abscess weights more than 20% in this test were 2-[2-(nitroimino)-1(2*H*)-pyridyl]acetophenone (**8**) and its reduction product *dl*-2-(nitroimino)-α-phenyl-1(2*H*)-pyridinethanol (**11**) which caused changes of −31 and −32% resp, in abscess wt. Removal of the O from the benzylic position (**20**) resulted in loss of activity. Acetophenones with substituents on the benzene and pyridine rings all showed changes in abscess wt of less than −20%.

Experimental Section

A.—2-Nitraminopyridine (122 g, 0.87 mole) was added to NaOEt [from Na (20 g, 0.87 g-atom) in EtOH (2 l.)], and the mixt was heated under reflux for 2 hr. Ethyl bromoacetate (145 g, 0.87 mole) was added dropwise over a period of 30 min and the mixt was heated for an addnl 5 hr. The mixt was cooled and the liquor was decanted. The residue was stirred with H_2O (2 l.), and the solid was filtered off to give 118 g (59.8%) yield of crude ethyl 2-nitroimino-1(2*H*)-pyridylacetate (1), which was purified by crystn.

B.—The alkyl halide (0.1 mole) was added to a mixt of the nitramino compd (0.1 mole) and Et_3N (0.2 mole) in refluxing EtOH (200 ml). The mixt was heated under reflux for 3 hr, cooled, and filtered. The filter cake was washed with EtOH and purified by crystn.

C.—The ester 1 (11.25 g, 0.05 mole) and the appropriate secondary amine (50 ml) were heated under reflux for 1.5 hr. The excess amine was removed by evapn *in vacuo*. The residue was triturated with C_6H_6, and the resulting solid was filtered off and purified by crystn.

D.—$NaBH_4$ (1.5 g, 0.04 mole) was added in 2 portions, 5 min apart, to **8** (5.4 g, 0.02 mole) in MeOH (100 ml). The mixt was stirred for an addnl 15 min, and the solvent was removed by evapn *in vacuo*. The residue was triturated with H_2O, filtered, and crystn.

E.—A mixt of the ester 1 (10 g) and 6 *N* HCl (100 ml) was heated on a steam bath for 10 min. The resulting mixt was concd to 0.25 vol under reduced pressure, cooled, and filtered. The product was purified by crystn.

F.—This is a modification of the procedure employed by Bader, *et al.*,[11] for the prep of 4-piperidinoacetophenone. The only differences are the use of 3 times their reported vol of DMSO and a heating time of only 90 min.

G.—The ester 1 (11.3 g, 0.01 mole), 95+% H_2NNH_2 (1.7 g), and anhyd EtOH were heated under reflux for 6 hr. The mixt was cooled, and the resulting hydrazide **5** was filtered off and purified by crystn.

Rearrangement of 2-[2-(Nitroimino)-1(2*H*)-pyridyl]acetophenone (8) in H_2SO_4.—Concd H_2SO_4 was cooled to −15° in a Dry Ice-*i*-PrOH bath and **8** (10 g) was added over a period of 1 min during which time the temp rose to 0° then quickly dropped to −15°. The cooling bath was removed and the temp was allowed to rise to +15°. The mixt was poured onto ice, the resulting solid was filtered off and washed with H_2O and crystd (DMF) giving 3.74 g (38.1%) of yellow material, mp 265–267° (lit. 272°).[8] This material was identical (mmp undepressed, and the ir spectra were superimposible) with a sample of 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (**10**) prepd according to Buu-Hoi and Xuong.[8] *Anal.* ($C_{13}H_9N_3O_2$) H, N; C: calcd, 65.27; found, 64.40.

Base Hydrolysis of Ethyl 2-(Nitroimino)-1(2*H*)-pyridylacetate (1).—NaOH (2 *N*, 100 ml) was added to the ester (**1**) (11.3 g, 0.05 mole) in EtOH (100 ml). The mixt was heated under reflux for 2 hr. The EtOH was removed by evapn *in vacuo*. The residue was triturated with H_2O and extd with C_6H_6. The aq phase was chilled and made acid to pH 2 with HCl. A solid formed which was filtered off and crystd (*i*-PrOH) to give 4.52 g (53% yield) of 2-pyridone-1(2*H*)-acetic acid (**3**), mp 225–228° (lit. 222°).[7] *Anal.* ($C_7H_7NO_3$) C, H, N.

Catalytic Reduction of the Nitrimino Ester (1).—The ester 1 in 80% EtOH (250 ml) was shaken under 3.1 kg of H_2/cm^2 using 5% Pd/C catalyst (1.5 g). When uptake stopped, the mixt was filtered through a celite pad and the solvent was removed from the filtrate. The residue (6.0 g) crystd (*i*-PrOH–H_2O) as white needles, mp 249–251° (lit. 248–250).[5] This material was identical (mmp undepressed, and the ir spectra were superimposible) with a sample of 2-imino-1(2*H*)pyridineacetic acid (**2**) prepd by the method of Chichibabin.[4] *Anal.* (C_7H_8N) C, H, N.

Acknowledgment.—The authors wish to thank Mr. Frank P. Palopoli for his help and encouragement.

(11) H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).

Notes

Antibacterial Nitrofuran Derivatives. 4. 5-Nitro-2-furaldehyde Hydrazoniumacethydrazones

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We have recently described the synthesis of a series of 5-nitro-2-furaldehyde aminoacethydrazones[1–3] with antibacterial activity. In this paper we have reported a new series of 5-nitro-2-furaldehyde hydrazoniumacethydrazones **4**.

Chemistry.—Compds 4 were synthesized by the route outlined in Scheme I. In several cases compds **2** and **3** could not be isolated because of their deliquescence. The structure of these compds was deduced by the following observations.

The structure $\rangle$NHCH$_2$COOC$_2$H$_5$ was excluded because it was not possible to obtain a base by making **2** alkaline. Treatment of **2** with Ag_2O or a strong anionic-exchange resin gave a compd with neither Br^- nor $C_2H_5O^-$ identified as betaine **6**. The structure of **6** was proved by subjecting the products to reductive cleavage with 10% Pd/C, whereupon NH_3 and the corresponding amino acids **7** where obtained. Similar results were obtained by Pollak, *et al.*[4]

By reaction of 1,1-disubstituted hydrazines (**1**) with bromoacetic acid we obtained the double salts **5**. These products by reductive cleavage of N–N bonds with 10% Pd/C yielded **7**, NH_3, and the corresponding secondary amines.

By passing **5** over a strong cationic exchanger and eluting with NH_4OH we obtained **6** and the corresponding products **1**.

(1) E. Massarani, D. Nardi, A. Tajana, and L. Degen, *J. Med. Chem.*, **14**, 633 (1971).
(2) D. Nardi, E. Massarani, S. Rossi, A. Tajana, and L. Degen, *ibid.*, **14**, 635 (1971).
(3) L. Degen, M. Salvaterra, S. Vella, D. Nardi, and E. Massarani, *Chemotherapy*, in press.
(4) G. Pollak, H. Yellin, and A. Carmi, *J. Med. Chem.*, **7**, 220 (1964).

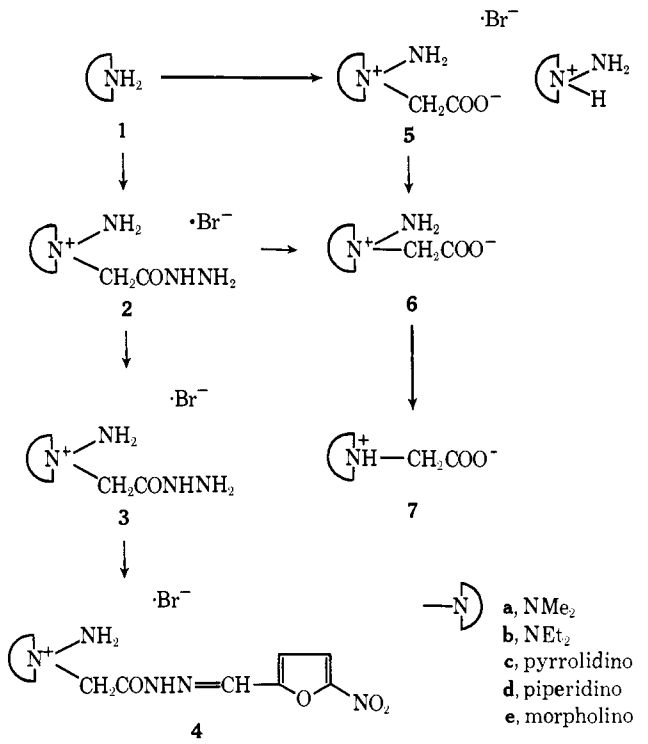
TABLE I

MINIMAL INHIBITORY CONCENTRATION (μg/ml) OF 5-NITRO-2-FURALDEHYDE HYDRAZONIUMACETHYDRAZONES[a]

No.	*E. coli*	*S. typhimurium*	*P. vulgaris*	*M. pyogenes*	*S. pyogenes*	*B. subtilis*	*Myco. tuberculosis*	*T. mentagrophytes*	LD_{50}, mg/kg ip (mice)
1	40	40	80	10	20	10	40	<5	350
2	40	40	160	20	40	40	10	80	230
3	80	40	80	5	80	10	40	10	130
4	20	40	80	5	80	5	40	<5	200
5	160	160	80	10	160	40	>160	80	560
Nitrofurantoin	5	40	80	10	5	10	>160		96

[a] All compds were inactive against *Ps. aeruginosa* and *C. albicans*.

SCHEME I



Biological Results.—The acute toxicity was determined ip on NMRI albino mice (18–20 g). All compds were tested for bacteriostatic activity *in vitro* as described[5] previously on the following microorganisms: *Escherichia coli* 100, *Salmonella typhimurium* 1090, *Pseudomonas aeruginosa* H2, *Proteus vulgaris* OX, *Micrococcus pyogenes* SG 511, *Streptococcus pyogenes* A 88, *Bacillus subtilis* ATCC 9466, *Mycobacterium tuberculosis* H_{37} Ra, *Trichophyton mentagrophytes* 1236, and *Candida albicans* 28. The results are summarized in Table I.

The products were also tested in mice on subacute im *M. pyogenes* infection of the mouse leg as previously described.[6] Only **1** was significantly active at 70 mg/kg (0.2 LD_{50}), whereas nitrofurantoin at 20 mg/kg (0.2 LD_{50}) was inactive. Compd **2**, which was the most active compd on *Myco. tuberculosis in vitro*, was tested *in vivo* in mice.[7] It exhibited significant activity at 9.1 mg/kg. Compds **1**, **3**, and **4** were not active when tested topically in the guinea pig against *T. mentagrophytes* 1236 according to the method of Arnold, *et al.*[8]

Experimental Section[9]

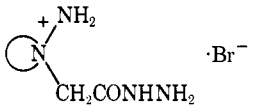
***N,N*-Dimethyl-*N*-carbethoxymethylhydrazonium Bromide (2a).**—To a soln of 3 g (0.05 mole) of *N,N*-dimethylhydrazine in 100 ml of anhyd Et_2O, were added 8.3 g (0.05 mole) of ethyl bromoacetate and the mixt was stirred at 0–5° for 24 hr. The crystals were collected and recrystd from EtOH–Et_2O; yield 9.8 g (87%), mp 97–99°. *Anal.* ($C_6H_{15}BrN_2O_2$) C, H, N, Br.

***N,N*-Pentamethylene-*N*-carbethoxymethylhydrazonium bromide (2d)** was obtd from *N*-aminopiperidine in a similar way; yield 45%, mp 130–132°. *Anal.* ($C_9H_{19}BrN_2O_2$) C, H, N, Br.

***N,N*-Dimethyl-*N*-acethydrazidehydrazonium Bromide (3a). Method A.**—A mixt of 11.3 (0.05 mole) of **2a**, 60 ml of EtOH, and 2.5 g (0.05 mole) of hydrazine hydrate was refluxed for 2 hr. After cooling the crystals were collected and recrystd (Table II).

TABLE II

N,N-DISUBSTITUTED-*N*-ACETHYDRAZIDEHYDRAZONIUM BROMIDES



N	Method	Yield, %	Crystn solvent	Mp, °C	Formula[a]
NMe_2	A	78	95% EtOH	132–134	$C_4H_{13}BrN_4O$
Pyrrolidino	A	42[b]	EtOH	122–124	$C_6H_{15}BrN_4O$
Piperidino	A	83[b]	EtOH	160–161	$C_7H_{17}BrN_4O$
Morpholino	A	26	95% EtOH	164–166	$C_6H_{15}BrN_4O_2$

[a] All compds were analyzed for C, H, N, Br. [b] The corresponding **2** esters were not isolated.

5-Nitro-2-furaldehyde *N,N*-Dimethyl-*N*-acethydrazone Hydrazonium Bromide (4a). Method B.—A mixt of 1.02 g (0.005 mole) of **3a**, 0.7 g (0.005 mole) of 5-nitro-2-furaldehyde, and 25 ml of EtOH was refluxed for 30 min. After cooling, the crystals were collected and recrystd (Table III).

***N*-Amino-*N*-carboxymethylmorpholinium Bromide *N*-Aminomorpholine Salt. (5e).**—To a soln of 2.04 g (0.02 mole) of *N*-aminomorpholine in 10 ml of anhyd Et_2O cooled to 0°, 1.39 g (0.01 mole) of bromoacetic acid in 10 ml of Et_2O was added, and the mixt was kept at 0° for 12 hr. The crystals were collected and recrystd from EtOH; yield 3 g (88%), mp 172–174°. *Anal.* ($C_{10}H_{23}BrN_4O_4$) C, H, N, Br.

***N*-Amino-*N*-carboxymethylmorpholine Betaine (6e). Method C.**—A 2% aq soln of **2e** was passed through a strong anionic exchanger Relite 2A column. The eluate was evapd to dryness *in vacuo*, and the residue was crystd.

Method D.—A 3% aq soln of **5e** was passed through a strong cationic exchanger Relite CFS column. Then the column was eluted with 1 *N* NH_4OH. The soln was evapd to dryness *in*

(5) E. Massarani, D. Nardi, L. Degen, and M. J. Magistretti, *J. Med. Chem.*, **9**, 617 (1966).

(6) D. Nardi, E. Massarani, A. Tajana, L. Degen, and M. J. Magistretti, *ibid.*, **10**, 530 (1967).

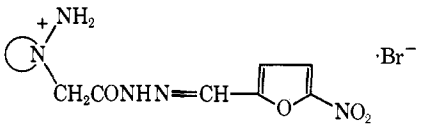
(7) E. Massarani, D. Nardi, R. Pozzi, L. Degen, and M. J. Magistretti, *ibid.*, **13**, 380 (1970).

(8) H. Arnold, L. Degen, J. Potel, and R. Rebling, *Arzneim.-Forsch.*, **14**, 68 (1964).

(9) Melting points are uncor and were determined in open glass capillaries on a Büchi apparatus. When analyses are indicated only by symbols of the elements, the anal. results obtained for those elements were within ±0.4% of the theor values.

TABLE III

5-NITRO-2-FURALDEHYDE HYDRAZONIUMACETHYDRAZONES



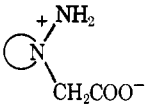
No.	N	Method	Yield, %	Crystn solvent	Mp, °C	Formula[a]
1	NMe_2	B	95	EtOH–H_2O	217	$C_9H_{14}BrN_5O_4$
2	NEt_2	B	30[b]	95% EtOH	184–186	$C_{11}H_{18}BrN_5O_4$[c]
3	Pyrrolidino	B	86	MeOH	217	$C_{11}H_{16}BrN_5O_4$
4	Piperidino	B	87	EtOH	199 dec	$C_{12}H_{18}BrN_5O_4$
5	Morpholino	B	69	EtOH–H_2O	228 dec	$C_{11}H_{16}BrN_5O_5$

[a] All compds were analyzed for C, H, N, Br. [b] The corresponding ester **2b** and hydrazide **3b** were not isolated because of their hygroscopicity. [c] *Anal.* C, H, N, O.

vacuo. The distn also removed the *N*-aminomorpholine. The residue was crystd (Table IV).

TABLE IV

BETAINES



N	Method	Yield, %	Crystn solvent	Mp, °C	Formula[a]
Pyrrolidino	C	75	EtOH–Et_2O	159–161	$C_6H_{11}NO_2$
Piperidino	C	50	EtOH–Et_2O	200–202	$C_7H_{14}NO_2$
Morpholino	C	37			
	D	87	95% EtOH–Et_2O	236–238	$C_6H_{12}NO_3$

[a] All compds were analyzed for C, H, N.

***N*-Pyrrolidinoacetic Acid (7c).**[10]—A soln of 1.44 g (0.01 mole) of **6c** in 20 ml of MeOH was hydrogenated in presence of 0.3 g of 10% Pd/C at atmospheric pressure and at room temp. When the absorption of H_2 ceased, the catalyst was filtered and the soln was evapd. The residue was crystd from *i*-PrOH–Et_2O; yield 1 g (78%), mp 138–140°. *Anal.* ($C_6H_{11}NO_2$) C, H, N.

This compd was obtd also by hydrolysis of ethyl *N*-pyrrolidinoacetate with 1 *N* HCl. After hydrolysis the soln was passed through a strong cationic exchanger Relite CFS and **7c** was eluted with 1 *N* NH_4OH. The soln was evapd to dryness *in vacuo* and the residue was crystd; yield 88%.

(10) By this procedure were obtained **7b**, **7d**, and **7e** [R. E. Bowman, *J. Chem. Soc.*, 1346 (1950); C. A. Bischoff, *Chem. Ber.*, **31**, 2839 (1898); A. L. Remizon, *Zh. Obshch. Khim.*, **34**, 3187 (1964); *Chem. Abstr.*, **62**, 4106 (1965)].

Some New Antibacterial Quinoxaline *N*,*N*-Dioxide Derivatives

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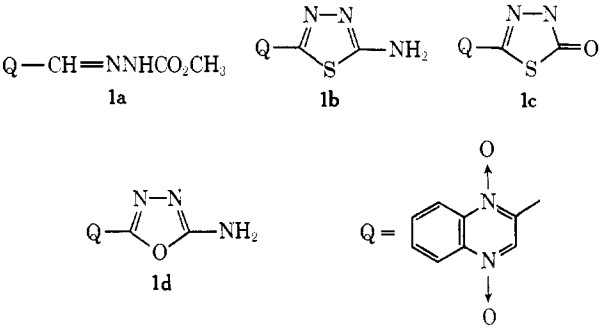
Several relatively simple derivatives of quinoxaline-2-carboxaldehyde 1,4-dioxide, notably the carbomethoxyhydrazone derivative[1] (**1a**), exhibit interesting antibacterial activity.[1,2]

We have now prepared the aminothiadiazole **1b** and the thiadiazolone **1c** from the corresponding thiosemicarbazone. The oxadiazole **1d** could be obtained from brominative oxidation of the corresponding semicarbazone, but resisted purification efforts.

The compounds were generally poorly soluble and difficult to purify. The thiadiazolone was not obtained analytically pure, but the structure was confirmed by the exact mass of the parent ion and a reasonable fragmentation pattern in the mass spectrum.



1a **1b** **1c**

1d

Biological Results.—Two of the derivatives, **1c** and **1d**, were active against a *Salmonella gallinarum* infection in chicks when fed in the diet at the 0.1% level, and the latter was partially effective at 0.025%; **1a** was highly active at the 0.025% level. Similarly **1b** was highly active against *Escherichia coli* infections in chicks at 40 mg/kg single oral dose, but this was only *ca.* 0.25 the activity of **1a**, and the other derivatives were inactive. **1b** was inactive *vs. E. coli* and *Staphylococcus Smith* infections in mice at levels at which **1a** was efficacious.

Experimental Section[3]

2-(5-Amino-1,3,4-thiadiazol-2-yl)quinoxaline 1,4-Dioxide (1b).—A mixt of 13.7 g (0.052 mole) of quinoxaline-2-carboxaldehyde 1,4-dioxide thiosemicarbazone and 42.0 g (0.156 mole) of $FeCl_3 \cdot 6H_2O$ in 1250 ml of H_2O was refluxed 4 hr, then filtered hot to give 13.3 g (97% yield) of yellow powder, mp 278–82° dec. Recrystn from a large amt of EtOH gave anal. pure material, mp 291–293° dec. *Anal.* ($C_{10}H_7N_5O_2S$) C, H, N, S.

2-(2-Quinoxalinyl)-Δ^2-1,3,4-thiadiazolin-5-one, Quinoxaline 1,4-Dioxide (1c).—Compd **1b** (11.0 g, 0.042 mole) in 45 ml of H_2O and 230 ml of concd H_2SO_4 was diazotized at 10° with 10.3 g (0.15 mole) of $NaNO_2$ in 45 ml of H_2O and stirred overnight at room temp. The reaction mixt was cooled below 0° as a total of 430 ml of 10 *N* NaOH soln was added dropwise with the addn of crushed ice to facilitate cooling. The resulting product was filtered and washed thoroughly with H_2O to give 9.7 g (88% yield) of brown powder, mp 270–273° dec. Another run gave an 89% yield of crude product as a yellow powder, mp 277–280° dec. Recrystn from 95% EtOH, glac HOAc, Me_2CO_3, or DMF was possible but in each case the mp was lower or the same and microanal. was worse than for the crude product. *Anal.* Calcd for $C_{10}H_6N_4O_3S$: C, 45.80; H, 2.31; N, 21.36; S, 12.23. Found: C, 43.46; H, 2.24; N, 20.45; S, 11.29. The mass spectrum exhibited a weak but correct molecular ion ($C_{10}H_6N_4O_3S$ Calcd: 260.0161. Found: 262.0152).

Acknowledgment.—The antibacterial testing was conducted under the direction of Dr. G. Kemp, Princeton, N. J., and Mr. G. Redin of Lederle Laboratories. The mass spectrum was run by T. L. Chang, American Cyanamid Company, Stamford Laboratories.

(1) Chas. Pfizer & Co., U. S. Patents 3,371,090, 3,433,871 (1968).

(2) Research Corporation, U. S. Patent 3,398,141 (1968).

(3) Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, anal. results obtained for these elements were within ±0.4% of the theor values.