1-(Fluorobenzyl)-4-amino-1*H*-1,2,3-triazolo[4,5-*c*]pyridines: Synthesis and Anticonvulsant Activity

James L. Kelley,*,† Cecilia S. Koble,† Ronda G. Davis,† Ed W. McLean,† Francis E. Soroko,‡ and Barrett R. Cooper‡

Divisions of Organic Chemistry and Pharmacology, Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709

Received April 28, 1995®

A series of (fluorobenzyl)triazolo[4,5-*c*]pyridines was synthesized and tested for activity against maximal electroshock-induced seizures in rodents. The most promising compound, **14** (BW 534U87), which is a carbon–nitrogen isoster of a purine anticonvulsant, has a profile in rodents that suggests **14** will be free of emesis and useful in the treatment of seizure disorders for which phenytoin is presently indicated.

Although a variety of drugs of diverse chemical structure are used in the treatment of epilepsy,[1] many patients fail to experience satisfactory seizure control with them, or they do so at the expense of significant side effects.[2,3] In light of the need for improved antiepileptic drugs, a research program was initiated to discover and develop potential antiepileptic agents with improved properties.[4–12] The potent anticonvulsant purine **30** (BW A78U) emerged from this program,[6,8] but clinical development was curtailed owing to emesis and nausea in phase 1A clinical trials.[10] In an effort to develop an analogue of **30** free of emesis, the structure of **30** was modified by isosteric replacement of the heterocyclic ring atoms.[9–12] Although analogues with imidazo[4,5-*c*]pyridine,[9] pyrrolo[2,3-*d*]pyrimidine,[10] triazolo[4,5–*d*]pyrimidine,[10] pyrazolo[3,4-*d*]pyrimidine,[10] imidazo[4,5-*d*]triazine,[11] pyrazolo[3,4-*d*]triazine,[11] imidazo[4,5-*c*]pyridazine,[12] imidazo[4,5-*d*]pyridazine,[12] and benzimidazole[12] ring systems were prepared, none exhibited properties appropriate for development as a candidate antiepileptic agent. However, we have discovered a series of triazolo[4,5-*c*]pyridine isosteric analogues of **30** that show potent activity against maximal electroshock-induced seizures (MES) in rats. The most promising compound, **14** (BW 534U87), is a carbon–nitrogen isoster of **30** with a pharmacological profile in rodents that suggests it will be free of emesis and useful in the treatment of seizure disorders for which phenytoin is presently indicated. The synthesis and anticonvulsant activity of this new series of seizure control agents are reported therein.

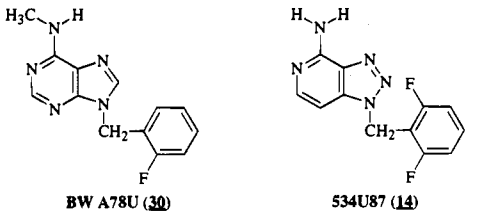
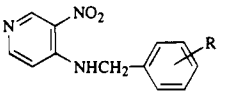


FIGURE 1.

Chemistry

Compounds **1**–**18** (Table 3) were prepared in six stages from 4-hydroxypyridine (Scheme 1). This pyridine was nitrated with fuming nitric acid to give 4-hydroxy-3-nitropyridine,[13–15] which was converted to the unstable 4-chloro-3-nitropyridine **I** with phosphorus pentachloride.[13–16] When **I** was reacted with the appropriate benzylamine, benzylaminopyridines **II** (**19**–**25**) were obtained in 54–93% yields. The nitropyridines **II** were reductively chlorinated with stannous chloride in hot concentrated hydrochloric acid[13,17,18] to provide 2-chloro-3-amino-4-(benzylamino)pyridines **III** (**26**–**29**). The structural assignment for **III** was confirmed by reaction of **26** with triethyl orthoformate to give 4-chloro-1-(2-fluorobenzyl)-1*H*-imidazo[4,5-*c*]pyridine.[9] The diaminopyridines **III** were treated with sodium nitrite in hydrochloric acid[19,20] to give **IV**. The triazolopyridine **IV** was not isolated, but it was reacted in situ with the

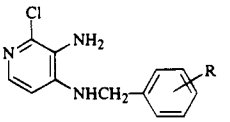
Table 1. Physical Properties of 3–Nitropyridines



no.	R	yield,[a] %	mp, °C	formula[b]
19	H	93[c]	99–103	$C_{12}H_{11}N_3O_2$
20	2-F	80	108–109	$C_{12}H_{10}FN_3O_2$
21	3-F	54[d]	94–97	$C_{12}H_{10}FN_3O_2$
22	4-F	75[c]	135–137	$C_{12}H_{10}FN3O_2$
23	2,6-F_2	88	148–149	$C_{12}H_9F_2N_3O_2$
24	2,5-F_2	77[c]	109–113	$C_{12}H_9F_2N_3O_2$
25	2-CF_3	73[e]	103–107	$C_{13}H_{10}F_3N_3O_2$

[a] All compounds were prepared by method A. [b] All compounds were analyzed for C, H, and N. [c] Recrystallized from cyclohexane–ethyl acetate. [d] Recrystallized from cyclohexane–2-propanol. [e] Recrystallized from cyclohexane.

Table 2. Physical Properties of 3-Amino-2-chloropyridines



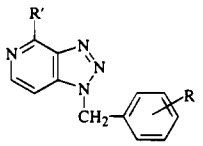
no.	R	yield,[a] %	mp, °C	formula[b]
26	2-F	84	185–187	$C_{12}H_{11}ClFN_3$
27	3-F	30[c]	175–178	$C_{12}H_{11}ClFN_3$
28	2,6-F_2	42[c]	222–225	$C_{12}H_{10}ClF_2N_3$
29	2-CF_3	82[c]	184–186	$C_{13}H_{11}ClF_3N3$

[a] All compounds were prepared by method B. [b] All compounds were analyzed for C, H, and N. [c] Recrystallized from cyclohexane–ethanol.

† Division of Organic Chemistry.
‡ Division of Pharmacology.
® Abstract published in *Advance ACS Abstracts,* September 1, 1995.

0022-2623/95/1838-4131$09.00/0

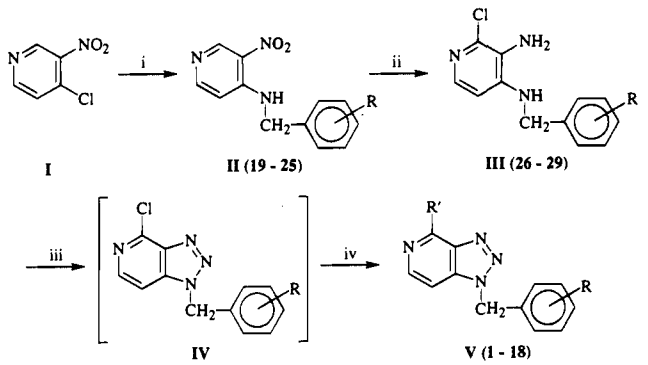
Table 3. Physical Properties of Triazolo[4,5-c]pyridines



no.	R′	R	method[a]	yield, %	mp, °C	formula[b,c]
1	NH_2	H	C	74[d]	253–258	$C_{12}H_{11}N_5$·HCl
2	$NHCH_3$	H	D	39[e]	269–273	$C_{13}H_{13}N_5$·HCl
3	NH_2	2-F	C	60[f]	281–283	$C_{12}H_{10}FN_5$·HCl
4	$NHCH_3$	2-F	D	79[f]	280–282	$C_{13}H_{12}FN_5$·HCl
5	$NHCH_2CH_3$	2-F	D	84[f]	258–260	$C_{14}H_{14}FN_5$·HCl
6	$NHCH_2CH_2CH_3$	2-F	D	90[f]	239–244	$C_{15}H_{16}FN_5$·HCl
7	$NHCH(CH_3)_2$	2-F	D	63[g]	215–219	$C_{15}H_{16}FN_5$·HCl
8	NHC_3H_5[j]	2-F	D	72[f]	245–247	$C_{15}H_{14}FN_5$·HCl
9	$NHCH_2C_3H_5$[j]	2-F	D	84[f]	246–248	$C_{16}H_{16}FN_5$·HCl
10	$N(CH_3)_2$	2-F	D	69[h]	248–252	$C_{14}H_{14}FN_5$·HCl
11	$N(CH_3)CH_2CH_3$	2-F	D	51[f]	205–208	$C_{15}H_{16}FN_5$·HCl·$^1/_4H_2O$
12	$NHCH_3$	3-F	D	90[f]	280–288	$C_{13}H_{12}FN_5$·HCl
13	$NHCH_3$	4-F	D	60[f]	283–285	$C_{13}H_{12}FN_5$·HCl
14	NH_2	2,6-F_2	C	78[i]	272–278	$C_{12}H_9F_2N_5$·HCl
15	$NHCH_3$	2,6-F_2	D	76[i]	278–284	$C_{13}H_{11}F_2N_5$·HCl
16	NH_2	2,5-F_2	C	78[i]	288–293	$C_{12}H_9F_2N_5$·HCl
17	$NHCH_3$	2,5-F_2	D	88[f]	273–278	$C_{13}H_{11}F_2N_5$·HCl
18	$NHCH_3$	2-CF_3	D	78[f]	278–282	$C_{14}H_{12}F_3N_5$·HCl

[a] See the Experimental Section. [b] All compounds were analyzed for C, H, and N. [c] All compounds were characterized and tested as the hydrochloride salts. [d] Precipitated from a solution of the free base in 2-methoxyethanol with concentrated hydrochloric acid followed by suspension in 2-propanol. [e] Recrystallized from water with concentrated hydrochloric acid. [f] Precipitated from a solution of the free base in ethanol with concentrated hydrochloric acid. [g] Recrystallized from 2-propanol with concentrated hydrochloric acid. [h] Recrystallized from 2-propanol. [i] Precipitated from a solution of the free base in 2-methoxyethanol with concentrated hydrochloric acid. [j] Cyclopropyl substituent.

Scheme 1[a]



[a] (i) 2-Fluorobenzylamine, Et_3N, H_2O/dioxane; (ii) $SnCl_2$, concentrated HCl, 90 °C; (iii) aqueous HCl, $NaNO_2$; (iv) NH_3, EtOH.

appropriate amine to give the 4-(alkylamino)triazolo-[4,5-c]pyridines **1**–**18** in 39–90% yields. The 4-amino derivatives were obtained by reaction of isolated **IV** with ammonia in ethanol at 125 °C.

Biological Results and Discussion

The compounds in Table 4 were evaluated for anticonvulsant activity in the MES test in male rats.[5] The lead compound, purine **30**, protected animals against MES with an ip ED_{50} of 1.7 mg/kg and an oral ED_{50} of 2.5 mg/kg.[6,8] The triazolopyridine analogue **4** also displayed potent activity against MES with ip and oral ED_{50}'s of 4.6 mg/kg. Thus, the triazolo[4,5–c]pyridine ring system of **4** serves as an effective isosteric replacement for the purine ring of **30**.

The effect of varying the 6-methylamino substituent of **4** was investigated (Table 4). The desmethyl analogue **3** (4-NH_2) was 6-fold less active ip. The monoalkylamino derivatives **5** (4-$NHCH_2CH_3$), **6** (4-$NH(CH_2)_2CH_3$), **7** (4-$NHCH(CH_3)_2$), and **9** (4-$NHCH_2C_3H_5$) were also less active by the ip or oral routes of administration. Only the cyclopropylamino analogue **8** retained good potency with ip and oral ED_{50}'s of 5.6 and 6.3 mg/kg, respectively. Addition of a second *N*-methyl substituent on **4** gave **10** (4-$N(CH_3)_2$), which showed activity comparable to both **4** and **8**. However, the ethyl analogue **11** (4-$N(CH_3)CH_2CH_3$) was more than 5-fold less active when tested ip.

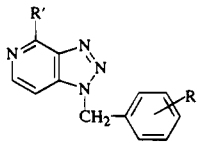
The effect of aryl substituents on anticonvulsant activity was investigated. The desfluoro analogue **2** and 3-fluoro analogue **12** were one-half as potent as **4**, whereas the 4-fluoro **13** was about 3-fold less potent. Substitution of a 2-CF_3 (**18**) group resulted in a greater than 5-fold loss in potency. Introduction of a second fluorine substituent gave three compounds (**14**, **15**, and **17**) with excellent activity by the oral route of administration with ED_{50}'s of 3.7, 5.3, and 4.3 mg/kg, respectively. Thus, preparation and evaluation of triazolopyridine analogues of purine **30** have led to several compounds with potent anticonvulsant activity against MES.

The most potent agents were evaluated in a variety of secondary pharmacological tests, and **14** emerged as the most promising candidate for further evaluation. Acutely administered **14** was not emetic in dog at multiples of the estimated anticonvulsant dose. The compound produced minimal effects in rats up to 1000 mg/kg po, and there were no untoward receptor, autonomic, or cardiovascular effects in the anticonvulsant dose range. Compound **14** is a candidate for clinical evaluation as an anticonvulsant for generalized tonic–clonic and complex–partial seizures in humans.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas–Hoover Unimelt and are uncorrected. NMR spectra were recorded on a Varian FT-80A, a Varian XL-

Table 4. Anticonvulsant Activity of Triazolo[4,5-c]pyridines against Maximal Electroshock-Induced Seizures[a]



no.	R′	R	MES ED_{50}, mg/kg[b,c] ip	MES ED_{50}, mg/kg[b,c] po
1	NH_2	H	8.7 ± 1.4	20 ± 1
2	$NHCH_3$	H	6.3 ± 1.4	10 ± 1
3	NH_2	2-F	28.4 ± 1.4	11.5 ± 2.4
4	$NHCH_3$	2-F	4.6 ± 1.1	4.6 ± 1.3
5	$NHCH_2CH_3$	2-F	8	10
6	$NH(CH_2)_2CH_3$	2-F	14.4 ± 3.1	>25
7	$NHCH(CH_3)_2$	2-F	14.2 ± 1.7	>25
8	NHC_3H_5	2-F	5.6 ± 1.1	6.3 ± 0.8
9	$NHCH_2C_3H_5$	2-F	40	
10	$N(CH_3)_2$	2-F	6.3	6.6
11	$N(CH_3)CH_2CH_3$	2-F	>25	
12	$NHCH_3$	3-F	10 ± 2	
13	$NHCH_3$	4-F	17	
14[d]	NH_2	2,6-F_2	6.3 ± 1.7	3.7 ± 1.4
15	$NHCH_3$	2,6-F_2	7.8 ± 1.4	5.3 ± 0.5
16	NH_2	2,5-F_2	18	
17	$NHCH_3$	2,5-F_2	5	4.3
18	$NHCH_3$	2-CF_3	>25	
30			1.7 ± 0.4	2.5 ± 0.2
phenytoin			10 ± 2	20 ± 3

[a] The compounds were tested for their ability to protect Charles River Wistar strain male rats against maximal electroshock-induced seizures as described in ref 5. The ED_{50} was the dose needed to protect 50% of the animals against the hind limb extensor component, and values were calculated by the method of Miller and Tainter (*Proc. Soc. Exp. Biol. Med.* **1944**, *57*, 261). [b] The compounds were administered as solutions or fine dispersions in water or 0.5% methyl cellulose. Samples that were not completely soluble were micronized to enhance the uniformity of sample delivery. [c] Where ED_{50} values are presented with a standard error, a minimum of 12 animals were used per dose level with four doses per compound. ED_{50} values without standard error were determined by using three doses of compound with six animals per point. [d] The Burroughs Wellcome Co. internal registration number for **14** is BW534U87.

100-15-FT, a Varian XL-200, or a Varian XL-300 spectrometer with Me_4Si as an internal standard. Mass spectra (~50 eV) were obtained from Oneida Research Services, Whitesboro, NY, using a Finnegan 4500 TFQ mass spectrometer. Each analytical sample has spectral data compatible with its assigned structure and moved as a single spot on TLC. Chromatograms were developed on Whatman 200 μm MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography[21] was performed on silica gel 60 (40–63 μm, E. Merck No. 9385). The analytical samples gave combustion values for C, H, and N within 0.4% of the theoretical values. Elemental analyses were performed by Atlantic Microlab, Inc.

Method A. 4[(2-Fluorobenzyl)amino]-3-nitropyridine (20). A mixture of 4-chloro-3-nitropyridine[13–16] (22.19 g, 0.140 mol), 2-fluorobenzylamine (16.04 g, 0.128 mol), and water/dioxane (8:3) (220 mL) was stirred at ambient temperature for 30 min. The reaction mixture was cooled in an ice bath, and triethylamine (107 mL) was added dropwise. A precipitate formed, and the mixture was stirred for 30 min at ice bath temperature followed by 15 h at ambient temperature. The suspension was diluted with water (300 mL). The solids were collected, dried, dissolved in dichloromethane, and added to silica gel 60. This mixture was spin evaluated *in vacuo*, and the residual solids were added to a column (5 cm × 25 cm) of silica gel 60 wetted with dichloromethane/ethyl acetate (5:1). The column was eluted with the same solvent using the flash chromatography technique. The appropriate fractions were combined and spin evaporated *in vacuo* to give 25.5 g (80%) of **20** as a bright yellow solid: mp 108–109 °C; UV (0.1 N hydrochloric acid + 5% methanol) λ_{max} 231 (ξ 16 600), 268 (ξ 14 700), 345 (ξ 4200), (pH 7.0 buffer + 5% methanol) 237 (ξ 22 600), 378 (ξ 5900), (0.1 N sodium hydroxide + 5% methanol) 237 (ξ 20 500), 378 nm (ξ 5400); NMR (DMSO-d_6) δ 9.05 (s, 1H, pyridine H-2), 8.89 (t, 1H, NH), 8.22 (d, 1H, J = 6 Hz, pyridine H-6), 7.4–7.1 (m, 4H, Ar), 6.84 (d, 1H, J = 6 Hz, pyridine H-5), 4.71 (d, 2H, J = 6 Hz, CH_2).

Method B. 3-Amino-2-chloro-4-[2-fluorobenzyl)amino]-pyridine (26). A mechanically stirred solution of **20** (12.31 g, 49.8 mmol) in concentrated hydrochloric acid (118 mL) was heated to 90 °C under a nitrogen atmosphere. Stannous chloride dihydrate (55.56 g, 246 mmol) was added in small portions over a 5-min period (the oil bath was removed until the reaction subsided). After an additional 30 min at 90 °C, the reaction mixture was cooled, diluted with water (200 mL), and spin evaporated *in vacuo*. The residue was diluted with water (200 mL) and cooled in an ice bath while concentrated ammonium hydroxide was added to adjust the pH to 7–8. The solids were collected and allowed to air-dry overnight. The solid was treated with ethyl acetate and filtered (12 × 200 mL); the combined extracts were washed with water, dried (sodium sulfate), and spin evaporated *in vacuo*. The residue was combined with the product from a separate reaction (12 g, 48.5 mmol) and dissolved in ethyl acetate. This solution was added to silica gel 60 and spin evaporated *in vacuo*. The residual solids were introduced in a column (5 cm × 30 cm) of silica gel 60 wetted with ethyl acetate. The column was eluted with ethyl acetate using flash chromatography. The appropriate fractions were combined and spin evaporated *in vacuo* to give 20.8 g (84%) of **26** as a white solid: mp 185–187 °C; UV (0.1 N hydrochloric acid + 5% methanol) λ_{max} 233 (ξ 17 900), 302 (ξ 14 900), (pH 7.0 buffer + 5% methanol) 262 (ξ 11 200), (0.1 N sodium hydroxide + 5% methanol) 262 nm (ξ 10 700); NMR (DMSO-d_6) δ 7.36–7.15 (complex m, 5H, Ar + pyridine H-6), 6.35–6.30 (d, 1H, pyridine H-5), 6.27–6.33 (overlapping, 1H, NH), 4.84 (2, 2H, NH_2), 4.41 (d, 2H, J = 5 Hz, CH_2Ar).

Method C. 4-Amino-1-(2-fluorobenzyl)-1*H*-1,2,3-triazolo[4,5-*c*]pyridine Hydrochloride (3). To an ice-cold solution of **26** (4 g, 15.9 mmol), 1 N hydrochloric acid (40 mL), concentrated hydrochloric acid (15 mL), and ethanol (75 mL) was added sodium nitrite (1.31 g, 18.9 mmol). The solution was stirred for 15 min, concentrated ammonium hydroxide was added to adjust the pH to 9–10, and the solution was extracted with chloroform (2 × 100 mL). The combined extracts were washed with water, dried (sodium sulfate), and spin evaporated *in vacuo*. A mixture of the residue and ammonia-saturated ethanol (200 mL) was heated (125 °C) overnight in a glass-lined, stainless steel vessel. The reaction mixture was cooled, and the solids were collected on a Büchner funnel. The solid was dissolved in 1.1 L of hot ethanol and then diluted with concentrated hydrochloric acid (200 mL). The mixture was concentrated and cooled to give a white solid, which was collected to give 2.68 g (60%) of **3** hydrochloride: mp 281–283 °C dec; UV (0.1 N hydrochloric acid + 5% methanol) λ_{max} 270 (ξ 11 500), (pH 7.0 buffer + 5% methanol) 291 (ξ 7400), (0.1 N sodium hydroxide + 5% methanol) 296 nm (ξ 5600); NMR (DMSO-d_6) δ 9.42 (br s, 2H, NH_2), 7.86 (d, 1H, J = 7 Hz, pyridine H-6), 7.5–7.2 (m, 5H, Ar + pyridine H-7), 6.02 (s, 2H, CH_2).

Method D. 1-(2-Fluorobenzyl)-4-(methylamino)-1*H*-1,2,3-triazolo[4,5-*c*]pyridine Hydrochloride (4). To an ice-cold solution of **26** (4.0 g, 15.9 mmol), 1 N hydrochloric acid (40 mL), concentrated hydrochloric acid (15 mL), and ethanol (120 mL) was added sodium nitrite (1.31 g, 18.9 mmol). The solution was stirred for 15 min, and 40% aqueous methylamine (100 mL) was added. The solution was refluxed with stirring for 30 min. The reaction mixture was cooled, and the solid was collected and washed with water. The solid was dissolved in hot ethanol (155 mL) and then diluted with concentrated hydrochloric acid (55 mL). The solution was cooled, and the white solid was collected to give 3.72 g (79%) of **4** hydrochloride: mp 280–282 °C dec; UV (0.1 N hydrochloric acid + 5% methanol) λ_{max} 280 (ξ 12 900), (pH 7.0 buffer + 5% methanol) 302 (ξ 8600), (0.1 N sodium hydroxide + 5% methanol) 306 nm (ξ 9000); NMR (DMSO-d_6) δ 10.2 (br m, 1H, NH), 7.84 (d,

1H, J = 7 Hz, pyridine H-6), 7.5–7.2 (m, 5H, Ar + pyridine H-7), 6.03 (s, 2H, CH_2), 3.13 (br s, 3H, CH_3).

Acknowledgment. The authors acknowledge the assistance of M. Notrica and C. J. Burchall who performed the anticonvulsant tests. Compound **23** was prepared by Dr. J. D. Wilson and M. J. Fugett of the Burroughs Wellcome Co. Chemical Development Laboratories. We thank Dr. B. S. Hurlbert, and Dr. G. E. Martin, and their staff for NMR spectra. We are indebted to D. T. Staton for the art work, the Burroughs Wellcome Co. Research Document Center for assistance in preparation of the manuscript, and L. M. Cotterman for proofreading the final draft.

References

(1) AMA Div. of Drugs. *AMA Drug Evaluations*, 5th ed.; American Medical Assoc.: Chicago, IL, 1983; p 295.
(2) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. Antiepileptic Drug Development: II. Anticonvulsant Drug Screening. *Epilepsia* **1978**, *19*, 409–428.
(3) Krall, R. L.; Penry, J. K.; Kupferberg, H. J.; Swinyard, E. A. Antiepileptic Drug Development: I. History and a Program for Progress *Epilepsia* **1978**, *19*, 393–408.
(4) Soroko, F. E.; Grivsky, E.; Maxwell, R. A. Cinromide (3-bromo-*N*-ethylcinnamamide), a Novel Anticonvulsant Agent. *J. Pharm. Pharmacol.* **1981**, *33*, 741–743.
(5) Mehta, N. B.; Diuguid, C. A. R.; Soroko, F. E. Potential Anticonvulsants. 1. 5-Benzylhydantoins. *J. Med. Chem.* **1981**, *24*, 465–468.
(6) Kelley, J. L.; Soroko, F. E. 9-(2-Fluorobenzyl)-6-(methylamino)-9*H*-purine Hydrochloride. Synthesis and Anticonvulasant Activity. *J. Med. Chem.* **1986**, *29*, 1133–1134.
(7) Kelley, J. L.; Krochmal, M. P.; Linn, J. A.; McLean, E. W.; Soroko, F. E. 6-(Alkylamino)-9-benzyl-9*H*-purines. A new Class of Anticonvulsant Agents. *J. Med. Chem.* **1988**, *31*, 606–612.
(8) Kelley, J. L.; Krochmal, M. P.; Linn, J. A.; McLean, E. W.; Soroko, F. E. 9-(2-Fluorobenzyl)-6-(alkylamino)-9*H*-purines. A New class of Anticonvulsant Agents. *J. Med. Chem.* **1988**, *31*, 1005–1009.
(9) Kelley, J. L.; Linn, J. A.; Rideout, J. L.; Soroko, F. E. Synthesis and Anticonvulsant Activity of 1-Benzyl-4-Alkylamino-1*H*-Imidazo-[4,5-c]pyridines. *J. Heterocycl. Chem.* **1988**, *25*, 1255–1258.
(10) Kelley, J. L.; Davis, R. G.; McLean, E. W.; Notrica, M.; Soroko, F. E.; Cooper, B. R.; Glen, R. C. Synthesis and Anticonvulsant Activity of *N*-Benzyl Pyrrolo[2,3-*d*]-, Pyrazolo[3,4–*d*]-, and Triazolo[4,5–*d*]pyrimidines. Imidazole Ring Modified Analogues of 9-(2-Fluorobenzyl)-6-(methylamino)-9*H*-purine. *J. Med. Chem.*, in press.
(11) Kelley, J. L.; Wilson, D. C.; Styles, V. L.; Soroko, F. E.; Cooper, B. R. 7-(2-Fluorobenzyl)-4-(substituted)-7*H*-imidazo-[4,5–d]-1,2,3-triazines and 7*H*-pyrazolo[3,4-*d*]-1,2,3-triazines. Synthesis and Anticonvulsant Activity. *J. Heterocycl. Chem.*, in press.
(12) Kelley, J. L.; Thompson, J. B.; Styles, V. L.; Soroko, F. E.; Cooper, B. R. Synthesis and Anticonvulsant Activity of 3*H*-Imidazo[4,5-*c*]pyridazine, 1*H*-Imidazo[4,5-*d*]pyridazine and 1*H*-Benzimidazole Analogues of 9-(2-Fluorobenzyl)-6-methylamino-9*H*-purine. *J. Heterocycl. Chem.*, in press.
(13) Houston, D. M.; Dolence, E. K.; Keller, B. T.; Patel-Thombre, U.; Borchardt, R. T. Potential Inhibitors of *S*-Adenosylmethionine-Dependent Methyltransferases. 8. Molecular Dissections of Carbocyclic 3-Deazaadenosine as Inhibitors of *S*-Adenosylhomocysteine Hydrolase. *J. Med. Chem.* **1985**, *28*, 467–471.
(14) Kruger, S.; Mann, F. G. Xanthones and Thioxanthones. Part VI. The Preparation and Properties of 9-Thia-3-aza-anthrone. *J. Chem. Soc.* **1955**, 2755–2763.
(15) Campbell, J. B.; Greene, J. M.; Lavagnino, E. R.; Gardner, D. N.; Pike, A. J.; Snoddy, J.; Taylor, E. C. Some New Methods for Preparing 2,3- and 3,4-Diaminopyridines. *J. Heterocycl. Chem.* **1986**, *23*, 669–672.
(16) Wright, G. C. Rearrangement of Ethyl 2-(3-Amino-4-pyridinyl)-hydrazinecarboxylate Hydrochloride to 1-Amino-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)one Hydrochloride. *J. Heterocycl. Chem.* **1976**, *13*, 601–603.
(17) Koenig, E.; Mields, M.; Gurlt, H. Nitrierungsprodukte des γ-Amino-pyridins. *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1179–1187.
(18) Mizuno, Y.; Itoh, T.; Saito, K. Studies on Condensed Systems of Aromatic Nitrogenous Series. XXIV. Synthesis of 4-Substituted 1*H*-Imidazo-[4,5-*c*]pyridines. *Chem. Pharm. Bull.* **1964**, *12*, 866–872.
(19) Shealy, Y. F.; Clayton, J. D.; O'Dell, C. A. Cyclopentyl Derivatives of 8-Azahypoxanthine and 8-Azaadenine. Carbocyclic Analogs of 8-Azainosine and 8-Azaadenosine (1). *J. Heterocycl. Chem.* **1973**, *10*, 601–605.
(20) Vince, R.; Brownell, J.; Daluge, S. Carbocyclic Analogues of Xylofuranosylpurine Nucleosides. Synthesis and Antitumor Activity. *J. Med. Chem.* **1984**, *27*, 1358–1360.
(21) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.

JM9503153