oxytocic activity for each analog were performed on six isolated uterine horns from three rats in natural estrus, determined on the morning of the assay by vaginal smear. The method used was that of Holton[21] as modified by Munsick,[22] utilizing Mg^{2+}-free van Dyke–Hastings solution as bathing fluid. Avian vasodepressor assays were performed on a minimum of three conscious chickens[23] according to the procedure of Coon.[24] The pressor properties of the polypeptides were determined on a minimum of five atropinized, urethane-anesthetized male rats following the procedures of the U.S. Pharmacopeia.[25] The antidiuretic acitivty was examined on six Inactin- and ethanol-anesthetized, hydrated male Sprague–Dawley rats, according to the method of Jeffers et al.,[26] as modified by Sawyer;[27] maximal depression of the rate of urine flow was taken as the effective response. Water transport across the toad urinary bladder was measured according to the method of Bentley[28] as modified by Eggena et al.[29]

Acknowledgment. The authors wish to thank Ms. Dasha Surovec for the careful performance of the bioassays. We are also grateful to Drs. P. Hoffman and C. Smith for reading and critiquing this paper.

References and Notes

(1) This work was supported in part by U.S. Public Health Service Grants AM-10080 and AM-18399. Abbreviations are in accordance with the IUPAC–IUB Tentative Rules on Biochemical Nomenclature, *Biochemistry*, **11**, 1726 (1972). The amino acids are of the L configuration. Additional abbreviations used are dG-OXY, [des-Gly-NH_2^9]oxytocin; dLG-OXY, [des-Gly-NH_2^9,des-Leu^8]-oxytocin; TLC, thin-layer chromatography.
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β-Lactam Antibiotics with *N*-Oxide Side Chains. 1. Quinoxaline *N*-Oxides

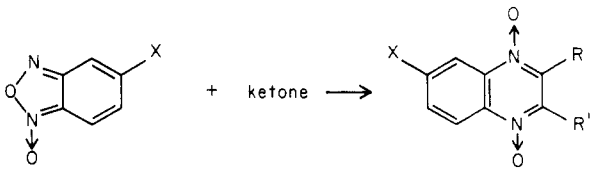
M. L. Edwards,* R. E. Bambury, and H. W. Ritter

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215. *Received September 13, 1974*

A series of penicillin derivatives of quinoxaline di-*N*-oxide carboxylic acids was prepared. These compounds were prepared from the acid chlorides and mixed anhydrides of the quinoxaline di-*N*-oxides. The compounds prepared exhibited minimal antibacterial activity against gram-negative organisms.

An important aspect of current research in β-lactam antibiotics is the attempt to design compounds with enhanced activity against gram-negative bacteria. One approach is side-chain modification. We have observed exceptional activity against *Salmonella* and *Proteus* species with certain quinoxaline di-*N*-oxides[1] and felt that synthesis of amides of 6-aminopenicillanic acid (6-APA) and 7-aminodesacetoxycephalosporanic acid (7-ADCA) from quinoxaline di-*N*-oxide carboxylic acids might give compounds with increased gram-negative activity. Quinacillin (**1**), an example of a quinoxaline penicillin, is without gram-negative activity.[2] Few other examples of

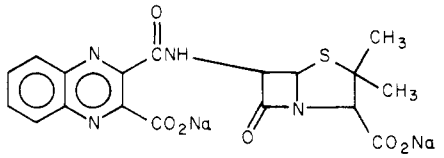
Table I



No.	X	Ketone	R	R'	Rxn conditions[a]	Mp, °C	% yield[b]
2	H	$CH_3C(=O)CH_2CO_2Et$	CO_2Et	CH_3	C	112-115[c]	60[g]
3	H	$C_6H_5C(=O)CH_2CO_2Et$	CO_2Et	C_6H_5	B	124	19
4	H	$EtOC(=O)^-CHCH_2CO_2EtNa^+$	CO_2Et	CO_2Et[d]	C	105-106	19
5	H	$C_6H_5C(=O)(CH_2)_4CO_2H$	$(CH_2)_3CO_2H$	C_6H_5	C	218-220	62
6	H	$CH_3C(=O)(CH_2)_2CO_2Et$	CH_2CO_2Et	CH_3	A, D[e]	150-151	31
7	H	$CH_3C(=O)(CH_2)_2CO_2Et$	CH_2CONH_2	CH_3	A	248-249	56
8	H	$CH_3C(=O)(CH_2)_3CO_2H$	$(CH_2)_2CO_2H$	CH_3	A	206-208	40
9	CO_2H	$CH_3C(=O)C_2H_5$	CH_3	CH_3	A	241[f]	85[g]
10	H	$C_6H_5C(=O)(CH_2)_2CO_2H$	C_6H_5	CH_3	A	195-197[h]	80

[a] A = methanolic NH_3; B = NaOEt-EtOH; C = NH_3-*n*-propyl alcohol; D = cyclohexylamine-MeOH. [b] Yield of analytically pure material. [c] Lit.[5] mp 132-134°C. Compound **2** is contaminated with unreacted benzofuroxan. [d] Product is mono-*N*-oxide. [e] Reaction time is longer than procedure A (1 week vs. 3 hr) but product is analytically pure. [f] Lit.[7] mp 243°C. [g] Crude yield. [h] Lit.[8] mp 194-196°C.

quinoxaline side-chain penicillins and no reports of their *N*-oxides were found in a literature search.



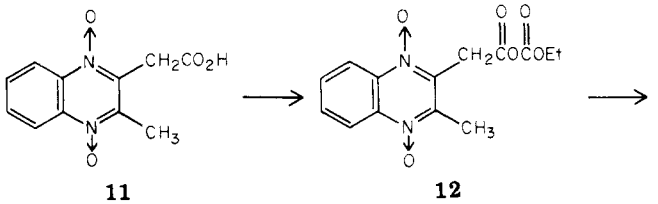
1

The starting quinoxaline di-*N*-oxide carboxylic acids were prepared from benzofuroxan using the Beirut reaction.[3] The reactants and the reaction conditions used are given in Table I. General procedures are given in the Experimental Section.

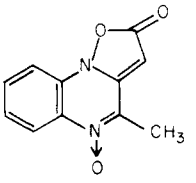
To our knowledge, **4** represents the first quinoxaline mono-*N*-oxide obtained from the Beirut reaction. The structure assignment of **4** was based on its CHN combustion analysis and spectra (see Experimental Section). Compound **7** was obtained instead of **6** when the reaction containing excess NH_3 was stirred for 72 hr instead of being worked up as described for **6**. Compound **10** is the result of decarboxylation of intermediate enamine (or enolate).[4] The esters were hydrolyzed by aqueous NaOH or were converted to salts by treatment with NaOH or KOH in alcohol.

The penicillins and cephalosporins were prepared from the acid chlorides or mixed anhydrides of the quinoxaline di-*N*-oxide carboxylic acids. A literature search gave two references of acid chlorides of heterocyclic *N*-oxide carboxylic acids. Boulton et al. reported the preparation of benzofuroxan carbonyl chloride from the acid and an excess of thionyl chloride.[5] Zinner and Fiedler have prepared the acid chloride of nicotinic acid *N*-oxide with oxalyl chloride.[6] No problems with deoxygenation as a competing reaction were mentioned, and use of the technique of Zinner and Fiedler gave the final products, albeit in low yield. In our hands, better yields were obtained using the mixed anhydride technique.

In two cases, we did observe reactions involving the *N*-oxide function. The reaction of **11** with ethyl chloroformate in $CHCl_3$ gave a bright yellow precipitate which was characterized as **13**. The reaction of **11** with oxalyl chloride or dicyclohexylcarbodiimide (in the presence of *p*-nitrophenol) also gave **13** as the only isolable product. The desired product (**18**) was obtained by limiting the



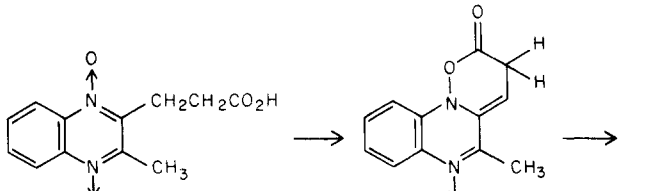
11 **12**



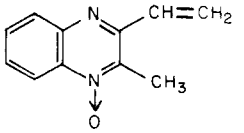
13

reaction time for the formation of **12** to 90 sec and then adding a solution of silylated 6-APA.

The scope of the intramolecular reaction was explored by preparing the mixed anhydrides of **8** and **5** with ethyl chloroformate and allowing the product to come to room temperature. Compound **8** under these conditions gave the mono-*N*-oxide **16**, which we feel arose via the unstable intermediate **15** by elimination of CO_2. The reaction of



8 **15**



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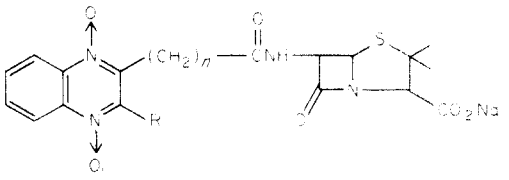
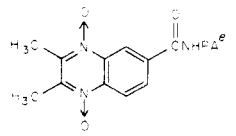
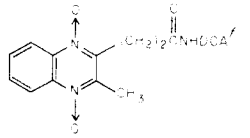
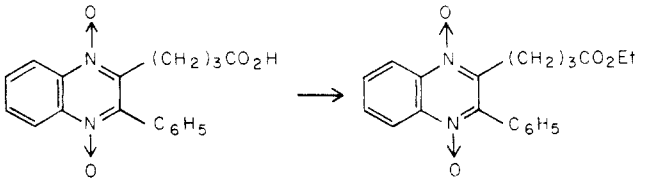
5 gave the ester **14**, and no reaction involving the *N*-oxide function was observed. Therefore, only when a five- or six-membered intermediate can be formed does the *N*-oxide become involved in the reaction under these conditions.

Table II



No.	n	R	Procedure[a]	Iodine titration[b]	MIC,[c] μg/ml	
					Staph. aureus	*Sal. schott.*
17	0	CH_3	A	73.6	100	1000
18	1	CH_3	B	78.5	100	1000
19	0	CO_2Et[d]	A	75.0	100	1000
20	0	C_6H_5	A	90.5	100	1000
21	3	C_6H_5	B	72.6	10	>1000
22	2	CH_3	B	82.5	10	>1000
23			B	70.3	100	>1000
24			B	108.1	1000	>1000
	Benzylpenicillin				10	10

[a] A = acid chloride; B = mixed anhydride. [b] For experimental details, see ref 8. Purity was estimated to be 80% or better by TLC and NMR. Samples were titrated against Pen G except **24**, for which cephalosporin C was the standard. [c] Seeded nutrient agar pour plates are inoculated with *Staphylococcus aureus* or *Salmonella schottmuelleri*. Sterile filter paper disks are placed on the surface of the hardened pour plate. These disks are wetted with 0.1 ml of sterile deionized water containing 10, 100, or 1000 μg/ml of test compound. Plates are incubated for 24 hr at 37°C. Any zone of bacterial growth inhibition is considered as compound activity. [d] Mono-*N*-oxide. [e] PA = penicillanic acid; the compound is a Na salt. [f] DCA = desacetoxycephalosporanic acid; the compound is a Na salt.



5 **14**

Seven penicillins and one desacetoxycephalosporin were prepared. The structures and screening results are given in Table II. In addition, all compounds were screened in vivo in the mouse against *Proteus mirabilis* and *Pseudomonas aeruginosa* and were inactive at 250 mg/kg. In an in vitro evaluation against penicillinase-producing *Staphylococcus aureus*, compounds **19**, **20**, and **24** showed zones of inhibition at 100 μg/ml. From these data it appears that the polar *N*-oxide function in the side chain did not produce an antibiotic with enhanced gram-negative antibacterial activity.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Ir spectra were determined in pressed KBr disks. NMR spectra in D_2O were obtained with DSS as an internal standard. Me_4Si was the internal standard for spectra determined in $CDCl_3$ and Me_2SO-d_6. Analyses indicated by symbols were ±0.4% of the theoretical values. Penicillins were characterized by ir and NMR (D_2O solution) spectra and purity was checked by TLC (silica gel, estimated purity 80% or better) and iodine titration.[9] 6-APA was silylated according to Glombitza.[10] Sodium 2-ethylhexanoate was added as a 2 *N* solution in 1-butanol. The $CHCl_3$ (alcohol free) and MeOH were spectroquality and were stored in glass containers.

Ethyl 3-Phenylquinoxaline-2-carboxylate 1,4-Dioxide (3). A mixture of benzofuroxan (27.2 g, 0.2 mol), EtOH (250 ml), ethyl benzoylacetate (36.6 g, 0.3 mol), and NaOMe (5.4 g, 0.1 mol) was heated at reflux for 6 hr and filtered. The filtrate was chilled and filtered. The product was recrystallized from MeOH to give 11.9 g of yellow solid: mp 124°; ir 1750, 1600, 1350, 1290, 1140, 770 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (t, *J* = 7 Hz, 3 H), 4.28 (q, *J* = 7 Hz, 2 H), 7.61 (s, 5 H), 7.84–8.09 (m, 2 H), 8.6–8.8 (m, 2 H). Anal. ($C_{17}H_{14}N_2O_4$) C, H, N.

Diethyl Quinoxaline-2,3-dicarboxylate 1-Oxide (4). A mixture of benzofuroxan (13.6 g, 0.1 mol), ethyl oxaloacetate sodium (21 g, 0.1 mol), NH_4Cl (5.4 g, 0.1 mol), and *n*-PrOH (300 ml) was heated at reflux for 6 hr and filtered. The filtrate was chilled and filtered. The white solid was recrystallized from MeOH to give 5.6 g of product, mp 105–106°. The ir spectrum showed two ester carbonyl absorptions at 1750 and 1730 cm^{-1}: ir 1750, 1730, 1580, 1490, 1370, 1260, 1220, 1100, 1045, 780 cm^{-1}; NMR ($CDCl_3$) δ 1.5 (t, *J* = 7 Hz, 6 H), 4.52 (q, *J* = 7 Hz, 2 H), 4.54 (q, *J* = 7 Hz, 2 H), 7.8–8.03 (m, 2 H), 9.3–11.5 (m, 2 H). Anal. ($C_{14}H_{14}N_2O_5$) C, H, N.

3-Phenyl-2-quinoxalinebutyric Acid 1,4-Dioxide (5). A mixture of benzofuroxan (13.6 g, 0.1 mol), benzoylvaleric acid (20.6 g, 0.1 mol), and *n*-PrOH (200 ml) was saturated with NH_3 gas, heated at reflux for 36 hr, and evaporated to dryness. The residue was suspended in aqueous NH_4OH and the suspension was filtered to remove unreacted benzofuroxan. The filtrate was acidified and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated. The residue was triturated with C_6H_6 to remove unreacted benzoylvaleric acid. The yellow solid which remained was recrystallized from MeOH to give 16 g of product: mp 216–218°; ir 1720, 1590, 1350, 1320, 1290, 1080, 770 cm^{-1}; NMR (Me_2SO-d_6) δ 1.8–2.5 (m, 4 H), 2.5–3.1 (m, 2 H), 7.6 (s, 5 H), 7.8–8.2 (m, 2 H), 8.3–8.7 (m, 2 H). Anal. ($C_{18}H_{16}N_2O_4$) C, H, N.

Ethyl 3-Methyl-2-quinoxalineacetate 1,4-Dioxide (6). Anhydrous NH_3 was bubbled through a mixture of benzofuroxan (27.2 g, 0.2 mol), ethyl levulinate (43.2 g, 0.3 mol), and MeOH (300 ml) until the exothermic reaction subsided. The mixture was stirred another hour, chilled, and filtered. The solid was recrystallized from MeOH to give 16 g of product: mp 150–151°;

ir 1720, 1520, 1340, 1220, 1080, 770 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3 H), 2.72 (s, 3 H), 4.22 (s, 2 H), 4.25 (q, J = 7 Hz, 2 H), 7.7–8.0 (m, 2 H), 8.5–8.8 (m, 2 H). Anal. ($C_{13}H_{14}N_2O_4$) C, H, N.

3-Methyl-2-quinoxalinepropionic Acid 1,4-Dioxide (8). Benzofuroxan (27.2 g, 0.2 mol) and 4-ketohexanoic acid (26.0 g, 0.2 mol) were suspended in methanol (300 ml). Anhydrous NH_3 was added until the mixture was at reflux. The reaction mixture was stirred for 0.5 hr, chilled, and filtered. The solid was dissolved in water and the product was precipitated from solution by addition of 1 N HCl. Recrystallization from methanol gave 19.8 g of yellow solid: mp 206–208° dec; ir 1720, 1520, 1360, 1340, 1310, 1140, 1090, 840, 780 cm^{-1}; NMR (Me_2SO-d_6) δ 2.67 (s, 3 H), 2.72–2.9 (m, 2 H), 3.16–3.3 (m, 2 H), 7.77–8.05 (m, 2 H), 8.32–8.55 (m, 2 H). Anal. ($C_{12}H_{12}N_2O_4$) C, H, N.

3-Methylquinoxaline-2-acetic Acid 1,4-Dioxide (11). Compound **6** (5.5 g, 0.02 mol) was suspended in 1 N NaOH and the mixture was stirred until solution occurred. The solution was acidified with 1 N HCl and the precipitate was filtered off, washed with water, and vacuum dried over P_2O_5 to give 2.3 g of yellow solid: mp 188–190°C; ir (KBr) 1720, 1650, 1520, 1460, 1425, 1310, 1280, 1230, 1080, 910, 830, 780, 640 cm^{-1}; NMR (TFA) δ 2.72 (s, 3 H), 4.2 (s, 2 H), 7.55–7.9 (m, 2 H), 8.15–8.5 (m, 2 H). Anal. ($C_{11}H_{10}N_2O_4$) C, H, N.

4-Methylisoxazolo[2,3-a]quinoxalin-2-(2H)-one 5-Oxide (13). Compound **11** (8.9 g, 0.04 mol) and NEt_3 (4 g, 0.04 mol) were dissolved in $CHCl_3$ (100 ml). The solution was chilled to −15° and ethyl chloroformate (4.4 g, 0.04 mol) was added. The mixture was stirred at −10° for 30 min and warmed slowly to 25° and the bright yellow precipitate was isolated by filtration. The filtrate was extracted with H_2O and aqueous $NaHCO_3$, dried, and evaporated. The residue was combined with the product already isolated and recrystallized from MeOH to give 6 g of product: mp 192–193°; ir 1760, 1520, 1350, 1325, 1225, 1120, 1080, 770 cm^{-1}; NMR ($CDCl_3$) δ 2.6 (s, 3 H), 5.19 (s, 1 H), 7.3–7.84 (m, 3 H), 8.38–8.75 (m, 1 H). Anal. ($C_{11}H_8N_2O_3$) C, H, N.

Ethyl 3-Phenyl-2-quinoxalinebutyrate 1,4-Dioxide (14). Compound **5** (1.33 g, 4.12 mmol) and triethylamine (412 mg, 4.12 mmol) were dissolved in $CHCl_3$ (10 ml) and the solution was chilled to −15°C. Ethyl chloroformate (445 mg, 4.12 mmol) was added and the mixture was stirred at −10° for 30 min and allowed to warm to room temperature. The mixture was stirred at 25°C for 18 hr, washed with aqueous $NaHCO_3$ and 1 N HCl, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (benzene–ethyl acetate, 3:1) to give 800 mg of a yellow gum: ir (film) 1725, 1340, 1280, 1180, 1095, 770, 705 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 4 Hz, 3 H), 1.8–2.45 (m, 4 H), 2.98 (t, J = 3 Hz, 2 H), 4.07 (q, J = 4 Hz, 2 H), 7.57 (s, 5 H), 7.72–7.97 (m, 2 H), 8.5–8.8 (m, 2 H). Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

2-Methyl-3-vinylquinoxaline 1-Oxide (16). Compound **8** (7.5 g, 0.03 mol) and NEt_3 (3 g, 0.03 mol) were dissolved in $CHCl_3$ (200 ml) and the solution was chilled to −10°. Ethyl chloroformate (3.2 g, 0.03 mol) was added and the mixture was stirred at −10° for 30 min and 25° for 18 hr. The solution was extracted with H_2O and aqueous $NaHCO_3$, dried, and evaporated. Two recrystallizations from MeOH gave 2.6 g of solid, mp 111–112°. The filtrate was concentrated and chromatographed (silica gel, $CHCl_3$) to give another 0.3 g: mp 117–118°; ir 1630, 1575, 1480, 1340, 1095, 1050, 1000, 925, 760 cm^{-1}; NMR (Me_2SO-d_6) shows a 12-line ABX pattern[11] for the three vinyl protons with lines at δ 5.68, 5.71, 5.85, 5.88, 6.38, 6.41, 6.67, 6.70, 7.07, 7.22, 7.32, 7.50, and 2.68 (s, 3 H), 7.7–8.18 (m, 2 H), 8.3–8.58 (m, 1 H). Anal. ($C_{11}H_{10}N_2O$) C, H, N.

Penicillin Preparation. Method A. The quinoxaline ester was added to a solution of 1 equiv of KOH in ethanol, the mixture was stirred for 24 hr, and the precipitated K salt was collected by filtration. The K salt was dried in vacuo at 50° for 18 hr. The salt was suspended in $CHCl_3$ (25 ml/0.01 mol) and 1 equiv of oxalyl chloride was added at −10°. The mixture was stirred at 0–10° for 2–4 hr and chilled to −40°. A suspension of 6-APA (0.01 mol) and hexamethyldisilazane in $CHCl_3$ (50 ml) was heated at reflux under N_2 until solution occurred. The solution was evaporated and the silylated 6-APA was redissolved in $CHCl_3$. A chilled solution ($CHCl_3$) of the silylated 6-APA and NEt_3 (0.01 mol) (25 ml/0.01 mol) was added to the acid chloride solution and the mixture was allowed to come to room temperature.

Dioxane (50 ml/0.01 mol) was added and the mixture was filtered to remove NEt_3·HCl. The filtrate was treated with H_2O (0.5 ml/0.01 mol) and the mixture was stirred for 30 min. The precipitated 6-APA was removed by filtration and the filtrate was treated with sodium 2-ethylhexanoate solution, diluted with ether, and filtered. The products were reprecipitated from MeOH with ether and dried in vacuo.

Method B. The quinoxaline acid (0.01 mol) was dissolved in $CHCl_3$ (25 ml) containing NEt_3 (0.01 mol) and the solution was chilled to −10°. Ethyl chloroformate (0.01 mol) was added and the mixture was stirred at −10° for 15–30 min.[12] A chilled solution of silylated 6-APA (0.01 mol) in $CHCl_3$ (25 ml) was added. The mixture was stirred 1 hr at −5 to −10°, warmed to 25°, diluted with dioxane (50 ml), and filtered. The filtrate was treated as in method A.

Spectral data for compound 17: ir 1780, 1680, 1630, 1510, 1335, 1320, 1060, 770, and 760 cm^{-1}; NMR (D_2O) δ 1.62 (d, J = 6 Hz, 6 H), 2.68 (s, 3 H), 4.34 (s, 1 H), 5.57–5.82 (m, 2 H), 7.85–8.15 (m, 2 H), 8.25–8.55 (m, 2 H).

References and Notes

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