Synthesis and Biological Evaluation of 9-[5′-(2-Oxo-1,3,2-oxazaphosphorinan-2-yl)-β-D-arabinosyl]adenine and 9-[5′-(2-Oxo-1,3,2-dioxaphosphorinan-2-yl)-β-D-arabinosyl]adenine: Potential Neutral Precursors of 9-[β-D-Arabinofuranosyl]adenine 5′-Monophosphate

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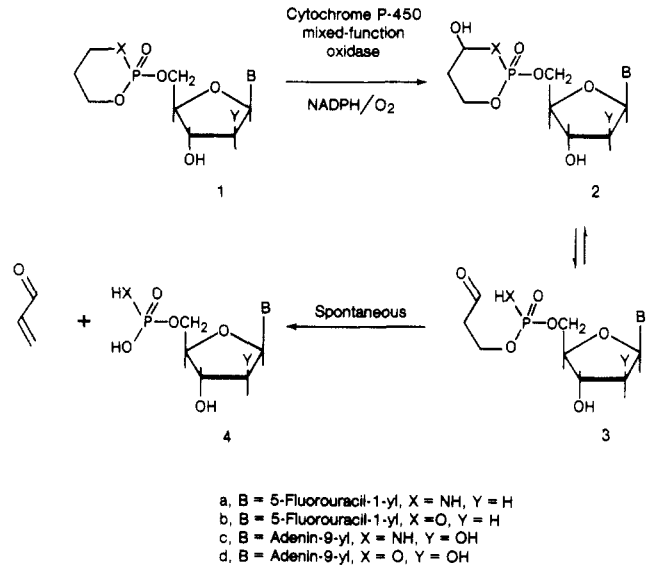
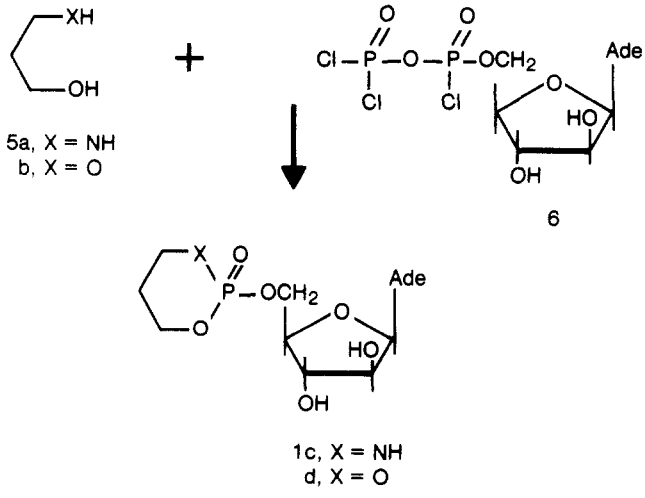
9-[5′-(2-Oxo-1,3,2-oxazaphosphorinan-2-yl)-β-D-arabinosyl]adenine (**1c**) and 9-[5′-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-β-D-arabinosyl]adenine (**1d**) were synthesized by reaction of 9-[β-D-arabinofuranosyl]adenine with phosphoryl chloride with 1-amino-3-propanol and 1,3-propanediol, respectively. **1c** consisted of a mixture of diastereomers, while **1d** was enantiomerically homogeneous. The structures of these compounds were established by spectral (^{1}H NMR, MS, UV) and elemental analyses. Both **1c** and **1d** were resistant to degradation by 5′-nucleotidase, alkaline phosphatase, venom phosphodiesterase, crude snake venom, adenosine deaminase, and adenylate deaminase. Neither compound was significantly biotransformed by mouse hepatic microsomal preparations in the presence of an NADPH-generating system. Compound **1c** was marginally effective at prolonging the life span of mice bearing P-388 leukemia; compound **1d**, however, was inactive.

Recently, we reported[1] the chemical syntheses and biological evaluation of 5-fluoro-5′-(2-oxo-1,3,2-oxazaphosphorinan-2-yl)-2′-deoxyuridine (**1a**) and 5-fluoro-5′-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-2′-deoxyuridine (**1b**) as potential membrane transport precursors of 5-fluoro-2′-deoxyuridine 5′-monophosphate (**4b**) a putative active metabolite of 5′-fluorouracil. Our hypothesis, which was based upon the mechanism of action of cyclophosphamide,[2] was that **1a** and **1b** would undergo biotransformation, in vivo, by hepatic P-450-dependent mixed-function oxidases to give the 4-hydroxy analogues **2a** and **2b** (Scheme I). It was anticipated that these compounds would penetrate into cells by passive diffusion and then undergo spontaneous ring opening to yield the acyclic tautomers **3a** and **3b**, which would subsequently dissociate with elimination of acrolein to give the phosphoramidate **4a** and the phospho monoester **4b**. Conversion of **4a** to **4b** was envisaged to occur by chemical or enzymic hydrolyses. However, unlike cyclophosphamide, compounds **1a** and **1b** were not significantly biotransformed when incubated with mouse hepatic mixed-function oxidases, thus thwarting the key primary step in the activation sequence. Since it was possible that the poor substrate properties of **1a** and **1b** for the mixed-function oxidases were not representative of those of 5′-cyclic nucleotides, in general, we decided to synthesize and evaluate the corresponding derivatives **1c** and **1d** of the purine nucleoside analogue, 9-[β-D-arabinofuranosyl]adenine (ara-A). The latter compound is effective against human viral encephalitis.[3] It has also been evaluated clinically as an antitumor agent.[4] In common with most nucleoside analgoues, ara-A is not independently active. It is sequentially phosphorylated by cellular kinases to ara-A 5′-triphosphate (ara-ATP), an inhibitor of DNA polymerase.[5] Ara-ATP is also incorporated into DNA.[6] Recently, Verhoef et al. reported that a human lymphoid cell line resistant to ara-A was deficient in deoxycytidine kinase and adenosine kinase, the enzymes that mediate the conversion of ara-A to ara-A 5′-monophosphate (ara-AMP).[7] The present study was undertaken in the hope that the cyclic nucleotides would act as latent precursors of ara-AMP and thus preclude the requirement for the initial phosphorylation step in the activation sequence.

Scheme I



Scheme II



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0022-2623/85/1828-1358$01.50/0

Chemistry. The cyclic 5′-phosphoramidate **1c** and the cyclic 5′-phosphate **1d** were synthesized directly from ara-A by a modification of the Yoshikawa reaction[8] for the preparation of 5′-nucleotides from unprotected nucleosides (Scheme II). Thus, ara-A was reacted with a twofold molar excess of partially hydrolyzed phosphoryl chloride in triethyl phosphate, and the intermediate phosphorodichloridate, **6**, was treated in situ with 3-amino-1-propanol (**5a**) or 1,3-propanediol (**5b**) in the presence of triethylamine. The crude reaction products were passed through a DEAE cellulose column (bicarbonate form) to remove ionic byproducts, and the neutral residues obtained by evaporation of the eluents were chromatographed on alumina to give **1c** and **1d** in 25% and 10% yields, respectively. Although **1c** appeared homogeneous by TLC on silica, it was resolved into two components in the ratio 1:1 by high-performance liquid chromatography (HPLC) on reversed-phase μ-Bondapak C-18. These components were shown by ^{1}H NMR and MS to be diastereomers; they arise because the phosphorus atom in **1c** is chiral. the dioxa analogue **1d**, by comparison, gave a single peak on HPLC analysis, consistent with the absence of a chiral atom in the phosphorinane ring.

The 5′-orientation of the cyclic phosphorinane substituents in **1c** and **1d** was apparent from the ^{1}H NMR spectra of these compounds in Me_2SO-d_6 at 360 Hz. Thus, the one-proton triplet at δ 5.07 in the spectrum of ara-A attributable to the $C_{5'}$-OH proton is absent in the spectrum of **1c** and **1d**. (The diastereomers of **1c** gave closely similar ^{1}H NMR spectra.) By comparison, the $C_{2'}$ OH and $C_{3'}$ OH resonances, which occur as one-proton doublets (J_{HOCH} = 5 Hz) at δ 5.59 and 5.48, respectively, in the spectrum of ara-A, were clearly present in the spectra of **1c** and **1d**, although they were displaced 0.2–0.3 ppm downfield. Further evidence indicating 5′-substitution is that the $C_{5'}$ H signal at δ 3.60–3.73 in the spectrum of ara-A is shifted to δ 4.05–4.30 and 4.22–4.42 in the spectra of **1c** and **1d**, respectively. The chemical shifts of the $C_{2'}$ H and $C_{3'}$ H resonances, in contrast, are unchanged. The methylene proton resonances of the phosphorinane ring in **1c** and **1d** occur at the anticipated field positions (see the Experimental Section).

The MS of the trimethylsilyl derivatives of the diastereomers of **1c** were identical and showed prominent molecular ions at *m/e* 674, corresponding to the tetrasubstituted parent compounds. The MS of **1d** showed similar fragment ions with a prominent molecular ion at *m/e* 603, corresponding to the N^6,2′,3′-tris(trimethylsilyl) derivative.[9]

Enzyme Studies. Because it is important to the success of our strategy that the 5′-cyclic compounds are resistant to degradation by enzymes that catabolize ara-A and ara-AMP, we investigated the stability of **1c** and **1d** in the presence of 5′-nucleotidase, alkaline phosphatase, venom phosphodiesterase, crude snake venom, adenosine deaminase, and adenylate deaminase. Neither compound was degraded after 2-h incubation with these enzymes.

When incubated with hepatic microsomal preparations from phenobarbital-treated mice for 1 h at 37 °C in the presence of an NADPH-generating system, a 5–10% decrease in the concentrations of **1c** and **1d** was evident. However, despite careful analysis of the incubates, identifiable metabolites such as adenine, ara-A, arabinosylhypoxanthine, ara-AMP, or ara-A 5′-phosphoramidate were not detected. Cyclophosphamide was over 80% degraded when incubated under similar conditions.

Table I. Effect of Neutral 9-β-D-Arabinosyladenine 5′-Monophosphate Derivatives on the Survival of BDF_1 Mice[a] Implanted Intraperitoneally with P-388 Leukemia[b]

compd	dose, mg/kg (qd, 1–9)	MST,[c] days	% ILS[d]
saline		9	
Ara-A	600	12	33[e]
1c	500	8	−11
	300	12	33[e]
	100	12	33[e]
1d	300	9	0

[a] Six mice per group; average weight 23 g. [b] 10^6 cells inoculated intraperitoneally on day 0. [c] Median survival time (MST) of 18 mice used as controls was 9 days. [d] Percentage increase in life span of treated animals (T) compared with saline-treated controls (C) was determined by the formula (T/C − 1) × 100. [e] $P < 0.05$.

Antitumor Screening. Compounds **1c** and **1d** were screened against murine leukemia P-388 (Table I). Administered intraperitoneally, daily, for 9 consecutive days at dosages of 100–300 mg/kg, **1c** was marginally effective at prolonging the life span of mice bearing intraperitoneally implanted leukemia P-388. At higher dosages (500 mg/kg), the mice evidenced symptoms of cumulative CNS toxicity reminiscent of certain cholinesterase inhibitors;[10] these animals died prior to the controls. Ara-A administered on the same schedule at 600 mg/kg (LD_{10} dosage) was, likewise, only marginally active. The cyclic ester **1d** administered similarly at dosages up to 300 mg/kg was ineffective.

Discussion

From the above data it is apparent that ara-A cyclic 5′-phosphoramidate (**1c**), like the parent nucleoside analogue ara-A, is only marginally effective at prolonging the life span of mice bearing leukemia P-388. The corresponding cyclic 5′-phosphate **1d** is inactive. The modest antitumor activity of ara-A, even at LD_{10} dosages, against leukemia P-388 has been attributed to its rapid biotransformation to arabinosylhypoxanthine, a comparatively nontoxic catabolite, by host and tumor deaminases.[11,12] However, this explanation is unlikely to account for the lack of antitumor activity of **1c** and **1d** since neither compound is a substrate for adenosine deaminase or deoxyadenylate deaminase. A more likely explanation is that the cyclic compounds are not significantly bioactivated in vivo as anticipated. Support for this interpretation is that **1c** and **1d** were only minimally biotransformed when incubated in vitro with mouse hepatic microsomal preparations under conditions where cyclophosphamide was extensively degraded. We have previously reported similar findings[1] with the corresponding 5′-cyclic derivatives of 5-fluoro-2′-deoxyuridine. The poor substrate properties of the 5′-cyclic compounds for the mixed-function oxidases are most likely due to their low lipid solubility. Although freely soluble in aqueous media, compounds **1a–d** were virtually insoluble in most common organic solvents (e.g., diethyl ether, ethyl acetate, chloroform). Hansch has reported[13] that lipophilic compounds are usually more readily biotransformed than their hydrophilic analogues, presumably because the cytochrome P-450 complex is intimately associated with the lipoidal membranes of the endoplasmic reticulum. If this interpretation is correct,

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then it might be possible to improve the affinity of **1c** and **1d** for the enzyme by using bioreversible lipophilic substituents (e.g., acyl groups) on the sugar or base moieties. However, this approach introduces additional complexity into the overall strategy. Currently, we are pursuing alternative solutions to the bioactivation problem. This work will be the subject of a future report.

Experimental Section

Proton magnetic resonance spectra (^{1}H NMR) were recorded at ambient temperature on a Varian Associates T-60A spectrometer, or on a Bruker HX-360 spectrometer in the Fourier transform mode, in $CDCl_3$ or Me_2SO-d_6 using tetramethylsilane as an internal standard. Mass spectra were obtained on a Finnigan Model 3300 quadrupole spectrometer in the electron-impact or chemical ionization mode with a direct inlet probe. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN, and the results are within ±0.4% of the theoretical values. All solvents were distilled immediately before use and were dried over freshly activated (300 °C/4 h) molecular sieves (type 4A) for at least 24 h. Nucleosides were dried over P_2O_5 under vacuum (0.10 torr) at 100 °C for 24 h before use. All reactions were conducted in dry glassware and were protected from atmospheric moisture. Evaporations were carried out on a rotary evaporator under reduced pressure at a bath temperature of <40 °C. The homogeneity of the products was determined by ascending TLC on silica-coated glass plates (silica gel 60 F 254, Merck) using ethyl acetate–2-propanol–water (4:2:1, top layer) as eluting solvent. Compounds were visualized under UV light (254-nm output) or with iodine vapor. Preparative separations were performed on columns of neutral alumina (MN-aluminum oxide, Brinkmann). Analytical HPLC was carried out in the reversed-phase mode on μ-Bondapak C-18 columns (30 cm × 4 mm i.d., 10-μm particle size). All phosphohydrolases and deaminases were purchased from Sigma Chemical Co., St. Louis, MO.

9-[5′-(2-Oxo-1,3,2-oxazaphosphorinan-2-yl)-β-D-arabinofuranosyl]adenine (1c). Ara-A (5.0 g, 18.7 mmol) was added, with stirring, to a cold (0 °C) solution of $(EtO)_3PO$ (75 mL), $POCl_3$ (3.43 mL, 37.4 mmol), and H_2O (0.34 mL, 18.9 mmol) contained in a 1-L, round-bottomed flask. The ara-A gradually went into solution during 2 h, and thereafter the reaction mixture was stirred for a further 6 h at 0 °C. Anhydrous toluene (approximately 130 mL) was added until the solution developed a slight turbidity. While the mixture was maintained at 0 °C, a solution of 3-amino-1-propanol (2.87 mL, 37.4 mmol) and Et_3N (18.1 mL, 130.9 mmol) in $CHCl_3$ (100 mL) was added dropwise, with stirring, over 2 h. The mixture was then allowed to warm to room temperature and was stirred for a further 24 h. Anhydrous toluene (300 mL) was added, and the flask was stored in a cold room at 4 °C for 48 h. The clear supernatant was carefully decanted, and the copious white semisolid was washed by decantation with dry ether (3 × 150 mL). The product was allowed to settle for 1 h between each washing. The residue was dissolved in ice-cold 2 M triethylammonium bicarbonate (TEAB), pH 7.7 (200 mL), and the solution was evaporated to dryness at <30 °C on a rotary evaporator. Residual TEAB was removed by further evaporations from ethanol (3 × 100 mL). The remaining solid was dissolved in H_2O (50 mL). Half of this solution was stored frozen, and the other half was transferred to a column (5 × 60 cm) of DEAE cellulose (Whatman DE 32) in the bicarbonate form. The products were eluted with H_2O (adjusted to pH 8.0 with a few drops of 6 N NH_3) at a flow rate of 5.0 mL/min. Fractions of 18 mL each were collected. The eluent was monitored by UV absorption at 254 nm, and select fractions were further analyzed by HPLC on a μ-Bondapak C-18 column (Waters Co.) using 0.05 M Tris buffer (pH 7.4)–methanol (3:1) as eluent at a flow rate of 2.0 mL/min. Fractions 45–70, which contained **1c** together with unreacted ara-A, were pooled and evaporated at <30 °C to give a semisolid. The DEAE cellulose column was then regenerated with 3.5 L of 1 M TEAB and washed with 3.0 L of H_2O. The foregoing procedure was then repeated, using the second half of the crude reaction mixture. The combined products were coevaporated several times with EtOH (3 × 50 mL) to remove residual TEAB, and the remaining product (ca. 3.0 g, which consisted of a 3:2 mixture of **1c** and ara-A) was dissolved in H_2O (15 mL). Alumina (10 g) was added, and the mixture was evaporated to dryness at <30 °C. After three further evaporations from EtOH (3 × 100 mL) and $CHCl_3$ (2 × 100 mL), a free-flowing powder was obtained that was transferred to a column of alumina (250 g) that had previously been made up in $CHCl_3$. The products were eluted with $CHCl_3$–MeOH–H_2O (4:2:1, bottom phase) and 5% MeOH. Fractions of 15 mL were collected, and the eluent was monitored by UV absorption at 254 nm and by HPLC analysis (μ-Bondapak C-18; 0.05 M Tris buffer (pH 7.4)–MeOH, 3:1, 2.0 mL/min). Compound **1c** was eluted first, followed by ara-A. Fractions containing **1c** were combined and evaporated to give a viscous oil that was dried over P_2O_5 under high vacuum for 24 h; the yield was 1.44 g (25%). HPLC analysis of this product indicated that it consisted of a 1:1 mixture of components. A sample (25 mg) of the product was resolved into its individual constituents by semipreparative reversed-phase chromatography on two Magnum ODS columns (Whatman) linked in series using H_2O–MeOH (85:15) as eluent at a flow rate of 1.5 mL/min. Fractions of 10 mL each were collected. Fractions 18–36 were combined and evaporated to give 8.5 mg of diastereomer A (viscous oil). Fractions 45–60 yielded 7.5 mg of diastereomer B (viscous oil). ^{1}H NMR (Me_2SO-d_6) (diastereomer A): δ 8.16 (s, 1 H, C_8 H), 8.13 (s, 1 H, C_2 H), 7.25 (s, 2 H, NH_2), 6.33 (d, 1 H, $C_{1'}$ H, J = 5 Hz), 5.82 (d, 1 H, $C_{2'}$ OH or $C_{3'}$ OH, J = 5 Hz), 5.75 (d, 1 H, $C_{3'}$ OH or $C_{2'}$ OH, J = 5 Hz), 5.19 (m, 1 H, NHP(O)), 4.05–4.30 (m, 6 H, $C_{2'}$ H, $C_{3'}$ H, $C_{5'}$ H, $OCH_2CH_2CH_2NH$), 3.97–4.30 (m, 1 H, $C_{4'}$ H), 2.95–3.12 (m, 2 H, $OCH_2CH_2CH_2NH$), 1.48–1.83 (m, 2 H, $OCH_2CH_2CH_2NH$). MS: m/e 674 (M^+), [$(SiMe_3)_4$ derivative]. UV (EtOH): λ_{max} 260 nm (ε = 13 300). Diastereomer B gave virtually identical analytical data. Anal. (diastereomeric pair) for ($C_{13}H_{19}N_6O_6P$) C, H, N.

9-[5′-(2-Oxo-1,3,2-dioxaphosphorinan-2-yl)-β-D-arabinofuranosyl]adenine (1d). The compound was prepared from ara-A (3.0 g, 11.2 mmol), $POCl_3$ (2.06 mL, 22.4 mmol), H_2O (0.20 mL, 11.2 mmol), 1,3-propanediol (1.65 mL, 22.4 mmol), and Et_3N (10.86 mL, 78.5 mmol) in $(EtO)_3PO$ (45 mL) as described for the synthesis of **1c**, except that proportionally smaller amounts of solvents and chromatographic materials were used. The compound eluted from alumina as a homogeneous band and was isolated as a viscous oil. The yield was 445 mg (10%). ^{1}H NMR (Me_2SO-d_6): δ 8.16 (s, 1 H, C_8 H), 8.14 (s, 1 H, C_2 H), 7.25 (s, 2 H, NH_2), 6.33 (d, 1 H, $C_{1'}$ H, J = 5 Hz), 5.86 (d, 1 H, $C_{2'}$ OH or $C_{3'}$ OH, J = 5 Hz), 5.79 (d, 1 H, $C_{3'}$ OH or $C_{2'}$ OH, J = 5 Hz), 4.22–4.42 (m, 6 H, $C_{5'}$ H, $OCH_2CH_2CH_2O$), 4.13–4.20 (m, 2 H, $C_{2'}$ H, $C_{3'}$ H), 4.00–4.05 (m, 1 H, $C_{4'}$ H), 1.68–2.15 (m, 2 H, $OCH_2CH_2CH_2$). MS: m/e 603 (M^+), [$(SiMe_3)_3$ derivative]. UV (EtOH): λ_{max} 260 nm (ε = 13 000). Anal. for ($C_{13}H_{18}N_5O_7P$·0.5H_2O) C, H, N.

Enzyme Experiments. 1. Phosphohydrolases. The substrate (0.7 μmol) in water (20 μL) was incubated at 37 °C for 2 h with (a) 5′-nucleotidase (*Crotalus adamanteus*) (20 μL, 2.25 units/mL) in 0.1 M Tris-HCl buffer–0.01 mM $MgCl_2$ (pH 9.0, 100 μL); (b) alkaline phosphatase (*Escherichia coli*) (20 μL, 2.18 units/mL) in 0.1 M glycine–sodium hydroxide buffer (pH 10.4, 100 μL); (c) phosphodiesterase I (*C. adamanteus*) (20 μL, 1.69 units/mL) in 0.1 M Tris-HCl buffer–0.01 mM $MgCl_2$ (pH 9.0, 100 μL); and (d) snake venom (*C. adamanteus*) (20 μL, 1.25 mg/mL) in 0.1 M Tris-HCl buffer–0.01 mM $MgCl_2$ (pH 9.0, 100 μL). After incubations were complete, 0.9 mL of EtOH was added and aliquots of the solution were analyzed by HPLC in the reversed-phase mode (μ-Bondapak C-18) using 0.05 M Tris-HCl buffer, pH 7.0, and methanol (85:15) as eluent at a flow rate of 2.0 mL/min.

2. Deaminases. (a) Adenosine Deaminase (Calf Intestine). A spectrophotometric assay was used.[14] It is based on the change in optical density at 265 nm that usually accompanies the conversion of 9-substituted adenines to their hypoxanthine analogues.[15]

The enzyme (0.1 mL, 5.1 units/mL), in 0.05 M phosphate buffer (pH 7.5), was added at room temperature to a solution of **1c** and **1d** (0.135 μmol) in 0.05 M phosphate buffer (pH 7.5, 2.9 mL). The

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absorption of the mixture was monitored at 265 nm on a Cary Model 14 recording spectrophotometer for 2 h.

After filtration through membrane cones (Amicon Centriflo F 25, Amicon Corp.) and concentration, the mixtures were analyzed for substrate and product by HPLC using the conditions described above. Control reactions were conducted with adenosine and ara-A.

(b) 5′-Adenylic Acid Deaminase (Rabbit Muscle). A spectrophotometric assay, similar to that described for adenosine deaminase, above, was used.

The enzyme (0.1 mL, 10.0 units/mL), in 0.05 M phosphate buffer (pH 7.5), was added at room temperature to a solution of **1c** and **1d** (0.130 μmol) in 0.05 M phosphate buffer (pH 7.5, 2.9 mL). The absorption of the mixture was monitored at 265 nm for 2 h. Control reactions were conducted with AMP and ara-AMP.

3. Cytochrome P-450 Dependent Mixed-Function Oxidases. BDF_1 mice were injected intraperitoneally with sodium phenobarbital (75 mg/kg) for 4 consecutive days. The animals were killed 24 h after the last injection, and the livers were excised. A 33% liver homogenate in 0.05 M Tris-HCl–0.15 M KCl–0.01 M $MgCl_2$ buffer (pH 7.4) was centrifuged at 10000*g* for 20 min at 4 °C. The supernatant fraction was aspirated and centrifuged at 105000*g* for 60 min at 4 °C. The microsomal pellet was washed by resuspension in the original volume of buffer containing 0.01 M EDTA and was then resedimented at 105000*g* for 30 min. The final pellet was reconstituted in the Tris–KCl–$MgCl_2$ buffer such that each mL of suspension contained microsomes from 0.33-g wet weight of liver. Each incubation mixture contained cyclic 5′-nucleotide (1 mM), NADH (0.4 mM), glucose 6-phosphate (5.0 mM), glucose 6-phosphate dehydrogenase (0.6 unit/mL), and 0.25 mL of microsomal suspension in a total volume of 1.25 mL. After 1 h at 37 °C, the incubates were transferred to Amicon Centriflo CF 25 membrane cones (Amicon Corp., Lexington, MA) and centrifuged at 2000 rpm (<1000*g*) in a swinging-bucket centrifuge for 75 min at 4 °C. The filtrates were analyzed by HPLC on a μ-Bondapak C-18 column using 0.05 M Tris buffer (pH 7.0)–methanol (85:15) as eluent or on a Partisil 10-SAX column (25 cm × 4.6 mm i.d., Whatman) using 0.01 M $(NH_4)_2HPO_4$ buffer (pH 6.6).

Antitumor Screening. Mice weighing 18–20 g were obtained from Jackson Laboratories, Madison, WI. Murine leukemia P-388 was maintained by weekly intraperitoneal passage in female DBA/2 mice. For antitumor screening, 10^6 cells were inoculated intraperitoneally into male BDF_1 mice. The test compounds, dissolved in sterile 0.9% saline, were administered intraperitoneally daily for 9 consecutive days beginning 24 h after tumor implantation. Control animals were injected on the same schedule with saline only. Animals were observed for 60 days or until the time of death. Antitumor activity was determined by comparing the median survival time of treated animals (*T*) with that of controls (*C*) and was expressed as the percentage increase in life span (% ILS), where % ILS = $(T/C - 1) \times 100$.

Acknowledgment. This research was supported by Grants CA 28001 and ACS CH 275, from the National Cancer Institute and the American Cancer Society, respectively.

Aminotetralone Analogues of Ketamine: Synthesis and Evaluation of Hypnotic and Locomotor Properties in Mice

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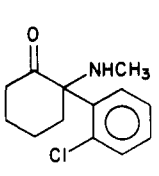
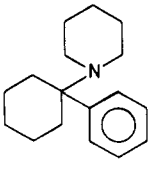
Ketamine and phencyclidine are structurally similar compounds that share many pharmacological actions, some of which are similar to the phenethylamines amphetamine and cathione. In order to integrate structural features of ketamine and cathinone, two groups of analogues, which are more conformationally restricted compared to the parent compounds, were synthesized for biological evaluation. These included 1-amino-1-methyl-2-tetralone and 2-amino-2-methyl-1-tetralone was well as several N-substituted derivatives of these molecules. Locomotor activity testing in mice revealed that 2-amino-2-methyl-1-tetralone caused an increase in locomotor activity while 1-amino-1-methyl-2-tetralone depressed spontaneous locomotor activity. None of the compounds produced hypnosis or profound ataxia.

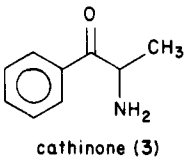
Ketamine, 2-(*o*-chlorophenyl)-2-(methylamino)cyclohexanone (**1**), a dissociative anesthetic agent, is a phencyclidine (**2**) derivative that produces a profound analgesia



ketamine (1)



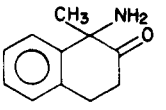
phencyclidine (2)



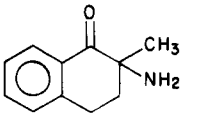
cathinone (3)

characterized by a trancelike, cataleptic state with mild hypertonus, cardiovascular stimulation, and a lack of respiratory depression at subhypnotic doses.[1,2] While reports have appeared regarding the influence of ring conformation upon the biological activity of phencyclidine, no similar data are available for ketamine.[3,4] The present study describes the syntheses and preliminary biological evaluations of a new group of ketamine analogues that are conformationally more rigid than the parent molecule.

These compounds can be visualized as having structures whose benzene rings are fused to a cyclohexanone ring, restricting conformational flexibility. The first group of prototypes that were prepared included derivatives of 1-amino-1-methyl-2-tetralone (**4**), and the second group



4



5

consisted of analogues of the isomeric 2-amino-2-methyl-1-tetralone (**5**). Compound **4** was chosen because of its

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