Acknowledgment. The authors are greatly indebted to the staff of the Department of Pharmacology for the diuretic screening of the compounds described in this paper and to Hanne G. Schmidt and W. Schlichtkrull for skillful technical assistance.

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†In this reference the term metanilic acid has been used erroneously for 3-aminobenzoic acid throughout.

4-Anilino-1-phenyl-3-pyrrolecarboxylic Acids. Analogs of the Fenamic Acids

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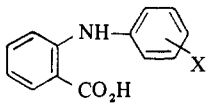
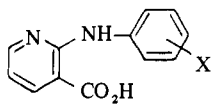
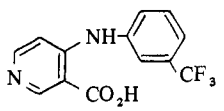
Substitution of a pyridine ring for the benzene ring of the antiinflammatory fenamic acids–flufenamic acid (**1a**), mefenamic acid (**1b**), and meclofenamic acid (**1c**)[1]–has given niflumic acid (**2a**, antiinflammatory),[2] clonixin (**2b**, antiinflammatory),[3] and triflocin (**3**, diuretic).[4] Incorporation of a thiophene ring in the molecule has produced the antiinflammatory analogs **4a–c**.[5] We now report the synthesis of several pyrrole analogs **9** of the fenamic acids.



1a, X = 3-CF_3
b, X = 2,3-$(CH_3)_2$
c, X = 2,6-Cl_2-3-CF_3

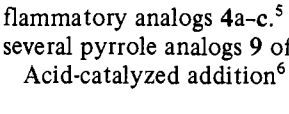


2a, X = 3-CF_3
b, X = 3-Cl-2-CH_3

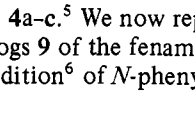


3

Acid-catalyzed addition[6] of *N*-phenylglycine ethyl ester to ethyl acrylate gave the diester **5**, which underwent Dieckmann cyclization to the known[7] β-keto ester **6**. Treatment of **6** with the appropriate anilines provided the enamino esters **7** (Table I). S dehydrogenation of **7** yielded the ethyl anilinopyrrolecarboxylates **8** (Table II), which were saponified to the desired acids **9** (Table III).



4a, X = 3-CF_3
b, X = 3-Cl-2-CH_3
c, X = 2,6-Cl_2



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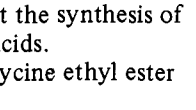
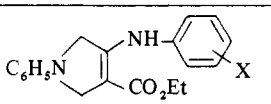


6

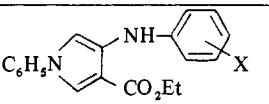
Compounds **9** were found† to be without activity in the rat paw carrageenin edema antiinflammatory assay,[8] the adjuvant-induced rat polyarthritis test,[9] and the phenyl-*p*-quinone writhing analgetic screen.[10]

Table I. Ethyl 4-Anilino-1-phenyl-3-pyrroline-3-carboxylates (7)



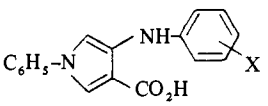
X	Mp, °C	Recrystn solv	Formula
H	129–130	Hexane	$C_{19}H_{20}N_2O_2$
3-CF_3	112–113	Hexane	$C_{20}H_{19}F_3N_2O_2$
2,3-$(CH_3)_2$	150–151	Hexane	$C_{21}H_{24}N_2O_2$
4-F	167–168	Hexane–C_6H_6	$C_{19}H_{19}FN_2O_2$

Table II. Ethyl 4-Anilino-1-phenyl-3-pyrrolecarboxylates (8)



X	Mp, °C	Recrystn solv	Formula
H	83	EtOH	$C_{19}H_{18}N_2O_2$
3-CF_3	81–82	EtOH	$C_{20}H_{17}F_3N_2O_2$
2,3-$(CH_3)_2$	80–81	EtOH	$C_{21}H_{22}N_2O_2$
4-F	100–101	EtOH	$C_{19}H_{17}FN_2O_2$

Table III. 4-Anilino-1-phenyl-3-pyrrolecarboxylic Acids (9)



X	Mp, °C	Recrystn solv	Formula
H	208	MeCN	$C_{17}H_{14}N_2O_2$
3-CF_3	189	MeCN	$C_{18}H_{13}F_3N_2O_2$
2,3-$(CH_3)_2$	192–193	MeCN	$C_{19}H_{18}N_2O_2$
4-F	212–213	MeCN	$C_{17}H_{13}FN_2O_2$

Experimental Section‡

***N*-(Carboxymethyl)-*N*-phenyl-β-alanine Diethyl Ester (5).** A mixt of 500 g (2.8 moles) of *N*-phenylglycine ethyl ester, 500 ml of ethyl acrylate, and 50 ml of HOAc was heated at 160° for 4 days in a bomb, cooled, dild with Et_2O, and filtered. The filtrate was washed with NaOH soln, dried ($MgSO_4$), and concd. The liquid was distd to provide, after collection of unreacted *N*-phenylglycine ethyl ester, 260 g (33%) of yellow liq, bp 195–210° (15–20 mm). Redistn of a small portion gave a colorless liquid, bp 200–204° (12 mm) [lit.[7] bp 210–211° (16 mm)]. *Anal.* ($C_{15}H_{21}NO_4$) C, H, N.

Ethyl 4-Oxo-1-phenyl-3-pyrrolidinecarboxylate (6). To a stirred mixt of 70 g (0.62 mole) of KO-*tert*-Bu and 3 l. of C_6H_6 was added dropwise during 1 hr 169 g (0.61 mole) of **5**. The mixt was heated under reflux for 3 hr, cooled, and filtered. The collected solid was suspended in 2 l. of H_2O, acidified with 45 ml of HOAc, and extd with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and concd to an oily solid. Recrystn (EtOH) gave 73 g (51%) of off-white crystals, mp 77–78°. Several recrystns gave colorless crystals, mp 97–98° (lit.[7]

†Animal testing was carried out by Drs. A. E. Sloboda and A. C. Osterberg of these laboratories.

‡Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. All compounds were analyzed for C, H, N, and F; found values were within ±0.4% of theoretical.

mp 69–70°; on other samples, mps between 69° and 87° were obsd). *Anal.* ($C_{13}H_{15}NO_3$) C, H, N.

Ethyl 4-Anilino-1-phenyl-3-pyrroline-3-carboxylates (7). A soln of 2.33 g (0.01 mole) of **6**, 0.012–0.015 mole of an aniline, and 50 ml of C_6H_6 was allowed to stand at room temp for 4 days, washed with 1 *N* HCl, dried ($MgSO_4$), and concd to a solid which was recrystd (see Table I).

Ethyl 4-Anilino-1-phenyl-3-pyrrolecarboxylates (8). A mixt of 1.0 g of **7** and 1.0 g of S was heated at 140° for 1 hr, cooled, dild with 8 ml of $CHCl_3$, filtered, and concd. The residue was chromatogd (three Analtech, Inc. Uniplate silica gel GF plates, 1000 μ thickness) with C_6H_6. The product bands were washed with $CHCl_3$, the soln was concd, and the residue was recrystd (see Table II).

4-Anilino-1-phenyl-3-pyrrolecarboxylic Acids (9). A mixt of 2.5 g of **8**, 60 ml of EtOH, and 60 ml of 1 *N* NaOH was heated under reflux for 1 hr, distd until 75 ml remained, dild with H_2O, filtered, and acidified with HOAc. The solid which sepd was collected and recrystd (see Table III).

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Some Derivatives of 9-Amino-9*H*-purine-6(1*H*)-thione†

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The anticancer activity of purine-6(1*H*)-thione, its 9-alkyl derivatives and compounds prepared from these thiones prompted the preparation and testing of some derivatives of 9-aminopurine-6(1*H*)-thione (**4**).[1]

The preparation and acidic hydrolysis of **3** to give **4** and the alkylation of the latter to give **1** and **2** has been reported.[2] Condensation of **1**, **2**, and **4** with C_6H_5CHO gave, respectively, **10**, **11**, and **14**. The reaction of **1** and **4** with 2,5-dimethoxytetrahydrofuran[3] gave the 9-pyrrol-1-yl-9*H*-purines **12** and **15**. Similarly condensation of **1** with 2,5-hexanedione gave **13**. Alkylation of the thione group of **3** with the appropriate alkyl halide gave **5**–**7**. A second alkylation of the acetamido group of **5** and **7** with $Br(CH_2)_4Cl$ gave **8** and **9**, respectively. Cyclization of **8** and **9** was effected with base to give the 9-pyrrolidin-1-yl-9*H*-purines **17** and **18**. Treatment of the latter with CF_3CO_2H removed the diphenylmethyl blocking group to give **16**.[4]

Compounds were tested against L1210 leukemic cells implanted ip in mice on single dose and chronic schedules.[5,6] The test results summarized in Table I indicate that the 9-aminopurines **2** and **4** and the 9-acetamidopurine **3** have activity and are less toxic than 6-mercaptopurine (6-MP). On the chronic schedule the activity of **2** is similar to that of 6-MP, whereas, the activities of **3** and **4** are lower. In con-

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Scheme I

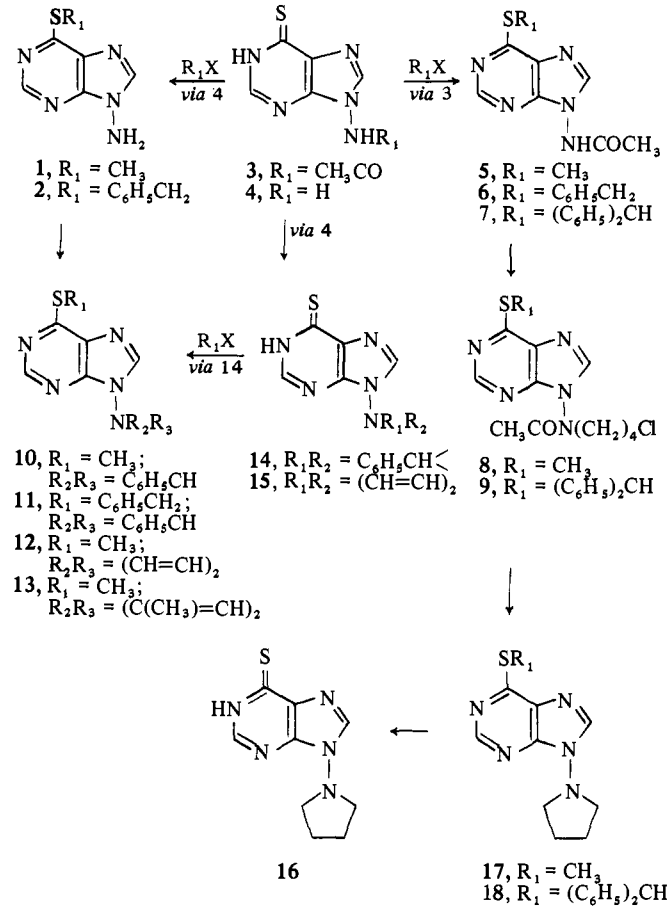

Table I. Activity of 9-Amino-9*H*-purine-6(1*H*)-thione and Derivatives against L1210 Leukemia Implanted Intraperitoneally

Compd	Dose, mg/kg per day	Schedule (ip)	ip L1210 (10^5 cells) Life span, days: Treated	Control	% ILS
6-MP[b]	380	day 2			39
	62	qd 2–16			60
2	62	qd 1–15	10.7	9.3	15
	93	qd 1–15	11.3	9.3	21
	140	qd 1–15	13.8	9.0	53[a]
	210	qd 1–15	12.7	9.3	36
3	177	day 1	9.3	8.7	6
	200	day 1	10.2	9.2	10
	266	day 1	13.4	8.7	54
	400	day 1	11.1	9.0	23[a]
	600	day 1		Toxic	
	100	qd 1–9	12.5	9.2	35
	200	qd 1–9	8.6	9.2	0
	400	qd 1–9		Toxic, chronic	
4	200	day 2	9.8	9.6	2
	266	day 2	9.8	8.5	15
	400	day 2	14.3	9.1	57[a]
	600	day 2		Toxic	
	72	qd 1–15	8.8	8.7	1
	120	qd 1–15	12.5	8.7	43
	200	qd 1–15	7.5	8.7	0
6	200	day 2	8.8	8.8	0
	266	day 2	10.6	9.2	15
	400	day 2	12.0	9.0	33
	600	day 2		Toxic, chronic	

[a] Average of 2 or 3 tests. [b] See ref 6.