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.

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Monocyclic Antibiotic β-Lactams

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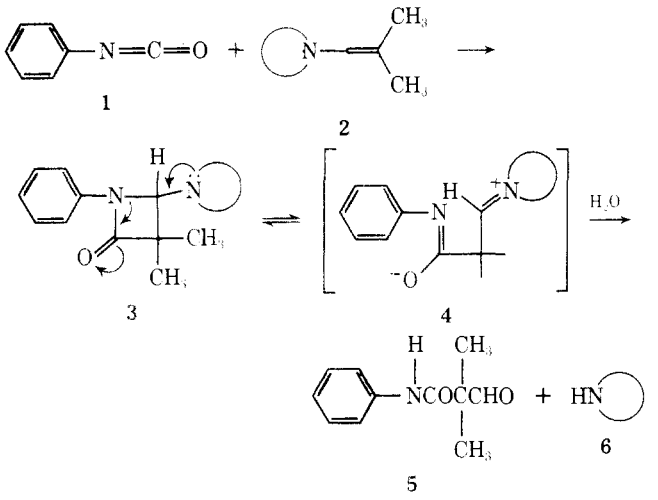
The preparation and antimicrobial activity of a series of β-amino-β-lactams (**3a–f**) are described. These compounds were prepared from the 2 + 2 cycloaddition of β,β-disubstituted enamines with aryl isocyanates; compounds **3a–f** underwent facile β-lactam ring fission between aminal carbon atom C_4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

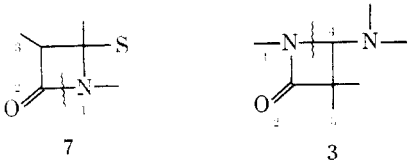
The β-amino-β-lactams were prepared by the 2 + 2 cycloaddition of β,β-disubstituted enamines with aryl isocyanates at temperatures between 0 and 60° and were all thick oils. The β-lactams were characterized by ir, NMR, and mass spectroscopy and by their hydrolysis to formylacetanilide derivatives which 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-

Scheme I. Synthesis and Decomposition of 4-Amino-β-lactam Derivatives



tive charge in the zwitterion **4**, as well as on the availability of the lone pair of electrons on the β-amino group in the β-lactam **3**. Thus, like the penicillins and the cephalosporins, the β-amino-β-lactams that we have described are "biologically unstable" compounds, though they have differing modes of fission as shown in Chart I. It is widely conceded

Chart I



that the penicillin type of activity stems from the acylation of the transpeptidase involved in bacterial cell-wall synthesis[4] via the fission of the N_1–C_2 bond in structure **7**. It is logical to assume that compounds **3** act via a related mechanism but that β-lactam bond fission occurs not between N_1 and C_2 but at the aminal carbon atom C_4 and the lactam nitrogen N_1. The theory is lent some support by the disappearance of all antibiotic activity by any structural modification of **3** that renders stability to the N_1–C_4 bond, such as the positioning of electron sources on the *N*-aryl substituent. The positioning of electron sinks on the *N*-aryl group, on the other hand, leads to enhanced activity. Also detrimental to activity is the elimination of the "lone-pair" effect. Salt formation at the 4-amino group using dimethyl sulfate renders the β-lactam completely stable but results in the total loss of antibiotic action (Scheme II).

Scheme II

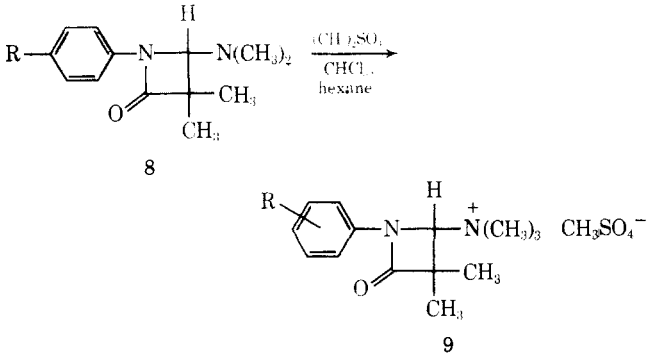
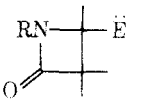


Table I lists some of the β-amino-β-lactam derivatives that we have screened and summarizes their levels and spectrum of activity.

The mechanism that we have proposed as being responsible for the antibiotic activity of the β-amino-β-lactams has additional, predictive value. We expect any structure, such as **10**, that possesses an electron-donating substituent



on the C_4 atom of the β-lactam ring will render to that molecule a degree of antibiotic action. We would like to stress, however, that the mechanism we have proposed is tentative and that the antibiotic activity of our and Bose's β-lactams could be due to factors other than the presence of the β-lactam ring.

At the present stage of our investigation and from the results described by Bose,[1] it does not appear that the monocyclic β-lactams are likely to approach the superior antibiotic activity of the natural and the semisynthetic penicillins and cephalosporins.

Experimental Section

Melting points are uncorrected and were measured using open-glass capillaries in conjunction with a Thomas-Hoover capillary tube melting point apparatus. Ir spectra were determined on a Perkin-Elmer Model 267 grating infrared spectrophotometer. NMR spectra were determined on a Varian T-60 spectrometer. Owing to the heat sensitivity of the β-amino-β-lactams, no combustion data could be obtained for these compounds as they decomposed in the combustion tube.

The antimicrobial data were obtained using standard agar dilution techniques. The compound was dissolved or suspended in the agar in a graded series of dilutions. The media were spot inoculated by conventional procedures and incubated under controlled conditions for a period designed to produce luxuriant growth of the test organism in the control medium containing no compound. The MIC, in micrograms per milliliter, is reported as the lowest concentration showing no growth when examined visually by the unaided eye.

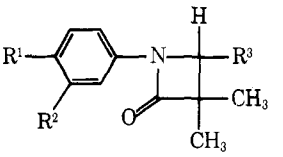
Synthesis of β-Amino-β-lactams. Compounds 3a–e were prepared by a process analogous to that for **3f** outlined below.

1-(3,4-Dichlorophenyl)-3,3-dimethyl-4-morpholino-β-lactam (3f). A mixture of 1.88 g (0.01 mol) of 3,4-dichlorophenyl isocyanate and 2.82 g (0.02 mol) of 4-(2-methylpropenyl)morpholine was stirred for 15 hr at 25°. Monitoring by ir showed the disappearance of the 2260-cm^{-1} isocyanate band and the appearance of the 1765-cm^{-1} β-lactam carbonyl. The excess enamine was removed with a vacuum pump and the remaining oil was used without further purification: yield 3.0 g (91.3%).

3,4-Dichloro-α-formyl-α-methylpropionanilide (5f). A mixture of 1.88 g (0.01 mol) of phenyl isocyanate and 2.82 g (0.02 mol) of 4-(2-methylpropenyl)morpholine was stirred for 15 hr at 25°. The oil was shaken with hexane to remove excess enamine and the hexane decanted. The remaining oil was taken up in ether, washed with an HCl solution (1:1 concentrated HCl–water) and water, and dried over $MgSO_4$. Upon evaporation of the ether, a colorless oil remained that crystallized when triturated with pentane. The white product was recrystallized from benzene–pentane: yield 1.5 g (57.5%); mp 100–102°; $\delta_{TMS}^{CDCl_3}$ 9.6 (s, 1, aldehyde), 8.43 (br s, 1, NH), 7.7 (m, 1, aryl), 7.2 (m, 2, aryl), and 1.4 (s, 6, $-CH_3$); ir (KBr) 3230, 1735, 1669, 1585, 1513, 1465, 1388, 1298, 1255, 1140, 1033, 900, 835, 815, and 700 cm^{-1}. Anal. ($C_{11}H_{11}Cl_2N_1O_2$) C, H, N.

[3,3-Dimethyl-4-oxo-1-(*p*-tolyl)-2-azetidinyl]trimethylammonium Methyl Sulfate (9). A mixture of 10 ml of *p*-tolyl isocyanate and 14.3 ml of freshly distilled *N,N*-dimethyl-2-(methylpropenyl)amine was stirred at 35° for 8 hr. Monitoring by ir showed the disappearance of the 2260-cm^{-1} isocyanate band and the appearance of the 1785-cm^{-1} β-lactam band. To this reaction mixture was added 50 ml of cyclohexane and 10 ml of $CHCl_3$, followed

Table I



Compd no.	R^1	R^2	R^3	$\bar{\nu}$, cm^{-1}, β-lactam C=O	$\delta_{TMS}^{CDCl_3}$ CH	$\delta_{TMS}^{CDCl_3}$ $(CH_3)_2$	Formula	Yield, %	Microorganism	MIC, μg/ml
3a	H	CF_3	NMe_2	1765	4.53 (s)	1.33 (s)	$C_{14}H_{17}F_3N_2O$	100	*Staphylococcus aureus* 3055	10
									S. aureus 3074	10
									Streptococcus fecalis X66	100
									Bordetella bronchiseptica	100
3b	H	Cl	NMe_2	1765	4.43 (s)	1.30 (s)	$C_{13}H_{17}ClN_2O$	100	*S. aureus* 3055	10
									S. aureus 3074	100
									S. fecalis X66	100
									B. bronchiseptica	100
3c	H	CF_3	-N O	1765	4.45 (s)	1.37 (s)	$C_{16}H_{19}F_3N_2O_2$	96.2	*S. aureus* 3055	10
									S. aureus 3074	100
									S. fecalis X66	100
3d	CH_3	Cl	-N O	1765	4.40 (s)	1.33 (s)	$C_{16}H_{21}ClN_2O_2$	95.0	*S. aureus* 3055	10
3e	H	Cl	-N O	1765	4.42 (s)	1.33 (s)	$C_{15}H_{19}ClN_2O_2$	93.0	*S. aureus* 3074	10
									S. fecalis X66	100
									B. bronchiseptica	100
3f	Cl	Cl	-N O	1765	4.44 (s)	1.33 (s)	$C_{15}H_{18}Cl_2N_2O_2$	91.3	*S. aureus* 3055	10
									S. aureus 3074	10
									B. bronchiseptica	100

by 5.0 ml of dimethyl sulfate. The mixture was stirred vigorously for 16 hr during which time the methylammonium sulfate salt precipitated. The precipitate was filtered, washed with 2-propanol, and dried: yield 8.55 g; mp 169–170°; δ_{TMS}^{DMSO} 7.4 (br s, 4, aryl), 5.95 (br s, 1), 3.5 (s, 3, $-CH_3$), 3.2 (s, 9, *n*-CH_3), 2.4 (s, 3, Ar-CH_3), 1.6 (d, 6, CH_3); ir (Nujol) 1785, 1418, 1240–1215 hood, 1195, 1060, 1015, and 750 cm^{-1}. Anal. ($C_{16}H_{26}N_2O_5S$) N.

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7-*N*-Amidinocephalosporins

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7-Aminocephalosporanic acid *tert*-butyl ester reacts quantitatively at −20° with iminium chlorides to give amidino derivatives. Removal of the *tert*-butyl protecting group with trifluoroacetic acid and treatment with 1 equiv of triethylamine yield the corresponding zwitterions. These compounds were less active than their penicillin analogs.

Amidino derivatives of penicillins have been recently synthesized[1] and are found to exhibit enhanced activity toward gram-negative microorganisms. Amidino analogs of cephalosporins have not previously been reported.

Several approaches to amidine synthesis are available: reaction of an amine with (i) an iminoether hydrochloride;[2] (ii) with an iminochloride;[3] or (iii) with an N-substituted iminium chloride.[4] The first two routes failed when applied to 7-aminocephalosporanic acid (7-ACA) *tert*-butyl ester. This failure was attributed to the fact that the amino group of 7-ACA is weakly basic. Therefore, the iminoether hydrochlorides in alcoholic solution underwent alcoholysis rather than the desired amidine formation.[5]

N-Substituted formiminium chlorides (**1**, R = H) are better species and react quantitatively with 7-ACA *tert*-butyl ester (**2**) under very mild conditions. Indeed, the reaction of **1** (R = H) with amine **2** yielded the amidinocephalosporin esters **3** (R = H) which were isolated as free