ity 22) by eq 4 from the present study.

Acknowledgment. The authors are indebted to Mr. R. J. Costello of the Department of Computer and Information Sciences for the statistical studies.

References and Notes

(1) M. E. Wolff and C. Hansch, *J. Med. Chem.*, 17, 898 (1974).
(2) G. Teutsch, L. Weber, G. Page, E. L. Shapiro, H. L. Herzog, R. Neri, and E. J. Collins, *J. Med. Chem.*, **16**, 1370 (1973).
(3) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
(4) C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, **90**, 4328 (1968).
(5) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
(6) Use of an alternate steric measure, a half-sphere volume, described by Teutsch et al.,[2] gives an equation of the same form and an almost identical statistical fit.

4-Amino-5-arylpyrimidines as Antiinflammatory Agents

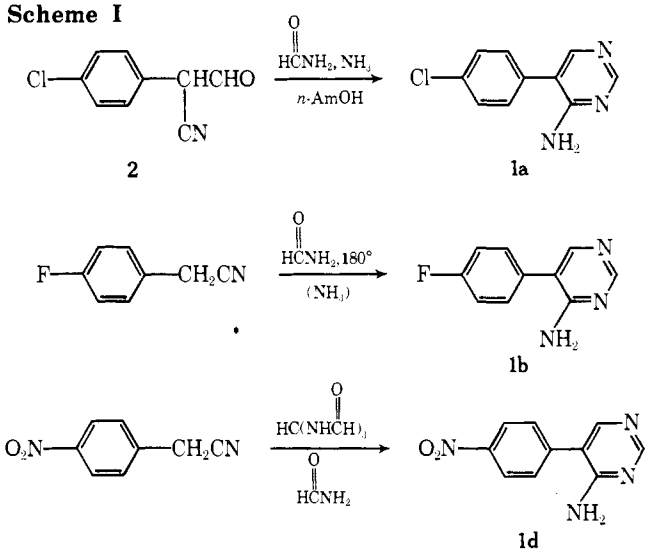
S. A. Lang, Jr.,* and E. Cohen

Metabolic Disease Therapy Research Section, Lederle Laboratories, Division of American Cyanamid Company, Pearl River, New York 10965. *Received October 7, 1974*

4-Amino-5-arylpyrimidines were synthesized by a variety of methods and have demonstrated antiinflammatory activity in the carrageenan-induced edema in the rat but displayed little activity against adjuvant-induced arthritis in rats or against uv-induced erythema in guinea pigs.

4-Amino-5-(*p*-chlorophenyl)pyrimidine (**1a**), which was obtained as a side product in a chemical sequence, was found to possess antiinflammatory activity in the rat carrageenan edema test. The title compounds, 4-amino-5-arylpyrimidines (**1**), were prepared by a variety of methods.[1-4] The treatment of phenylcyanoacetaldehydes (**2**) with formamide in refluxing *n*-amyl alcohol in a stream of NH_3 or with excess formamide at 170–179° gave **1** as the predominate product.[2] Other methods used involved heating of arylacetonitriles with excess formamide,[1] sometimes in a stream of NH_3,[3] producing moderate yields of **1**. Tris(formamino)methane[4-6] when reacted at 190° with arylacetonitriles gave good yields of 4-amino-5-arylpyrimidines[4] (Scheme I). The monoacylpyrimidine **4b** was obtained by refluxing **1e** in acetic acid–acetic anhydride.[2,3] The diacetylpyrimidine **4a** was obtained by heating **1a** in acetic anhydride–pyridine[2,3] on a steam bath.

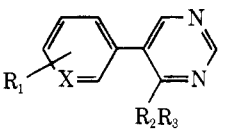
Scheme I



Pharmacology. The mono- and diacyl derivatives of several pyrimidines were prepared and were also active in the carrageenan-induced edema in the rat but also lacked activity in follow-up tests.

The acute antiinflammatory activity of the pyrimidines was determined using Royal Hart, Wistar strain rats. The differences in edema were considered to be due to drug efficacy and are expressed as a control (C)/treated (T) (untreated/treated) efficacy ratio (the ratio of mean edema of eight control animals which did not receive drugs over the mean edema of two treated rats). If the C/T ratio is equal to or greater than 1.41, the test was repeated with two additional rats. If the mean C/T in the four rats is equal to or greater than 1.43 the compound was accepted as active. The results are summarized in Table I.

Table I. Carrageenan-Induced Edema in the Rat

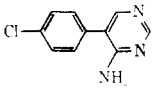
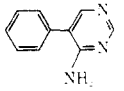
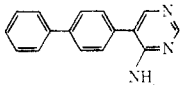
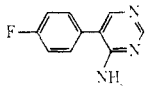
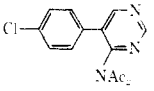
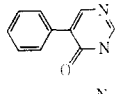
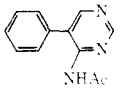
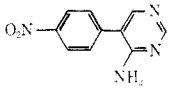
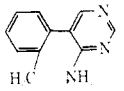
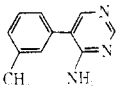
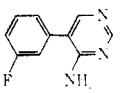
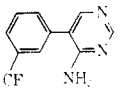
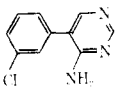
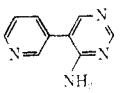
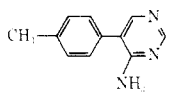
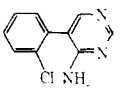
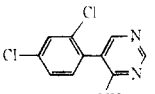
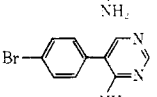


Compd	R_1	R_2	R_3	X	C/T[a]
1a	*p*-Cl	NH_2		CH	1.93
1b	*p*-F	NH_2		CH	1.83
1c	*p*-CH_3	NH_2		CH	2.24
1d	*p*-NO_2	NH_2		CH	<1.43
1e	H	NH_2		CH	5.10
1f	*p*-Ph	NH_2		CH	<1.43
1g	*o*-CH_3	NH_2		CH	3.28
1h	*m*-CH_3	NH_2		CH	3.99
1i	*m*-F	NH_2		CH	<1.43
1j	*m*-CF_3	NH_2		CH	<1.43
1k	*m*-Cl	NH_2		CH	2.52
1l	*o*-Cl	NH_2		CH	2.61
1m	2,4-Cl_2	NH_2		CH	<1.43
1n	*p*-Br	NH_2		CH	2.35
3a	*p*-Cl	NAc	Ac	CH	1.95
3b	H	H	NAc	CH	3.71
4a		OH		CH	2.55
4b		NH_2		N	<1.43
Controls (historical)					1.00
Aspirin					2.83

[a] Mean value (average value of four rats).

The carrageenan-induced edema is a general test for the discovery of antiarthritic agents[7] but is nonspecific and a large number of miscellaneous drugs with varying pharma-

Table II. Preparation of 4-Amino-5-arylpyrimidines

Compd	No.	Mp, °C	% yield[a]	Formula	Analyses	Recrystn solvent
	1a	198–201	28	$C_{10}H_8ClN_3$	*b*	$CHCl_3$
	1e	153–155	58	$C_{10}H_9N_3$	*c*	$CHCl_3$
	1f	245–248	18	$C_{16}H_{13}N_3$	C, H, N	$CHCl_3$–hexane
	1b	169–172	62	$C_{10}H_8FN_3$	C, H, N, F	$CHCl_3$
	3a	110–112	75	$C_{14}H_{12}ClN_3O_2$	C, H, N, Cl	$CHCl_3$–CCl_4
	4a	175–178	60	$C_{10}H_8N_2O$	*d*	$CHCl_3$
	3b	139–143	56	$C_{12}H_{11}N_3O$	*e*	$CHCl_3$–CCl_4
	1d	248–250	72	$C_{10}H_8N_4O_2$	*b*	$CHCl_3$
	1g	100–102	41	$C_{11}H_{11}N_3$	C, H, N	$CHCl_3$
	1h	148–150	78	$C_{11}H_{11}N_3$	C, H, N	$CHCl_3$–hexane
	1i	149–151	48	$C_{10}H_8FN_3$	C, H, N, F	$CHCl_3$–hexane
	1j	150–153	26	$C_{11}H_8F_3N_3$	C, H, N, F	$CHCl_3$–CCl_4
	1k	136–139	83	$C_{10}H_8ClN_3$	C, H, N, Cl	$CHCl_3$–CCl_4
	4b	196–199	23	$C_9H_8N_4$	C, H, N	$CHCl_3$
	1c	164–167	35	$C_{11}H_{11}N_3$	*d*	$CHCl_3$–hexane
	1l	180–183	45	$C_{10}H_8ClN_3$	C, H, N, Cl	CCl_4
	1m	178–181	15	$C_{10}H_7Cl_2N_3$	C, H, N, Cl	$CHCl_3$
	1n	219–222	75	$C_{10}H_8BrN_3$	C, H, N, Br	$CHCl_3$

[a] Isolated and recrystallized yields. [b] Reference 3. [c] References 1 and 2. [d] Reference 4. [e] References 2 and 3.

cological activity, without established antiarthritic value, give positive results.[8]

The aminopyrimidines were subsequently evaluated for efficacy in adjuvant-induced arthritis in rats and uv-induced erythema in guinea pigs but displayed no activity.

Experimental Section

Chemistry. All melting points are uncorrected and were observed on a Mel-Temp apparatus. Ir were recorded on a Perkin-Elmer 137 and unless otherwise noted were recorded as a KBr pellet. NMR were recorded on a Varian HA-100. All solvents were dried and used as is. The arylcyanoacetaldehydes were prepared by literature procedures.[9]

4-Amino-5-(*p*-fluorophenyl)pyrimidine (1b). A suspension of 7.5 g (0.042 mol) of the ammonium salt [prepared by placing 2-(*p*-fluorophenyl)-2-cyanoacetaldehyde in liquid NH_3 and allowing evaporation] in 15 ml of formamide was heated to 185° while a stream of dry NH_3 was bubbled through. After 3.5 hr, the solution was poured into aqueous HCl and extracted with $CHCl_3$. The aqueous phase was made basic with aqueous NaOH. The solid was collected and recrystallized from $CHCl_3$: mp 169–172° (4.92 g, 62%); NMR ($CDCl_3$) 6.40 (NH_2, exchange), 7.1–7.6 (m, 4), 7.90 (s, 1), 8.32 (s, 1). (See Table II.)

4-Amino-5-(*p*-chlorophenyl)pyrimidine (1a). A solution of 20 g (0.13 mol) of *p*-chlorophenylacetonitrile and 25 ml of formamide was heated at 190° for 8 hr. After cooling, the mixture was poured into HCl and extracted with $CHCl_3$. The aqueous phase was basified with NaOH and the solid collected. Recrystallization from methanol (charcoal) gave a white powder: mp 198–201° (lit.[3] mp 203–204°); yield 7.5 g (28%).

4-Amino-5-(*p*-tolyl)pyrimidine (1c). A mixture of *p*-tolylacetonitrile (25 g, 0.18 mol), tris(formamino)methane (53 g, 0.36 mol), and *p*-toluenesulfonic acid (3 g) in 35 ml of formamide was heated at 150° for 5 hr. The solution was poured into water; the solid was collected and recrystallized from chloroform–hexane: mp 166–168° (lit.[4] mp 166.5–167°); yield 11.7 g (35%).

4-Amino-5-(3-pyridyl)pyrimidine (4b). A mixture of the cyanoaldehyde (20 g, 0.14 mol) and formamide (25 ml) was heated to reflux for 14 hr while a stream of dry NH_3 was passed through. After cooling, the sludge was poured into H_2O, acidified and treated with charcoal, and extracted with $CHCl_3$. Basification gave a solid which was recrystallized from $CHCl_3$–CCl_4: mp 196–199° (5.4 g, 23%); NMR ($CDCl_3$–DMSO-d_6), 6.2 (NH_2, exchange), 7.4 (d of d, 1, J = 9.0 and 5.0 Hz), 7.7 (t of d, 1, J = 9.0 and 2.0 Hz), 8.05 (s, 1), 8.45 (s, 1), 8.65 (m, 2).

4-Amino-5-(*p*-chlorophenyl)pyrimidine Diacetate (2a). A solution of 4 g (0.019 mol) of 4-amino-5-(*p*-chlorophenyl)pyrimidine in 15 ml of acetic anhydride and 10 ml of pyridine was heated on a steam bath for 2 hr. The solution was poured into ice water and, after 1 hr, extracted with $CHCl_3$. The solvent was removed and the solid recrystallized from $CHCl_3$–hexane: mp 110–112° (4.2 g, 75%); NMR ($CDCl_3$) 2.2 (s, 6), 7.2 (d, 2, J = 9 Hz), 7.5 (d, 2, J = 9 Hz), 8.85 (s, 1), 9.25 (s, 1). The HCl salt was prepared by dissolving the diacetate in ether and adding ethereal HCl. The solid collected had mp 198–203° (lit.[3,6] mp 200–204°).

4-Amino-5-phenylpyrimidine Acetate (3b). A solution of 5 g (0.029 mol) of 4-amino-5-phenylpyrimidine in 10 ml of acetic anhydride and 15 ml of HOAc was refluxed for 2 hr. The solution was poured into ice water and extracted with $CHCl_3$. The solvent was removed and the residue recrystallized from $CHCl_3$–hexane: mp 139–143° (lit.[2,3] mp 139–140°); yield 3.47 g (56%).

Pharmacologic Testing. Rats were fasted overnight prior to dosing but had free access to water. The drugs were administered in an aqueous suspension by gavage in a volume of 1.7 ml/50-g rat,[7] which corresponds to a dosage of 250 mg/kg.

The phlogistic agent used was a sterile 1% suspension of carrageenan in 0.9% sodium chloride. A volume of 0.05 ml was injected into the plantar tissue of the right-hind paw via a 26-gauge needle. Measurements were recorded 5 hr after drug administration and 4 hr after challenge. Volumes of both control (untreated) and treated inflamed volumes were determined.

Acknowledgments. We wish to acknowledge Mr. L. Brancone and staff for microanalysis, Mr. W. Fulmor and Mr. G. O. Morton for required spectral data, Dr. G. Van Lear for his mass spectral discussions, and Dr. A. Sloboda and staff for the pharmacological data.

References and Notes

(1) A. Novelli, *An. Asoc. Quim. Argent.*, **31**, 23 (1943).
(2) W. Davies, A. W. Johnson, and H. A. Piggolt, *J. Chem. Soc.*, 352 (1945).
(3) H. Piggolt and W. Davies, *J. Chem. Soc.*, 347 (1945).
(4) J. A. Hyatt and J. S. Swenton, *J. Org. Chem.*, **37**, 3216 (1972).
(5) H. Bredereck, R. Compper, H. Rempfer, K. Klemm, and H. Keck, *Chem. Ber.*, **92**, 329 (1958).
(6) G. Tsatsarones and F. E. Effenberger, *Chem. Ber.*, **94**, 2876 (1961); G. Tsatsarones and A. Kehayoglow, *J. Org. Chem.*, **35**, 438 (1970).
(7) C. A. Winter, E. A. Risley, and B. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544, 547 (1962).
(8) C. J. E. Niemegeers, F. J. Verbruggen, and P. A. J. Janssen, *J. Pharm. Pharmacol.*, **16**, 810 (1964).
(9) P. L. Julian, J. J. Oliver, R. H. Kimball, A. B. Pike, and G. D. Jefferson, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 487.

Monocyclic Antibiotic β-Lactams

Riaz F. Abdulla* and Kenneth H. Fuhr

Lilly Research Laboratories, Division of Eli Lilly and Company, Greenfield, Indiana 46140. *Received November 20, 1974*

The preparation and antimicrobial activity of a series of β-amino-β-lactams (**3a–f**) are described. These compounds were prepared from the 2 + 2 cycloaddition of β,β-disubstituted enamines with aryl isocyanates; compounds **3a–f** underwent facile β-lactam ring fission between aminal carbon atom C_4 and the lactam nitrogen N_1. The resulting formylacetanilide derivatives were devoid of antibiotic activity.

The appearance of a report[1] on the antibiotic activity of some monocyclic β-lactams prompts us to communicate our findings on the antimicrobial activity of derivatives of simple β-lactams, structurally unrelated to the penicillins or the cephalosporins. Upon perusal of the antibiotic activity of monocyclic β-lactams,[1] we observed that no mention was made of the synthesis and screening of β-amino-β-lactam derivatives which had been known for some time.[2]

The β-amino-β-lactams were prepared by the 2 + 2 cycloaddition of β,β-disubstituted enamines with aryl isocyanates at temperatures between 0 and 60° and were all thick oils. The β-lactams were characterized by ir, NMR, and mass spectroscopy and by their hydrolysis to formylacetanilide derivatives which were crystalline solids devoid of antibiotic activity. Scheme I shows the preparative sequence. The hydrolysis presumably occurs by the irreversible attack of water on the zwitterionic species 4 to give the formylacetanilide **5**. The zwitterion 4 cannot be detected in the series of β-lactams under study but has been implicated as a viable intermediate in related systems.[3] The degree of instability of the molecule **3** depends to a great extent on the ability of the *N*-aryl substituent to delocalize the nega-