Nitrones. 7. α-Quinoxalinyl-N-substituted Nitrone 1,4-Dioxides[1a]

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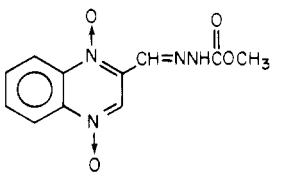
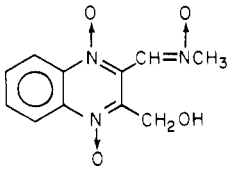
A series of α-quinoxalinyl-N-substituted nitrone 1,4-dioxides has been synthesized and evaluated as antibacterial and antiprotozoal agents. Structure–activity relationships are discussed. Of the compounds tested, α-(3-methyl-2-quinoxalinyl)-*N*-methylnitrone 1,4-dioxide (**2**) was the most active agent in vivo against the gram-negative and the gram-positive organisms.

In previous work we have found excellent antibacterial activity from nitrone-bearing heterocycles.[1a] In this paper we wish to report the preparation of a series of quinoxalinylnitrone 1,4-dioxides, of which some members have outstanding activity.

Since McIlwain's synthesis of quinoxaline 1,4-dioxides,[2] several interesting reports concerning their antibacterial activity in animals have appeared.[3,4] These reports claimed appreciable in vivo activity although the in vitro activity was rather weak. Recently Thrasher[5] reported that Carbodox[6] (A) possesses growth-promoting activity in swine, and Padeiskaya and co-workers[7] studied the chemotherapeutic effect of 85 quinoxaline and quinoxaline 1,4-dioxides in acute bacterial infections.



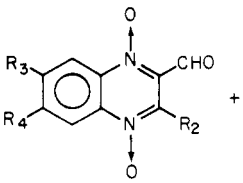
A



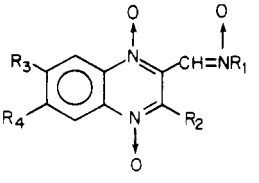
B

At the outset of this work, only two compounds containing both a quinoxaline 1,4-dioxide and a nitrone group, namely *N*-[*p*-(dimethylamino)phenyl]-α-(3-methyl-2-quinoxalinyl)nitrone 1,4-dioxide and *N*-[*p*-(dimethylaminophenyl]-α-(2-quinoxalinyl)nitrone 1,4-dioxide, were reported in the literature. These compounds showed no chemotherapeutic activity in animals.[8] Subsequent to completion of our work, several compounds of similar nature have appeared in the literature,[9] and a patent describing some of the present work[10] has issued.

Following Johnston's procedure,[11] 2-formylquinoxaline 1,4-dioxide, 2-formyl-3-methylquinoxaline 1,4-dioxide, and analogues were prepared by selenium dioxide oxidation of the appropriate 2-methyl compound.[12] The desired nitrones (E) (**1**–**25**, Table I) were readily prepared by condensation of the above aldehydes (C) with the appropriate N-substituted hydroxylamines (D) (eq 1). The



C + R_1NHOH D



E

14-85% (1)

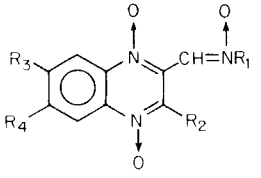
reactions generally proceeded to give a single isolable product. However, in the preparation of **13**, an imine by-product was isolated in 20% yield along with **13**. This imine was prepared by reaction of the aldehyde with 2-chloroethylamine hydrochloride and probably arises from the latter being present in the hydroxylamine.[13] The infrared spectra of the quinoxalinylnitrone 1,4-dioxides showed bands of CH=N→O and 1,4-dioxide groups at 1570–1620[14] and 1330–1335[15] cm^{-1}, respectively. The NMR spectra were also consistent with the quinoxalinylnitrone 1,4-dioxide structures.

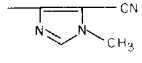
Biological Activity. All of the compounds described above were evaluated in vivo and in vitro antibacterial activity against the gram-negative and the gram-positive microrganisms in the various screens. The testing protocol was identical with that described in our previous article.[1a] The in vitro antibacterial activity of the quinoxalinylnitrone 1,4-dioxides is, in general, rather weak compared to the in vivo antibacterial activity. The apparent discrepancy between the in vitro and in vivo activities has been noted for other quinoxaline 1,4-dioxides and a nonmetabolic rationale has appeared in the literature.[16] The most active compound in vivo is α-(3-methyl-2-quinoxalinyl)-*N*-methylnitrone 1,4-dioxide (**2**). All variations from this basic structure led to a decrease in antibacterial activity with the exception of compound **8** which had antibacterial activity comparable to **2**. Compound **27**, lacking *N*-oxide groups at positions 1 and 4 of the quinoxaline nucleus, was completely ineffective. This demonstrates that the antibacterial activity of these compounds rests on the presence of *N*-oxide groups at positions 1 and 4 of the quinoxaline nucleus, on the nature of the N substituents (R_1) of nitrone groups, and on the nature of the R_2 groups at position 3. Although metabolism of the quinoxalinylnitrone 1,4-dioxides was not thoroughly investigated in a study of possible metabolites of **2**, the 3-hydroxymethyl compound (B) was prepared and was shown not to occur as a metabolite in mice.[17] Only compound **2** showed exceptional antibacterial activity against the gram-negative *Proteus mirabilis* and *Salmonella schottmuelleri* in experimental infection in mice (Table II). Simultaneous comparison of antibacterial activity of compound **2** was made with standard antibacterial agents. The ED_{50} of the most active compound **2** relative to chloramphenicol and nifuratrone[18] was determined according to a published procedure[1a] and is shown in Table II. Acute LD_{50} values of **2**, chloramphenicol, and nifuratrone[18] were determined by single oral, subcutaneous, or intraperitoneal administration to mice, weighing 18–20 g (Table II). None of these compounds showed antiprotozoal activity against *Histomonas meleagridis* in turkeys.

Experimental Section

Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were obtained with a Beckman IR-5 infrared spectrophotometer (KBr). NMR spectra were obtained with a Varian A-60 spectrometer, using

Table I. α-Quinoxalinyl-N-substituted Nitrone 1,4-Dioxides



Compd no.	R_1	R_2	R_3	R_4	Prepn method	Mp, °C	Recrystn solvent	Yield,[a] %	Formula	Analyses
1	CH_2CH_2OH	CH_3	H	H	B	164-165 dec	CH_3NO_2	66	$C_{12}H_{13}N_2O_4$	C, H, N
2	CH_3	CH_3	H	H	A	171-173 dec	CH_3NO_2	65	$C_{11}H_{11}N_3O_3$	C, H, N
3	CH_3	H	H	H	A	219-220 dec	CH_3NO_2-EtOH	59	$C_{10}H_9N_3O_3$	C, H, N
4	C_6H_5	CH_3	H	H	C	164-165 dec	C_6H_6	67	$C_{10}H_{13}N_3O_3$	C, H, N
5	CH_2CH_2OH	H	H	H	B	205-207 dec	EtOH-CH_3NO_2	67	$C_{11}H_{11}N_3O_4$	C, H, N
6	$CH(CF_3)CH_3$	CH_3	H	H	A	207-208 dec	EtOH	29	$C_{13}H_{12}F_3N_3O_3$	C, H, N, F
7	$CH_2CH(CH_3)OH$	CH_3	H	H	B	181-183 dec	EtOH	72	$C_{13}H_{15}N_3O_4$	C, H, N
8	CH_3	CH_3	CH_3	H	A	180 dec	CH_3NO_2	32	$C_{12}H_{13}N_3O_3$	C, H, N
9	CH_2CH_3	CH_3	H	H	B	177-178 dec	EtOH	44	$C_{12}H_{13}N_3O_3$	C, H, N
10	C_6H_{11}[b]	CH_3	H	H	D	206-208 dec	EtOH	66	$C_{16}H_{19}N_3O_3$	C, H, N
11	CH_3	CH_3	OCH_3	H	A	180-182 dec	CH_3NO_2	61	$C_{12}H_{13}N_3O_4$	C, H, N
12	CH_2CH_2OEt	CH_3	H	H	B	156-158 dec	EtOH	61	$C_{14}H_{17}N_3O_4$	C, H, N
13	CH_2CH_2Cl	CH_3	H	H	A	151 dec	EtOH	70	$C_{12}H_{12}ClN_3O_3$	C, H, N, Cl
14	CH_3	CH_3	CF_3	H	A	181-182 dec	EtOH	35	$C_{12}H_{10}F_3N_3O_3$	C, H, N, F
15	$CH(CH_2Cl)_2$	CH_3	H	H	A	160 dec	CH_3CN-EtOH	49	$C_{13}H_{13}Cl_2N_3O_4$	C, H, N, Cl
16		CH_3	H	H	C	220-221 dec	CH_3NO_2	25	$C_{15}H_{12}N_6O_3$	C, H, N
17	$CH(CH_2OH)_2$	CH_3	H	H	B	202-203 dec	EtOH	34	$C_{13}H_{15}N_3O_5$	C, H, N
18	CH_3	CH_3	Cl	Cl	A	174-175 dec	CH_3NO_2	14	$C_{11}H_9Cl_2N_3O_3$	C, H, N, Cl
19	$CH(CH_3)CH_2OH$	CH_3	H	H	B	190-191 dec	CH_3NO_2	72	$C_{13}H_{15}N_3O_4$	C, H, N
20	n-$C_{10}H_{21}$	CH_3	H	H	A	105-108	EtOH	70	$C_{20}H_{29}N_3O_3$	C, H, N
21	CH_3	CH_3	Cl	H	A	189-190 dec	CH_3NO_2	43	$C_{11}H_{10}ClN_3O_3$	C, H, N, Cl
22	$CH_2CH(Cl)CH_3$	CH_3	H	H	B	174 dec	EtOH	54	$C_{13}H_{14}ClN_3O_3$	C, H, N, Cl
23	$CH_2CH_2OC(=O)CH_3$	CH_3	H	H	B	177-178 dec	CH_3NO_2-EtOAc	42	$C_{14}H_{15}N_3O_5$	C, H, N
24	CH_3	CH_3	NO_2	H	A	198 dec	CH_3NO_2	17	$C_{11}H_{10}N_4O_5$	C, H, N
25	p-ClC_6H_4	CH_3	H	H	C	203 dec	CH_3NO_2	85	$C_{16}H_{12}ClN_3O_3$	C, H, N, Cl

[a] Yield is of purified product. [b] Cyclohexyl.

Table II. Comparison of Compound 2 with Standard Antibacterial Agents[a]

Bacteria used	Compd 2	Chloramphenicol	Nifuratrone[b]
In Vivo ED_{50}, mg/kg			
Escherichia coli	10	41	27
Klebsiella pneumoniae	6	20	39
Pasteurella multocida	7	11	<50
Proteus mirabilis	18	52	53
Proteus vulgaris	35	>100	
Pseudomonas aeruginosa	>250[c]		>100
Salmonella enteriditis	2	29	47
Salmonella schottmeulleri	1.5	9.0	8
Salmonella typhimurium	16	16	30
Salmonella typhosa	10	24	31
Shigella paradysenteriae	13		46
Shigella dysenteriae	62	61	
Diplococcus pneumoniae I	32		>100
Listeria monocytogenes	>100	>100	>100
Staphylococcus aureus	74	27	26
Streptococcus pyrogenes	35	27	47
Acute LD_{50}, mg/kg			
Oral	>1000	2640	518
Subcutaneous	596		417
Intraperitoneal	596	1320	

[a] Method described in ref 1a. [b] Reference 18. [c] Route of drug administration was subcutaneous.

Me_4Si as an internal standard: s signifies singlet; d, doublet; m, multiplet; and un, unresolved. Evaporation of solvents was done under reduced pressure using a rotary evaporator. The progress of reactions was routinely followed by thin-layer chromatography (TLC). Analyses for elements indicated by the symbols were within ±0.4% of the calculated values for all the new compounds.

α-(3-Methyl-2-quinoxalinyl)-N-substituted Nitrone 1,4-Dioxides. Method A. A mixture of 2-formyl-3-methylquinoxaline 1,4-dioxide (2.04 g, 0.01 mol) and N-substituted hydroxylamine hydrochloride (0.01 mol) in warm 95% EtOH (30 mL) containing $NaHCO_3$ (1.01 g, 0.012 mol) was stirred. A yellow solid began to precipitate after ca. 1 h. The mixture was filtered and the filter cake taken up in hot CH_3NO_2, treated with charcoal, and filtered. Evaporation of the filtrate gave bright yellow nitrones. In the case of **13**, TLC with EtOAc as a developing solvent showed two spots, corresponding to Schiff's base **26** (R_f 0.52) and the other to **13** (R_f 0.21). The two products were easily separated by silica gel[19] column chromatography in 20 and 62% yields, respectively, or by isolation of **13** in 70% yield by careful fractional recrystallization at room temperature.

Method B. The hydroxylamino alcohol oxalate (0.005 mol) was added portionwise to a warm solution of 2-formyl-3-methylquinoxaline 1,4-dioxide (2.04 g, 0.01 mol) in 95% EtOH (30 mL) containing $NaHCO_3$ (1.01 g, 0.012 mol) and the mixture was stirred 1 h at room temperature. After work-up and recrystallization, bright yellow nitrones were obtained.

Method C. A mixture of 2-formyl-3-methylquinoxaline 1,4-dioxide (2.04 g, 0.01 mol) and N-substituted hydroxylamine (0.01 mol) in $CHCl_3$ (40 mL) was refluxed for 0.5 h. After cooling, the solvent was removed. Et_2O (40 mL) was added to the residue and the mixture was chilled to ca. 0 °C, causing precipitation of the yellow nitrones.

Method D. α-(3-Methyl-2-quinoxalinyl)-N-cyclohexylnitrone 1,4-Dioxide (10). A solution of 2-formyl-3-methylquinoxaline 1,4-dioxide (9.50 g, 0.047 mol) and *N*-cyclohexylhydroxylamine (5.40 g, 0.047 mol) in absolute EtOH (130 mL) was stirred at room temperature for 16 h to give a yellow solid (9.40 g, 64%), mp 206–207 °C. An analytical sample, mp 206–208 °C, was prepared by recrystallization of the solid from absolute EtOH: ν max 1565 (CH=N→O) and 1333 cm^{-1} (1,4-dioxide); NMR (Me_2SO-d_6) δ 8.65–7.85 (m, 5 H, C_6H_4 + CH=N→O), 4.37 (un, 1 H, –CH), 2.38 (s, 3 H, CH_3), and 2.25–0.08 [un, 10 H, $-(CH_2)_5$] (Table I).

2-Chloro-N-[(3-methyl-2-quinoxalinyl)methylene]ethylamine 1,4-Dioxide (26). A solution of 2-formyl-3-methylquinoxaline 1,4-dioxide (1.02 g, 0.005 mol) and 2-chloroethylamine hydrochloride (0.58 g, 0.005 mol) in 15 mL of absolute EtOH (15 mL) containing $NaHCO_3$ (0.05 g, 0.006 mol) was stirred. A yellow solid began to precipitate after ca. 20 min. Stirring was continued for an additional 1 h. After cooling to ca. 0 °C the solid was filtered to give crude product (1.2 g).

Recrystallization of the product from EtOH gave a yellow solid (0.56 g, 42%): mp 136 °C (violent dec); ν max 1640 (C=N) and 1320 cm^{-1} (1,4-dioxide); NMR ($CDCl_3$) δ 8.80–7.75 (m, 5 H, C_6H_4 + CH=N), 4.26 (m, 4 H, $-CH_2CH_2-$), and 2.60 (s, 3 H, CH_3). Anal. ($C_{12}H_{12}ClN_3O_2$) C, H, Cl, N.

α-(3-Methyl-2-quinoxalinyl)-N-methylnitrone (27). A mixture of 2-formyl-3-methylquinoxaline (17.22 g, 0.10 mol), methylhydroxylamine hydrochloride (8.35 g, 0.10 mol), and $NaHCO_3$ (10.88 g, 0.12 mol) in 95% EtOH (150 mL) was refluxed for 2 h. The solvent was removed and the black residue was recrystallized from absolute EtOH to give pale yellow needles (14.10, 66%): mp 142–144 °C (softened at 129 °C); ν max 1534 (CH=N→O) and 1205 cm^{-1} (N→O); NMR ($CDCl_3$) δ 8.23–7.58 (m, 5 H, C_6H_4 + CH=N→O), 4.38 (s, 0.7 H), and 3.99 (s, 2.27 H) [total area 3 H; probably a mixture of syn and anti =N-(→O)CH_3], and 2.78 (s, 3 H, CH_3). Anal. ($C_{11}H_{11}N_3O$) C, H, N.

6,7-Dichloro-2,3-dimethylquinoxaline 1,4-Dioxide (28). This compound was prepared from 6,7-dichloro-2,3-dimethylquinoxaline[12] (27.13 g, 0.12 mol) according to methods described previously in the literature.[12] Recrystallization of the crude product from $CHCl_3$–95% EtOH gave a yellow solid (14.50 g, 47%), mp 216–222 °C dec. An analytical sample, mp 231–232 °C dec, was obtained by recrystallizing this material from CH_3NO_2–95% EtOH (1:4): ν max 1316 cm^{-1} (1,4-dioxide); NMR ($CDCl_3$) δ 8.77 (s, 2 H, C_6H_2–) and 2.73 (s, 6 H, 2 × CH_3).

2-Formyl-6- (or 7-) methoxy-3-methylquinoxaline 1,4-Dioxide (29). 2,3-Dimethyl-6-methoxyquinoxaline 1,4-dioxide[12] (27.75 g, 0.126 mol) was dissolved in EtOAc (250 mL), resublimed SeO_2 (15.00 g, 0.135 mol) was added, and the mixture was stirred under reflux for 5 h. EtOAc was removed and the residue was triturated with anhydrous Et_2O. Recrystallization of this material from EtOAc–CH_2Cl_2 gave orange crystals (14.75 g, 51%): mp 184–186 °C dec; ν max 1698 (C=O), 1323 (1,4-dioxide), and 1235 cm^{-1} (–CO–); NMR ($CDCl_3$) δ 10.68 (s, 1 H, CHO), 8.54 (d, 1 H, C_6H), 7.95–7.35 (m, 2 H, C_6H_2), 4.03 (s, 3 H, OCH_3), and 2.81 (s, 3 H, CH_3). Anal. ($C_{11}H_{10}N_2O_4$) C, H, N.

2-Formyl-3,6- (or 3,7-) dimethylquinoxaline 1,4-Dioxide[20] (30). Following the procedure described above 2,3,6-trimethylquinoxaline 1,4-dioxide[12] (25.73 g, 0.126 mol) and SeO_2 (15.00 g, 0.135 mol) were allowed to react to give crude dioxide (16.60 g, 60%). An analytical sample, mp 163–166 °C (softened at 159 °C), was obtained by recrystallizing the solid from EtOAc: ν max 1709 (C=O) and 1325 cm^{-1} (1,4-dioxide); NMR ($CDCl_3$) δ 10.68 (s, 1 H, CHO), 8.67–7.50 (m, 3 H, C_6H_3), 2.84 (s, 3 H, CH_3), and 2.64 (s, 3 H, CH_3). Anal. ($C_{11}H_{10}N_2O_3$) C, H, N.

Similarly 2-formyl-3-methyl-6- (or 7-) trifluoromethylquinoxaline 1,4-dioxide (**31**), 2-formyl-3-methyl-6- (or 7-) nitroquinoxaline 1,4-dioxide (**32**), 2-formyl-3-methyl-6- (or 7-) chloroquinoxaline 1,4-dioxide (**33**), and 6,7-dichloro-2-formyl-3-methylquinoxaline 1,4-dioxide (**34**) were prepared by oxidation of the appropriate 2,3-dimethylquinoxaline 1,4-dioxide and used without purification.[21]

References and Notes

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(18) USAN name for *N*-(2-hydroxyethyl)-α-(5-nitro-2-furyl)-nitrone.
(19) Silica gel was purchased from Gebr. Hermann, D. 5000 Köln-Ehrenfeld, Grüner Weg 8-10, West Germany, under the name Kieselegel.
(20) J. D. Johnston, U.S. Patent 3 344 022 (1967).
(21) Attempts to purify them by several recrystallizations were unsuccessful.

β-Lactam Antibiotics Derived from Nitrogen Heterocyclic Acetic Acids. 1. Penicillin Derivatives

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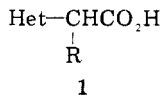
In an attempt to synthesize antibacterial agents effective against gram-negative bacteria, penicillin derivatives were prepared from substituted and unsubstituted 1,4-dihydro-2-oxopyridine-1-acetic acids, 1,4-dihydro-4-oxopyridine-1-acetic acids, and 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acids. The unsubstituted derivatives displayed moderate activity against gram-negative bacteria; however, substitution (alkyl, chloro, nitro, acetyl, and cyano) on the heterocyclic ring of these acetic acids and (alkyl, phenyl) in the α position decreased the activity of the penicillin derivatives against gram-negative organisms.

One of the goals of our antibiotic research program is the synthesis of a parenterally effective broad-spectrum penicillin. Our route to this goal was side-chain modification, i.e., coupling novel carboxylic acids with 6-aminopenicillanic acid (6-APA). We synthesized a number of acids with the general structure 1 (Table I), in which an acetic acid residue is bonded to the nitrogen in a heterocyclic ring. This publication will discuss the synthesis of the nitrogen heterocyclic acetic acids, the coupling of the acids to 6-APA, and the antibacterial activity of the resulting derivatives.



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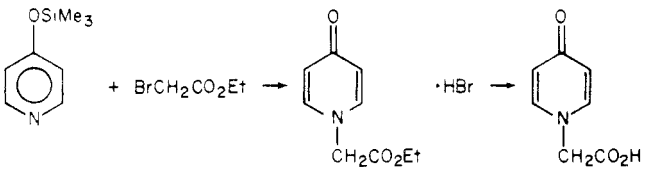
A variety of routes was utilized in the synthesis of the heterocyclic acids. The most direct route (method B, Table I) was the reaction of the hydroxy-substituted heterocycle with chloroacetic acid in aqueous alkali. In several examples, a two-step sequence was utilized: reaction of the hydroxy-substituted heterocycle with ethyl bromoacetate in ethanol which contained 1 equiv of potassium hydroxide, followed by hydrolysis of the ester (method A). For compound 18, the sequence illustrated by Scheme I was the most convenient preparation. The 2,4-pyrimidinedione-1-acetic acids with acetyl or cyano groups at C-5 were prepared by the procedure of Shaw and co-workers[1,2] (Scheme II).

The acids prepared were coupled with 6-APA by the mixed anhydride, acid chloride, or imidazolide technique. The penicillin derivatives are tabulated in Table II. These derivatives all assayed (I_2 titration) a minimum of 75% pure and gave spectra (IR, NMR) which were in agreement with the assigned structure.

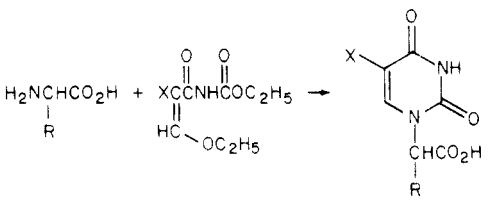
Although we synthesized a variety of acids, the most interesting antibacterial activity was found with derivatives of three classes: 1,2-dihydro-2-oxopyridine-1-acetic acids, 1,4-dihydro-4-oxopyridine-1-acetic acids, and 1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acids (Table III). The compounds were evaluated against fatal infections in

Scheme I



20 18

Scheme II



R = H, CH_2, Ph; X = CN, C(=O)CH_3

mice using four bacteria, two gram positive (*Staphylococcus aureus* and *Streptococcus pneumoniae*) and two gram negative (*Salmonella schottmuelleri* and *Escherichia coli*). The compounds were not all evaluated simultaneously so comparisons between compounds will be qualitative in nature.

The penicillins derived from acids other than the three groups of main interest exhibited minimal activity against gram-negative organisms (compounds **21–24**). Those derived from the 2-pyridone acids (**25–30**) demonstrated activity against *Salmonella*, but *E. coli* activity was lost on substitution of the pyridone ring (**26, 28–30**) or in the α position (**27**). A similar structure–activity relationship was observed in the 4-pyridone and 2,4-pyrimidinedioneacetic acid series. Optimum activity appeared to be in the unsubstituted derivatives in all three cases.

Several of the compounds were designed to be resistant to destruction by β-lactamase by insertion of groups in the α position of the side chain[3] (**27, 38,** and **39**) or on the heterocyclic ring (**26**). All compounds were evaluated in