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-

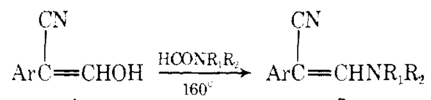
Table I. Effects of Compounds on Carrageenan-Induced Edema of the Rat Paw

Compd no.	No. of rats	*C/T* ratio
2h	4	2.55
2j	4	1.91
1	4	2.86
Aspirin	32	2.8

amino-2-phenylacrylonitriles (**3**) were prepared[1,2] by the reaction of arylcyanoacetaldehydes (**4**) with substituted formamides and these are shown in Table III.

The activity of **1** prompted the synthesis of possible metabolites. One reasonable metabolite of β-aminocinnamonitrile (**1**) is β-aminocinnamamide (**7**). Treatment of ethyl phenylpropiolate (**5**) with concentrated NH_3 at room temperature or liquid NH_3 at −30° gave phenylpropiolamide (**6**). The treatment of **6** with concentrated NH_3 at 80° or ethyl phenylpropiolate with liquid NH_3 at 30° gave the desired material, β-aminocinnamamide (**7**). A number of derivatives were prepared by similar reactions and are listed in Table IV.

1 2



4 3

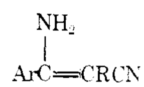
$$PhC{\equiv}CCO_2Et \longrightarrow PhC{\equiv}CCONH_2 \longrightarrow PhC(NH_2){=}CCONH_2$$

5 → 6 → 7 (5 → 7)

Pharmacology. The method used was similar to that described by Winter, *et al.*[3] Royal Hart, Wistar strain rats were used and the drugs in aqueous suspension were administered by gavage at a dosage of 250 mg/kg. Measurements were taken 5 hr after drug administration (4 hr after carrageenan challenge). Results are expressed as a control (C)/treated (T) efficacy ratio (edema of control animals/edema of treated animals). Those compounds with ratios greater than 1.41 were accepted as active.

The results of testing these compounds on the suppression of carrageenan edema in rats are presented in Table I. Only compounds **1**, **2h**, and **2j** showed any activity in this assay. None of the metabolites or related compounds had any antiinflammatory activity. Further tests with **1** in ultraviolet-induced erythema in guinea pigs proved negative.

Table II. Derivatives of β-Aminocinnamonitriles

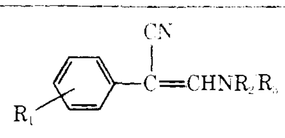


2

Compd no.	Ar	R	Yield, %	Mp, °C	Formula	Analyses
2a	2-Naphthyl	H	22	88–90	$C_{13}H_{10}N_2$	C, H, N
2b	*p*-$CH_3C_6H_5$	H	52	104–107	$C_{10}H_{10}N_2$	*a*
2c	*p*-$CH_3C_6H_5$	CH_3	18	103–106	$C_{11}H_{12}N_2$	C, H, N
2d	3-Pyridyl	H	22	104–106	$C_8H_7N_3$	C, H, N
2e	*p*-FC_6H_5	H	68	110–112	$C_9H_7FN_2$	C, H, N, F
2f	*o*-ClC_6H_5	H	57	108–111	$C_9H_7ClN_2$	C, H, N, Cl
2g	*m*-$CH_3C_6H_5$	H	65	75–78	$C_{10}H_{10}N_2$	C, H, N
2h	2-Pyridyl	CH_3	13	108–112	$C_9H_9N_3$	H, N; C[b]
2i	*p*-Biphenyl	H	28	187–189	$C_{15}H_{12}N_2$	C, H, N
2j	C_6F_5	H	35	89–92	$C_9H_3F_5N_2$	C, H, N; F[c]
2k	2-Pyridyl	H	42	112–115	$C_8H_7N_3$	C, H, N
2l	4-Pyridyl	H	56	209–212	$C_8H_7N_3$	C, H, N

[a] Lit.[4] mp 108–109°. [b] C: calcd, 67.90; found, 68.36. [c] F: calcd, 40.58; found, 40.17.

Table III. Aminoarylacrylonitrile Derivatives



3

Compd no.	R_1	R_2	R_3	Mp, °C	Formula	Analyses
3a	H	H	CH_3	97–100	$C_{10}H_{10}N_2$	*a*
3b	H	H	C_6H_5	159–162	$C_{15}H_{12}N_2$	*b*
3c	H	CH_3	C_6H_5	56–59	$C_{16}H_{14}N_2$	C, H, N
3d	*p*-Cl	CH_3	CH_3	84–85	$C_{11}H_{11}ClN_2$	C, H, N
3e	*p*-Cl	H	CH_3	62–66	$C_{10}H_9ClN_2$	C, H, N, Cl
3f	H	CH_3	CH_3	73–76	$C_{11}H_{12}N_2$	*c*
3g	H	C_2H_5	C_2H_5	68–71	$C_{13}H_{16}N_2$	*d*

[a] Lit.[1] mp 99.5–100.5°. [b] Lit.[1] mp 157.5–158.5°. [c] Lit.[2] mp 79–80°. [d] Lit.[2] mp 74–75°.

Table IV. Phenylpropiolate Derivatives

$R_2R_3C{=}CHCOR_1$ **7** $\quad$ $R_2C{\equiv}CCOR_1$ **6**

Compd no.	R_1	R_2	R_3	Mp or bp (mm), °C	Formula	Analyses
7a	NH_2	NH_2	C_6H_5	167–170	$C_9H_{10}N_2O$	*a*
6a	NH_2	C_6H_5		115–117	C_9H_7NO	*b*
6b	$NHCH_2C_6H_5$	C_6H_5		108–110	$C_{16}H_{13}NO$	C, H, N
7b	OC_2H_5	$NH(C_2H_5)$	H	52–54(1.5 mm)	$C_7H_{13}NO_2$	C, H, N
7c	OC_2H_5	$N(CH_3)_2$	H	83–85(1 mm)	$C_7H_{13}NO_2$	C, H, N

[a]Lit.[5] mp 164°. [b]Lit.[6,7] mp 104–106°.

Experimental Section

Melting points were observed on a Mel-Temp apparatus and are uncorrected. Elemental analyses (Lederle Microlabs) were correct within ±0.4%. Infrared and nmr spectra of all compounds were consistent with the assigned structure.

β-Aminocinnamonitriles. General Procedure. Sodium (2.7 g, 0.12 g-atom) was dissolved in liquid ammonia (100 ml) at −33°. A solution of acetonitrile or propionitrile (0.094 mol) in 10 ml of ether was added over a 5–10-min period. The flask was cooled in a Dry Ice–acetone bath and arylnitrile (0.085 mol) in 25 ml of THF added. The ammonia was allowed to evaporate; the residue was treated with H_2O under N_2 and extracted with $CHCl_3$. Solvent removal and recrystallization gave the β-aminocinnamonitriles listed in Table II.

β-Amino-α,p-dimethylcinnamonitrile (2c). Sodium (2.7 g, 0.12 g-atom) was dissolved in liquid NH_3 (100 ml) at −33°. A solution of propionitrile (5.2 g, 6.6 ml, 0.94 mol) in 10 ml of ether was added over ~3 min. The flask was placed in a Dry Ice–acetone bath and *p*-toluonitrile (10 g, 0.085 mol) in 25 ml of ether was added dropwise. The ammonia was evaporated overnight. The residue was treated with H_2O under N_2 and then extracted with $CHCl_3$. Solvent removal and recrystallization from ethyl acetate–hexane (charcoal) gave **2c** as yellow plates: mp 103–106° (2.63 g, 18%). *Anal.* ($C_{11}H_{12}N_2$) C, H, N.

β-Amino-2-naphthylacrylonitrile (2a). Sodium (2.0 g, 0.09 g-atom) was dissolved in 125 ml of liquid NH_3 and to this was added over a 5-min span, 3.67 g (0.071 mol) of acetonitrile in 10 ml of ether. The solution was then cooled in a Dry Ice–acetone bath and 10 g (0.065 mol) of 2-cyanonaphthylene in a minimum amount of dry ether was added rapidly within 5 min of the acetonitrile addition. The solution was allowed to stir in the Dry Ice bath for 1.5 hr and the ammonia was then allowed to evaporate. Water was cautiously added under N_2 and this was extracted with ether. The ether was removed and the residue recrystallized from $CHCl_3$–hexane: mp 85–90° (2.8 g, 22%). *Anal.* ($C_{13}H_{10}N_2$) C, H, N.

3-Amino-2-phenylacrylonitriles. General Procedure.[1,2] A suspension of arylcyanoacetaldehyde (**4**, 0.20 mol) and substituted formamide was heated at 150° for 4–6 hr. The excess formamide was removed *in vacuo* and the residue was recrystallized from acetone–hexane, giving the aminophenylacrylonitrile **3** listed in Table III.

3-N-Methylamino-2-phenylacrylonitrile (3c). A suspension of 20 g (0.16 mol) of α-cyanophenylacetaldehyde and *N*-methylformanilide was heated at 180° for 6 hr. The excess amide was removed *in vacuo* and the residue was recrystallized from acetone–hexane, giving white crystals: mp 56–59° (12.8 g, 36%). *Anal.* ($C_{16}H_{14}N_2$) C, H, N.

3-Dimethylamino-2-(p-chlorophenyl)acrylonitrile (3d). A solution of 20 g (0.11 mol) of α-cyanophenylacetaldehyde in 50 ml of DMF was heated at 180° for 7 hr. The solvent was removed *in vacuo* and the solid was recrystallized from $CHCl_3$–hexane giving 4.65 g (18%) of yellow needles: mp 84–85°. *Anal.* ($C_{11}H_{11}ClN_2$) C, H, Cl, N.

β-Aminocinnamide (7). A suspension of phenylpropiolamide (5 g, 0.054 mol) in concentrated NH_3 (100 ml) was heated at 80° overnight. The clear solution was cooled, giving 1.5 g (26.8%) of material, mp 167–170° (acetone), as light yellow plates (lit.[5] mp 164°) (Table IV).

Stirring ethyl phenylpropiolate in liquid NH_3 at 30° in a bomb gave good yields (80%) of β-aminocinnamide.

Phenylpropiolamide (6). A suspension of ethyl phenylpropiolate (10 g, 0.057 mol) in 50 ml of concentrated NH_3 was stirred overnight. The solid was collected by filtration and recrystallized from $CHCl_3$: mp 115–117° (yield 3.2 g, 38.6%) (lit.[6,7] mp 104–106°).

Phenylpropiolamide could also be obtained by stirring ethyl phenylpropiolate in liquid NH_3 at −30°.

N-Benzyl-3-phenylpropiolamide (6b). A two-phase system of ethyl phenylpropiolate (12.5 g, 0.072 mol), benzylamine (25 ml), and water (28 ml) was stirred vigorously overnight. The solid was collected and recrystallized (acetone–hexane): mp 108–110° (7.5 g, 44.3%). *Anal.* ($C_{16}H_{13}NO$) C, H, N.

Ethyl 3-Ethylaminoacrylate (7b). A mixture of ethyl propiolate (12.5 g, 0.128 mol) and 50 ml of 20% aqueous ethylamine was stirred at room temperature overnight. The solution was extracted with $CHCl_3$. Distillation gave 10.2 g (55.7%) of product [bp 52–54° (1.8 mm)]. *Anal.* ($C_7H_{13}NO_2$) C, H, N.

Ethyl 3-Dimethylaminoacrylate (7c). A mixture of ethyl propiolate (12.5 g, 0.128 mol) and 40 ml of aqueous dimethylamine was allowed to stir overnight. The solution was extracted with $CHCl_3$ and the organic phase distilled: bp 83–84.5° (1 mm) of clear liquid (8.6 g, 47%). *Anal.* ($C_7H_{13}NO_2$) C, H, N.

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