study of the CD curves of various 2,5-anhydrohexonic acids (see Figure 1) has shown[6] that the sign of the Cotton effect at 210–220 nm is determined by the configuration of the chiral center at C-2. When the COOH is above the plane of the ring, the Cotton effect is negative and vice versa. The positive Cotton effect of acid **4** suggested that it possessed the COOH group below the plane of the ring. Nitrile **2** and acids **3** and **4** were accordingly assigned the D-lyxo configuration. The NMR spectrum of 2,5-anhydro-4-deoxy-3,6-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexonitrile (**2**) showed, among other proton signals, a doublet for H-2 (δ 5.80 ppm, J = 5.0 Hz). Its mass spectrum showed a weak molecular ion at *m/e* 441 and peaks caused by the loss of oxygen, nitrogen monoxide, and two *p*-nitrobenzoic acid groups at *m/e* 425, 411, and 107, respectively. Hydrolysis of **2** with hydrogen chloride in the presence of a limited quantity of water gave a crystalline 2,5-anhydro-4-deoxy-3,6-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexonic acid (**3**). Like its precursor, acid **3** showed a doublet for H-2 (δ 5.66 ppm, J = 5.5 Hz) and its mass spectrum showed a peak corresponding to M − CO_2H at *m/e* 415. The protecting groups of compound **3** were removed by treatment with a KOH solution affording 2,5-anhydro-4-deoxy-D-*lyxo*-hexonic acid (**4**) in quantitative yield. Refluxing equimolar amounts of the acid **4** with 4,5,6-triaminopyrimidine in the presence of hot aqueous hydrochloric acid yielded 2,5-anhydro-4-deoxy-D-*lyxo*-hexonoyl-4,5,6-triaminopyrimidine (**5**) in 30% yield. This compound showed an amide band at 1690 cm^{-1} and its NMR spectrum showed a singlet for H-2 at δ 7.75 ppm and multiplets for the sugar ring protons between δ 4.36 and 2.15 ppm. Its mass spectrum showed a strong molecular ion at *m/e* 269 and an M^+ − H_2O peak at 251 as well as a strong peak at *m/e* 125 due to the triaminopyrimidine (Scheme I).

The desired C-nucleoside 8-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (**6**) was obtained by heating amide **5** to 215° for a few minutes. Its NMR showed a doublet at δ 4.60 ppm (J = 4 Hz) assigned to H-1′, and its mass spectrum was very similar to that of the corresponding erythro derivative, 8-(3′-deoxy-β-D-*erythro*-pentofuranosyl)adenine.[2]

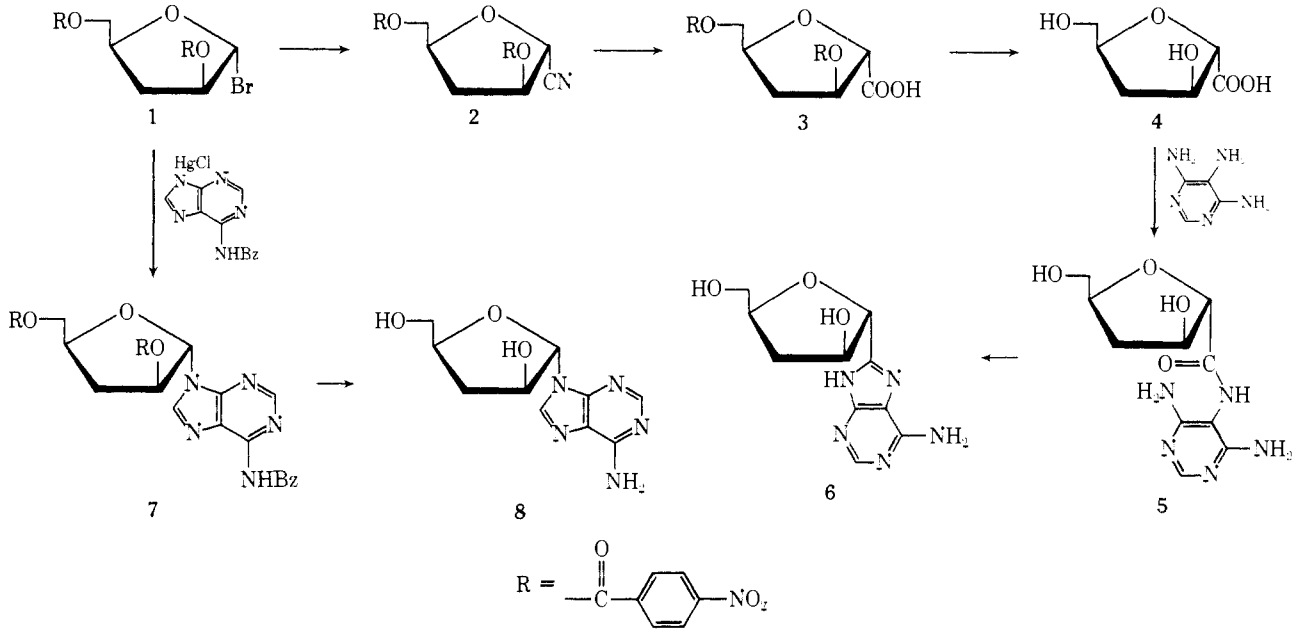
For the synthesis of 9-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine, the bromide **1** was refluxed with 6-(benzamido)chloromercuriopurine in the usual manner.[7] The resulting nucleoside (**8**) showed NMR and mass spectra quite similar to those of cordycepin, 9-(3′-deoxy-β-D-*erythro*-pentofuranosyl)adenine,[8] except for the fact that the anomeric proton which appeared at δ 6.08 had a coupling constant of 1 Hz instead of 2.2 Hz for cordycepin. The anomeric configuration of **8** was established by studying its CD curve (see Figure 2) which showed positive Cotton effect for the envelope at 258–260 nm. Adenosine and other β-adenine nucleosides have negative Cotton effects for this envelope.[9]

The antimalarial activity of 8-(β-D-ribofuranosyl)adenine, 8-(β-D-arabinofuranosyl)adenine, 8-(3′-deoxy-β-D-*erythro*-pentofuranosyl)adenine, and 8-(3′-deoxy-α-D-*threo*-pentofuranosyl)adenine (**6**) has been tested for blood schizontocidal antimalarial activity by the Rene Laboratory of Miami at the request of the Walter Reed Army Institute of Research.[10] The compounds were found inactive and devoid of toxicity at doses up to 640 mg/kg. Similar results were obtained for the corresponding 2,5-anhydroaldohexonic acid amides of 4,5,6-triaminopyrimidines which are the analogs of compound **5**.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. Evaporations were conducted under diminished pressure in a rotary evaporator at 40–45°. Specific rotations were measured, in a 0.2-dm tube, with a Bendix-NPL polarimeter. NMR spectra were recorded at 60 MHz for compounds **2–5** and 100 MHz

Scheme I



for compounds 6–8 with Varian A-60 and HA-100 spectrometers, respectively. Mass spectra were recorded with a Varian M-66 mass spectrometer by Mr. M. P. Gilles. Thin-layer chromatography (TLC) was performed either on plates of Merck silica gel G or plates of silica gel precoated with a fluorescent indicator (Eastman Kodak Catalog No. 6060) with sulfuric acid spray or uv light, respectively, for detection. For column chromatography, silica gel (60–200 mesh, J. T. Baker) was used with a Gibson automatic fraction-collector. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

2,5-Anhydro-4-deoxy-3,6-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexononitrile (2). A suspension of mercuric cyanide (65 g) in nitromethane (650 ml) and benzene (65 ml) was refluxed and 80 ml of mixture distilled over to remove traces of moisture. The suspension was cooled to 0–5° and 3-deoxy-2,5-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosyl bromide (1,[5] 24 g) was added. The mixture was stirred under anhydrous conditions at ambient temperature for 65 hr and then filtered into a mixture of cold aqueous 1 *N* KBr solution (1 l.) and methyl alcohol (150 ml) and then stirred for 30 min. The solution was extracted with dichloromethane (10 × 150 ml) and the combined extracts were washed successively with 1 *N* KBr (3 × 200 ml) and water (200 ml) and dried over $MgSO_4$.[11] Evaporation under reduced pressure gave a syrup which crystallized from ethyl acetate: yield 8.5 g. A further yield of crystalline solid (4.0 g) was obtained through chromatography of the mother liquor on silica gel using benzene–ethyl acetate (9:1): total yield, 58.4%. After recrystallization 2,5-anhydro-4-deoxy-3,6-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexononitrile had mp 146°; $[\alpha]^{20}D$ +59.76° (*c* 1, $CHCl_3$); R_f 0.44 (hexane–acetone 7:3); NMR data ($CDCl_3$) δ 8.23 (phenyl protons), 5.80 (d, J = 5 Hz, H-2), 4.73 (m, H-3), 4.60 (m, H-5, 6,6′), 2.96 (m, H-4), 2.6 (m, H-4). Anal. Calcd for $C_{20}H_{15}N_3O_9$: C, 54.42; H, 3.40; N, 9.52. Found: C, 54.59; H, 3.50; N, 9.51.

2,5-Anhydro-4-deoxy-3,6-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexonic Acid (3). A solution of 2,5-anhydro-4-deoxy-3,6-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexononitrile (**2**, 8.8 g, 0.02 mol) in dioxane (20 ml), water (0.90 ml, 0.05 mol), and 5 *M* hydrogen chloride in dioxane (8 ml) was heated at 50° for 8 hr. It was evaporated to dryness and taken into dioxane (5 ml) and ether (1 ml). The precipitated ammonium chloride was filtered off and the filtrate evaporated to a thick syrup which crystallized from ethyl acetate: yield 5.4 g (58.7%). After recrystallization 2,5-anhydro-4-deoxy-3,6-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexonic acid had mp 151–153°; $[\alpha]^{20}D$ +54.5° (*c* 1, $CHCl_3$); R_f 0.38 (EtOAc–MeOH 6.5:3.5) and 0.45 (benzene–MeOH 1:1); NMR data ($CDCl_3$) δ 8.20 (phenyl protons), 5.66 (d, J = 5.0 Hz, H-2), 4.68 (m, H-3, 5), 4.43 (d, J = 5.0 Hz, H-6,6′), 2.75 (m, H-4), 2.08 (m, H-4′). Anal. Calcd for $C_{20}H_{16}N_2O_{11}$: C, 52.17; H, 3.50; N, 6.09. Found: C, 51.93; H, 3.66; N, 6.08.

2,5-Anhydro-4-deoxy-D-*lyxo*-hexonic Acid (4). A mixture of 2,5-anhydro-4-deoxy-3-di-*O*-*p*-nitrobenzoyl-D-*lyxo*-hexonic acid (**3**, 2.3 g, 0.05 mol), dioxane (10 ml), and 30% KOH (aqueous, 10 ml) was kept at ambient temperature for 24 hr. It was then passed through a column of cation exchange resin (Dowex-50W X-8, H^+) and the precipitated *p*-nitrobenzoic acid filtered off. The filtrate was evaporated to 35 ml and cooled to 0° to precipitate more *p*-nitrobenzoic acid which was filtered off. The filtrate was then evaporated to a thick syrup, yield 0.80 g (98%), which was free of *p*-nitrobenzoic acid (NMR). It crystallized from ethyl acetate (1.5 ml)–ethanol (0.1 ml) in needles: mp 118–119°; $[\alpha]^{20}D$ +59.4° (*c* 0.5,

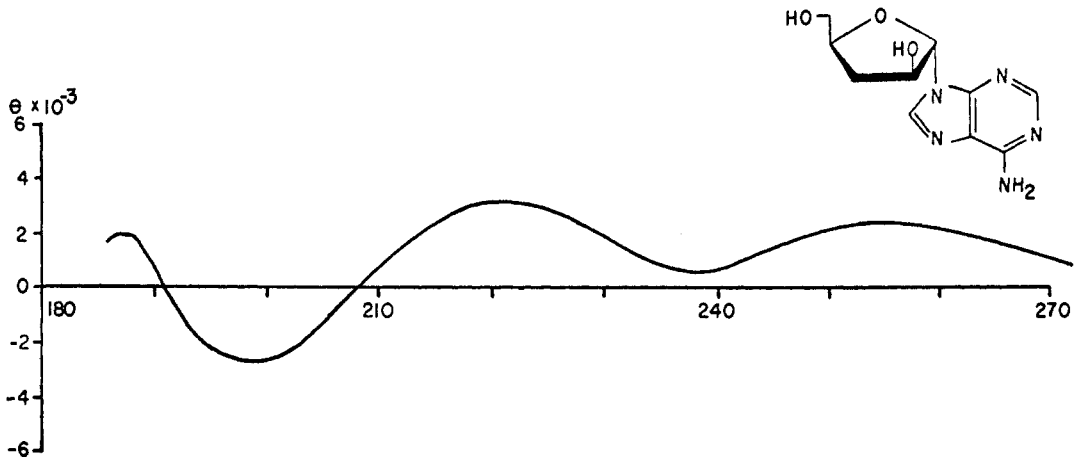


Figure 2.

MeOH); R_f 0.66 (*i*-PrOH–pyridine 19:1); ν_{max}^{KBr} 3350 (OH), 1760 cm^{-1} (COOH); NMR data (DMSO-d_6) δ 4.26 (m, H-2, H-3, H-5), 3.40 (d, J = 5 Hz, H-6,6′), 2.00 (m, H-4,4′), and 6.03 (3-OH, which disappeared after D_2O exchange). Anal. Calcd for $C_6H_{10}O_5$: C, 44.44; H, 6.21. Found: C, 44.50; H, 6.13.

2,5-Anhydro-4-deoxy-D-*lyxo*-hexonoyl-4,5,6-triaminopyrimidine (5). A solution of 2,5-anhydro-4-deoxy-D-*lyxo*-hexonic acid (**4**, 0.80 g, 0.005 mol) and 4,5,6-triaminopyrimidine (0.75 g, 0.006 mol) in 1 *M* HCl (10 ml) was refluxed under a nitrogen atmosphere for 6 hr. It was evaporated to a syrup which was repeatedly coevaporated with water (10 ml) and benzene (3 × 20 ml) to remove the HCl. The yellow-brown residue was dissolved in water (2 ml) and applied on a column (2 × 30 cm) of Dowex 50W X-8 (H^+) and eluted successively with water (500 ml) and 2.5 and 3.7% NH_4OH (500 ml each). The yellow-colored basic effluent (pH 8–9) was evaporated down to a syrup (0.5 g) which was dissolved in water (10 ml) and filtered through charcoal. The yellow crystalline 2,5-anhydro-4-deoxy-D-*lyxo*-hexonoyl-4,5,6-triaminopyrimidine, yield 0.4 g (30.1%), had mp 216–217°; $[\alpha]^{20}D$ +7.43° (*c* 0.4, H_2O); R_f 0.34 (benzene–MeOH 2:1); ν_{max}^{KBr} 3250 (broad peak OH, NM_2), 1635 cm^{-1} (CONH); NMR data (DMSO-d_6) δ 7.76 (s, H-2), 4.36 (m, H-2, H-3′, H-5′), 3.51 (d, J = 5 Hz, H-6,6′), 2.15 (m, H-4,4′), and 5.82 (OH disappears in D_2O). Anal. Calcd for $C_{10}H_{15}N_5O_4$: C, 44.61; H, 5.62; N, 26.01. Found: C, 44.44; H, 5.57; N, 26.15.

8-(3′-Deoxy-α-D-*threo*-pentofuranosyl)adenine (6). Powdered 2,5-anhydro-4-deoxy-D-*lyxo*-hexonoyl-4,5,6-triaminopyrimidine (**5**, 1.0 g) was placed in a boiling tube and heated under a helium atmosphere at 215°. It melted immediately and was stirred for 2 min and then kept at 160° for 10 min. The light brown solid formed in the tube was extracted with hot water (500 ml) and the extract concentrated to a volume of 50 ml. The product crystallized out as faint yellow needles: yield 0.66 g (68.5%); mp 267–268°; $[\alpha]^{20}D$ +79.6° (*c* 1, H_2O); R_f 0.74 (chloroform–methanol–water 12:8:1); ν_{max}^{KBr} 3250 cm^{-1} (OH, NH_2); NMR data (DMSO-d_6) δ 8.13 (s, H-2), 7.00 (s, NH_2 disappeared after D_2O exchange), 4.60 (d, J = 4 Hz, H-2′), 4.33 (m, H-3′, H-5′, OH), 3.55 (d, J = 5 Hz, H-6,6′), 2.16 (m, H-4,4′). Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.17; N, 27.88. Found: C, 48.02; H, 5.13; N, 27.89.

6-Benzamido-3′-deoxy-2′,5′-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosylpurine (7). A suspension of 6-(benzamido)chloromercuriopurine (4.6 g) in xylene (700 ml) was distilled to 550 ml and refluxed with a suspension of 3-deoxy-2,5-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosyl bromide (**1**, 4.95 g) in xylene (50 ml) for 3 hr. The solution was then cooled to room temperature and the precipitated solid filtered off and dissolved in warm dichloromethane (500 ml) and washed successively with 30% aqueous potassium iodide solution (5 × 100 ml) and water (2 × 100). The syrupy residue obtained from evaporation (yield 3.8 g, 58%) was chromatographed on a column of silica gel (35 × 4 cm) eluted first with 1.15 l. of ethyl acetate–benzene in the ratio of 1:1.5 and then with 1 l. of the same mixture in the ratio of 3:1. Fractions (15 ml in volume) were collected and monitored on TLC. Fractions 26–42 were combined and upon evaporation yielded 2.4 g of chromatographically pure 6-benzamido-3′-deoxy-2′,5′-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosylpurine (**7**) which crystallized from ethyl acetate in needles: mp 172–174°; R_f 0.341 in ethyl acetate–benzene (4:1); $[\alpha]^{22}D$ +62.72° (*c* 1, $CHCl_3$). Fractions 50–62 yielded, after evaporation, a lesser pure product (0.4 g) which required two crystallizations from ethyl acetate for chromatographic purity. Anal. Calcd for $C_{31}H_{22}N_7O_{10} \cdot H_2O$: C, 55.52; H, 3.60; N, 14.62. Found: C, 55.72; H, 3.67; N, 14.76.

9-(3′-Deoxy-α-D-*threo*-pentofuranosyl)adenine (8). 6-Benzamido-3′-deoxy-2′,5′-di-*O*-*p*-nitrobenzoyl-α-D-*threo*-pentofuranosylpurine (**7**, 1.3 g, 0.002 *M*) was mixed with a freshly prepared solution of sodium methoxide in methanol (0.05 *N*, 75 ml). The mixture was refluxed for 2 hr and the clear solution was left at 20° for 15 hr. The solvent was evaporated off and the residue was dissolved in water (40 ml). The aqueous solution was neutralized with 5% acetic acid (3 ml), washed with ether (3 × 50 ml) and chloroform (2 × 50 ml), and evaporated down to a volume of 5 ml. 3′-Deoxy-α-D-*threo*-pentofuranosyladenine (**8**) crystallized out in needles: mp 242°; R_f 0.55 in chloroform–ethanol (8:5); $[\alpha]^{20}D$ +79.60° (*c* 1, H_2O). Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.17; N, 27.88. Found: C, 47.74; H, 5.24; N, 27.92.

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β-Aminocinnamonitriles as Potential Antiinflammatory Agents

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A number of β-aminocinnamonitriles have been prepared by the reaction of salts of acetonitrile and propionitrile with benzonitrile. These materials were evaluated in the carrageenan antiinflammatory screen in Royal Hart, Wistar strain rats. Despite good weight gains with the parent molecule, β-aminocinnamonitrile (1), only marginal activity was found in related compounds and some possible "metabolites."

Initial antiinflammatory activity seen in β-aminocinnamonitrile (1) prompted the synthesis of a series of related compounds, **2**. The nature of the aryl group in **2** was modified from substituted phenyl, to naphthyl, and to heterocyclic systems. The best synthetic approach involved the reaction of anions of acetonitrile or propionitrile with appropriate arylnitriles, giving reasonable yields of the desired materials and these are shown in Table II. Nmr studies ($CDCl_3$) show that compound **2** exists primarily (90%) in the enamine structure. In addition, in systems substituted in the α position, double bond isomers exist. This is in agreement with related systems.[1] Several isomeric 3-