with stirring. After stirring for 30 min at 3°, 5 ml of 5% NaH-CO<sub>3</sub> was added, and the CCl<sub>4</sub> layer was sepd, dried (MgSO<sub>4</sub>), and concd *in vacuo*. Tlc of the crude product revealed the presence of approximately equal amts of 3 compounds. Preparative tlc on Brinkman silica gel plates served to sep the compds. The fastest moving compd was not obtained in pure form. The component of intermediate mobility was eluted from the silica gel with CHCl<sub>4</sub>-EtOH (1:1) and crystd from Et<sub>2</sub>O-C<sub>6</sub>H<sub>14</sub> to give 0.1733 g (17%) of **9**: mp 214.5-216.5;  $\nu_{max}$  3600, 1737, 1730, and 1720 cm<sup>-1</sup>;  $[\alpha]D - 23.7^{\circ}$ . Anal. (C<sub>28</sub>H<sub>38</sub>O<sub>6</sub>) C, H.

The slowest moving compd was crystd from Et<sub>2</sub>O-C<sub>6</sub>H<sub>14</sub> to yield 0.1793 g (18%) of **10**: mp 193-195°;  $\nu_{max}$  3600, 1738, 1730, and 1718 cm<sup>-1</sup>;  $[\alpha]D - 103.5°$ . Anal. (C<sub>26</sub>H<sub>38</sub>O<sub>6</sub>) C, H.

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# Angiotensin II Analogs. 5. [2-Glycine]angiotensin II and Related Analogs<sup>1</sup>

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The amino and carboxyl groups of the aspartyl residue in angiotensin II, Asp-Arg-Val-Tyr-Ile(or Val)-His-Pro-Phe, are not essential for pressor activity although they do possess features which are necessary for maximal activity. Thus the elimination of the NH<sub>2</sub> group or the carboxymethyl group of the aspartyl residue of angiotensin II gives analogs which retain half of the pressor activity of the parent compound.<sup>2,3</sup> Many analogs have been synthesized in attempts to discover which features of these functional groups are responsible for the enhanced pressor activity. However, these analogs, which are listed in Table I, do not reveal which property of the aspartic acid residue makes the greatest contribution to the pressor activity. One reason for this may be the proximity of the guanidino group of arginine which appears to make a greater contribution to the observed pressor activity. The presence of this guanidino group may overshadow the contributions of aspartic acid or its analogs making evaluation of these contributions more difficult.

This report describes some analogs of angiotensin II containing glycine in place of arginine which were synthesized in the hope that the elimination of the guanidino function would give a system which would be more

 Part 4: E. C. Jorgensen, G. C. Windridge, and T. C. Lee, J. Med. Chem., 13, 744 (1970). This investigation was supported in part by Public Health Service Research Grants AM 08066 and AM 06704 from the National Institutes of Arthritis and Metabolic Diseases and Training Grant No. 5 T01 GM 00728 from the National Institute of General Medical Sciences. The abbreviations used to denote amino acid derivatives and peptides are those recommended in *Biochemistry*, 5, 2485 (1966).

(2) B. Riniker and R. Schwyzer, Helv. Chim. Acta, 47, 2357 (1964).

(3) R. Schwyzer, ibid., 44, 667 (1961).

#### TABLE I

### ANGIOTENSINS MODIFIED IN POSITION 1

Peptide	Pressor activity
Asp-Arg-Val-Tyr-Val-His-Pro-Phe	100
D-Asp-Arg-Val-Tyr-Val-His-Pro-Phe	1504
$\beta$ -Asp-Arg-Val-Tyr-Val-His-Pro-Phe	150•
Asn-Arg-Val-Tyr-Val-His-Pro-Phe	100
Glu-Arg-Val-Tyr-Val-His-Pro-Phe	150
Pyroglu-Arg-Val-Tyr-Val-His-Pro-Phe	150°
Gly-Arg-Val-Tyr-Val-His-Pro-Phe	50 <sup>d</sup>
Succinyl-Arg-Val-Tyr-Val-His-Pro-Phe	50ª
Arg-Val-Tyr-Val-His-Pro-Phe	50ª

<sup>a</sup> B. Riniker and R. Schwyzer, *Helv. Chim. Acta*, **47**, 2357 (1964). <sup>b</sup> W. Rittel, B. Iselin, H. Kappeler, B. Riniker, and R. Schwyzer, *ibid.*, **40**, 614 (1958). <sup>c</sup> E. Schroder, *Justus Liebigs Ann. Chem.*, **691**, 232 (1966). <sup>d</sup> See R. Schwyzer, *Helv. Chim. Acta*, **44**, 667 (1961).

sensitive to the contributions of the aspartyl residue. Glycine was chosen as a replacement for arginine because it seemed undesirable to replace the very polar guanidinopropyl side chain with a hydrophobic one.

Asp-Gly-Val-Tyr-Ile-His-Pro-Phe was prepared in solution from the purified heptapeptide and Z-Asp-(OBzl)-ONp and the protecting groups were removed by catalytic hydrogenolysis because of the reported danger of succinimide formation when peptides containing an Asp(OBzl)-Gly sequence are exposed to HBr during cleavage of the peptide from a solid-phase polymer.<sup>4</sup> Model experiments appeared to confirm this side reaction. The same approach was used in the syntheses of Asn-Gly-Val-Tyr-Ile-His-Pro-Phe and succinamyl-Gly-Val-Tyr-Ile-His-Pro-Phe although the danger of cyclization was less in these cases. Succinvl-Gly-Val-Tyr-Ile-His-Pro-Phe was prepared on the solid-phase polymer<sup>5</sup> and purified by anion-exchange chromatography. The pressor activities and durations of response were determined in the rat as described earlier.6

### **Results and Discussion**

The pressor activities of the peptides described in this paper and related peptides reported earlier are shown in Table II. These results show that  $CO_2H$ makes no contribution to the pressor activity of  $[Gly^2]$ angiotensin II, while  $CONH_2$  is unfavorable. This is clearly in conflict with the results found in angiotensin II itself, suggesting that the  $Gly^2$  series may not be a valid system for studying the contributions of aspartic acid to the pressor activity of angiotensin II.

The decreased pressor activity of peptide IV compared with VI and the equivalent pressor activity of V and VI is consistent with the suggestion<sup>7,8</sup> that the terminal amino group in VI might be binding at the "guanidino" binding site since neither a carboxyl nor a carboxamido group need be expected to aid in, and could interfere with, binding at this site. The low

<sup>(4)</sup> M. A. Ondetti, A. Deer, J. T. Sheehan, J. Pluscec, and O. Kocy, *Biochemistry*, 7, 4069 (1968).

<sup>(5)</sup> R. B. Merrifield, *ibid.*, **3**, 1385 (1964).

<sup>(6)</sup> E. C. Jorgensen, G. C. Windridge, and T. C. Lee, J. Med. Chem., 13, 352 (1970).
(7) E. C. Jorgensen, G. C. Windridge, W. Patton, and T. C. Lee, *ibid.*,

<sup>(1) 2.</sup> C. Jogensen, G. C. Windridge, W. Patter, and T. C. Lee, 1963, (2) F. C. Legensen, G. C. Windridge, W. Patter, and T. C. Lee, in

<sup>(8)</sup> E. C. Jorgensen, G. C. Windridge, W. Patton, and T. C. Lee, in "Peptides: Chemistry and Biochemistry," B. Weinstein and S. Lande, Ed., Marcel Dekker, Inc., New York, N. Y., 1970, pp 113-125.

TABLE II [Gly<sup>2</sup>] ANGIOTENSIN II ANALOGS

		Pressor	Relative
		activ-	dura-
		$ity^a$	tion <sup>a</sup>
II	Succinyl-Gly-Val-Tyr-Ile-His-Pro-Phe	1	100
III	Succinamyl-Gly-Val-Tyr-Ile-His-Pro-Phe	2	100
IV	Asn-Gly-Val-Tyr-Ile-His-Pro-Phe	3.	100
V	Asp-Gly-Val-Tyr-Ile-His-Pro-Phe	10	100
VI	Gly-Gly-Val-Tyr-Ile-His-Pro-Phe	$10^{b,c}$	80
VII	Ac-Gly-Gly-Val-Tyr-Ile-His-Pro-Phe	$0.4^{b}$	100
VIII	Ac-Gly-Val-Tyr-Ile-His-Pro-Phe	1 <sup>d</sup>	100

<sup>a</sup> Relative to [Asn<sup>1</sup>, Val<sup>5</sup>] angiotensin II (Hypertensin-CIBA) = 100. <sup>b</sup> See E. C. Jorgensen, G. C. Windridge, W. Patton, and T. C. Lee, J. Med. Chem., **12**, 733 (1969). <sup>c</sup> Best recent value expressed on a molar basis. <sup>d</sup> See E. C. Jorgensen, G. C. Windridge, and T. C. Lee, J. Med. Chem., **13**, 352 (1970). <sup>e</sup> Pavars and Cipens, Latv. PSR Zinat. Akad. Vestis, Kim. Ser., 250 (1970); Chem. Abstr., **73**, 56406 (1970), reported 3-5% for the Val<sup>5</sup> analog.

activities of II and III, which would not be expected to interact with the "guanidino" binding site, suggest that a  $CO_2H$  or a  $CONH_2$  group alone cannot make a significant contribution to the pressor activity (cf. VII and VIII) even though they apparently do so in the presence of the guanidino group of arginine in position 2. Thus it appears, at present, that the guanidino group is the feature in the N-terminal dipeptide which is primarily responsible for the high pressor activity of angiotensin II relative to the hexapeptide, Val-Tyr-Ile-His-Pro-Phe.

#### **Experimental Section**<sup>9</sup>

p-Nitrophenyl Succinamate (I).—A stirred soln of 2.93 g (25 mmoles) of succinamic acid and 4.87 g (35 mmoles) of p-nitrophenol in DMF was maintained at C-5° while a soln of 5.15 g (25 mmoles) of DCI in 25 ml of DMF was added. The reaction mixt was stirred at 0° for 2 hr then overnight at room temp. It was filtered and the filtrate was evapd *in vacuo* at 30°. The residue was triturated with a mixt of Et<sub>2</sub>O (50 ml) and H<sub>2</sub>O (50 ml), then the resulting solid was filtered and air dried to yield 1.25 g. This solid was crystd from 20 ml of EtOAc giving 1.00 g (17%) as colorless plates: mp 128–130°; tlc, one spot,  $R_{\rm fI}$ , 0.40 (Cl +,<sup>10</sup> yellow color with NH<sub>3</sub>). Anal. (C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>) C, H, N.

Succinyl-Gly-Val-Tyr-Ile-His-Pro-Phe (II).—Boc-Gly-Val-Tyr(Bzl)-Ile-His(Bzl)-Pro-Phe-polymer,<sup>6</sup> 0.90 g (0.15 mmole), was deprotected and neutralized as previously described<sup>6</sup> and then acylated with 30 mg (0.30 mmole) of succinic anhydride in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> contg 0.042 ml (0.30 mmole) of Et<sub>3</sub>N for 2 hr. The polymer was washed with CH<sub>2</sub>Cl<sub>2</sub> ( $3 \times 20$  ml) and CF<sub>3</sub>COOH ( $3 \times 20$  ml) and suspended in CF<sub>3</sub>COOH (10 ml) and anisole (1 ml), and a stream of HBr (scrubbed with satd resorcinol in Cr<sub>6</sub>H<sub>5</sub> and with CaCl<sub>2</sub>) was bubbled through the suspension for 1 hr. The suspension was filtered by suction, and the polymer was washed with CF<sub>3</sub>COOH (2 × 10 ml). The filtrate was evapd on

(10) D. E. Nitecki and J. W. Goodman, Biochemistry, 5, 665 (1966).

a rotary evaporator at 30°, and the residue was lyophilized from AcOH. The resulting powder was dissolved in 15 ml of 50% MeOH contg 2% AcOH, 150 mg of 10% Pd/C was added, and the suspension was stirred under 3 atm of H<sub>2</sub> for 48 hr at room temp. The catalyst was filtered off (filter aid) and washed with AcOH. The filtrate was evapd *in vacuo* at 30° and the residue was lyophilized from AcOH giving 140 mg.

A portion (95 mg) of this crude peptide was dissolved in 25 ml of 0.05 *M* AcOH, adjusted to pH 5.0 with 30% NH<sub>4</sub>OH, and applied to a 1.5 × 83 cm column of AG 1 X2 (acetate) packed in the same buffer. The column was eluted with a gradient, linear in acetate, formed by running 700 ml of 0.5 *M* AcOH, adjusted to pH 4.0 with 30% NH<sub>4</sub>OH, into 700 ml of the starting buffer. Fractions of 12 ml were collected at a flow rate of 10 ml/hr. The desired peptide emerged as a sym peak after 1200 ml. The soln was lyophilized to give 32 mg of white powder, homogenous on electrophoresis at pH 1.85 ( $E_{\rm H}$ , 0.30) and pH 3.5 ( $E_{\rm H}$ , 0.15) and on tlc ( $R_{\rm f}$ II, 0.68;  $R_{\rm f}$ III, 0.28;  $R_{\rm f}$ IV, 0.53;  $R_{\rm f}$ V, 0.90), Cl +, Pauly +, ninhydrin -. A 72-hr acid hydrolysate had Gly 0.98, Val 0.99, Tyr 0.97, Ile 0.96, His 1.02, Pro 1.00, Phe 0.99; peptide content, 87%.

Succinamyl-Gly-Val-Tyr-Ile-His-Pro-Phe (III).—To a soln of 50 mg (0.05 mmole) of Gly-Val-Tyr-Ile-His-Pro-Phe<sup>6</sup> in 2 ml of purified DMF<sup>11</sup> were added 0.02 ml (0.15 mmole) of Et<sub>3</sub>N and 24 mg (0.10 mmole) of p-nitrophenyl succinamate (I). After 24 hr at 25°, electrophoresis showed a strong Pauly +, ninhydrin – spot at  $E_{\rm H}$  0.30 (pH 1.85) and  $E_{\rm H}$  0.22 (pH 3.5); no heptapeptide was detected. The peptide was ptd by addn of 6 ml of EtOAc; the ppt was centrifuged and washed with EtOAc (3 × 5 ml) and Et<sub>2</sub>O (3 × 5 ml), then lyophilized from 1 N AcOH giving 35 mg (70%) of white powder. The showed one Pauly + spot,  $R_4$ II, 0.65;  $R_4$ III, 0.40;  $R_4$ N, 0.91. A 72-hr acid hydrolysate had Gly 1.00, Val 1.01, Tyr 0.98, Ile 1.00, His 1.00, Pro 1.00, Phe 0.99; peptide content, 82%. Asn-Gly-Val-Tyr-Ile-His-Pro-Phe (IV).—To a soln of 25 mg

(0.025 mmole) of Gly-Val-Tyr-Ile-His-Pro-Phe<sup>6</sup> in 1 ml of purified DMF were added 0.010 ml (0.075 mmole) of Et<sub>3</sub>N and 20 mg (0.050 mmole) of p-nitrophenyl benzyloxycarbonylasparaginate. After 24 hr at 25° the peptide was pptd by adding 3 ml of EtOAc and the ppt was centrifuged, washed with EtOAc (3 ml) and with  $Et_{2}O$  (3  $\times$  3 ml), and then lyophilized from AcOH giving 25 mg of white powder. This protected peptide was dissolved in 6 ml of 95% AcOH and hydrogenated at 1 atm over 25 mg of 10%Pd/C for 90 min. The suspension was filtered (filter aid) and the catalyst was washed with AcOH. The filtrate was lyophilized giving 21 mg (80%) of white powder. This product showed one Pauly + spot on electrophoresis;  $E_{\rm H}$ , 0.58 (pH 1.85);  $E_{\rm H}$ , 0.50 (pH 3.5); and on tlc,  $R_{\rm f}$ II, 0.49;  $R_{\rm f}$ III, 0.32. A 72-hr acid hydrolysate had Asp 0.99, Gly 0.97, Val 1.00, Tyr 0.92, Ile 0.95, His 1.03, Pro 0.97, Phe 0.95; peptide content 82%. Low values for Tyr in peptides contg Asp or Asn have been noted previously.12,13

Asp-Gly-Val-Tyr-Ile-His-Pro-Phe (V).—To a soln of 25 mg (0.025 mmole) of Gly-Val-Tyr-Ile-His-Pro-Phe<sup>6</sup> in 1 ml of purified DMF were added 0.018 ml (0.075 mmole) of Bu<sub>3</sub>N and 25 mg (0.050 mmole) of Z-Asp(OBzl)-ONp.<sup>14</sup> After 24 hr at 25° the peptide was pptd by adding 6 ml of EtOAc, the ppt was centrifuged and washed with EtOAc (2 × 6 ml) and with Et<sub>2</sub>O (6 ml). The product (19 mg) was redissolved in 1 ml of DMF and again pptd with 10 ml of EtOAc to remove some Z-Asp(OBzl). The ppt was washed with 10 ml of EtOAc and lyophilized from AcOH giving 13.5 mg of white powder.

The protected peptide was dissolved in 5 ml of 50% AcOH and hydrogenated over 15 mg of 10% Pd/C at 1 atm for 4 hr. The mixt was filtered (filter aid), the catalyst was washed with AcOH, and the filtrate was lyophilized giving 9 mg. Electrophoresis (pH 3.5) showed a strong spot,  $E_{\rm H}$  0.23, and a faint spot  $E_{\rm H}$ 0.48, both Cl<sup>10</sup> and Pauly +). The showed a strong Pauly + spot,  $R_{\rm f}$ II, 0.48;  $R_{\rm f}$ III, 0.18; and a faint spot,  $R_{\rm f}$ II, 0.53. The ir spectrum had no succinimide carbonyl bands at 1680 or 1730 cm<sup>-1</sup>. A 72-hr acid hydrolysate had Asp 1.09, Gly 1.01, Val 1.02, Tyr 0.88, He 0.99, His 0.95, Pro 1.04, Phe 1.00; peptide content, 77%.

(13) R. Paul and G. W. Anderson, J. Org. Chem., 27, 2094 (1962).

<sup>(9)</sup> Melting points (Thomas-Hoover Uni-Melt) are corrected. Amino acid analyses were performed on a Spinco Model 116 amino acid analyzer using the standard 4-hr methodology. Peptides were hydrolyzed under  $N_2$  at 110° in const boiling HCl contg alanine as an internal standard. Peptide content was calcd in terms of free peptide rather than the hydrated salt. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif. Where analyses are indicated only by symbols of the elements, analytical results obtained were within  $\pm 0.4\%$  of the theoretical values. Precoated silica gel G plates (E. Merck) were used for tlc with the following solvent systems: I, EtOAc; II, n-BuOH-AcOH-H2O (3:1:1); III, 2-BuOH-3% NH2 (100:44); IV, n-BuOH-AcOH-H<sub>2</sub>O (4:1:5, upper phase); V, pyridine-H<sub>2</sub>O (4:1). Electrophoresis was carried out on Whatman No. 1 paper at 5000 V using AcOH-HCOOH buffer, pH 1.85, or AcOH-pyridine buffer, pH 3.5, in a Savant apparatus. E<sub>H</sub> indicates the electrophoretic mobility relative to His = 1.00. Ir spectra were measured on a Perkin-Elmer Model 337 instrument using 0.5% of the peptides in KBr.

<sup>(11)</sup> A. B. Thomas and E. G. Rochow, J. Amer. Chem. Soc., 79, 1843 (1957).

<sup>(12)</sup> R. G. Shepherd, S. D. Willson, K. S. Howard, P. H. Bell, D. S. Davies, S. B. Davis, E. A. Eigner, and N. E. Shakespeare, *ibid.*, **78**, 5067 (1956).

<sup>(14)</sup> S. Guttmann, Helv. Chim. Acta, 44, 721 (1961).

A 10-mg portion of the protected peptide prepd as above was treated with HBr-CF<sub>3</sub>COOH for 30 min at 25°, evapd on a rotary evaporator at 25°, and then lyophilized from AcOH giving 8 mg. The ir spectrum showed succinimide carbonyl bands at 1680 and 1730 cm<sup>-1</sup> of comparable intensity to those in an equimolar mixt of the heptapeptide and succinimide.

# Antibacterial Nitrofuran Derivatives. 2. 5-Nitro-2-furaldehyde Aminoacethydrazones

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The nitrofuran derivatives used in the treatment of bacterial infections of the urinary tract show only a slight water solubility, a property which limits pharmaceutical formulations and therapeutic use. A series of 5-nitro-2-furaldehyde aminoacethydrazones with the following structure were synthesized in order to obtain new antibacterial nitrofurans with a better water solubility.

These products were prepared by condensing the 5nitro-2-furaldehyde with the corresponding aminoacethydrazides. organisms: Escherichia coli 100, Salmonella typhimurium 1090, Pseudomonas aeruginosa H2, Proteus vulgaris OX, Micrococcus pyogenes SG511, Streptococcus pyogenes A88, Bacillus subtilis ATCC 9466, Clostridium novyi, Mycobacterium tuberculosis  $H_{37}$ Ra, Trichophyton mentagrophytes 1236, and Candida albicans 28.

None of the compounds, or nitrofurantoin, exhibited significant activity against *Cl. novyi*, *M. tuberculosis*, *T. mentagrophytes*, and *C. albicans*. The monoalkylamino-acethydrazones (1-7) showed an *in vitro* antibacterial activity generally higher than that of nitrofurantoin. The dialkylaminoacethydrazones (8-18) showed an *in vitro* antibacterial activity comparable to that of nitrofurantoin.

The urinary excretion was determined in rats. The urinary excretion of monoalkylaminoacethydrazones was highest for the ethylamino derivative 2 and decreased with lengthening of the side chain. The dialkylamino derivatives were scarcely excreted in the urine whereas a slight excretion was observed for the *N*-dimethylamino (15) and pyrrolidino (12) derivatives. By contrast the *N'*-methylpiperazino derivative (13)<sup>1</sup> was excreted to a large extent.

Only 13 was active in experimental infections. It exhibited an activity comparable to 19 in a systemic infection of mice with *Strep. pyogenes* C 203 and a higher activity than 19 in infections of mice with *S. typhimurium* 1086 and in im infection of mice with *Staphylococcus aureus* 742. Compd 13 was active on the ascending *P. vulgaris* urinary tract infection of rats.<sup>2,3</sup>

$O_2 N - CH - NNHCOCH_2 R$									
No.	E. coli	S. typhi- murium	Ps. aeruginosa	P. vulgaris	M. pyogenes	Strep. pyogenes	B. subtilis	Drug urinary excretion	LD50, mg/kg ip
1	10	10	<b>4</b> 0	40	2.5	20	1.25	4	188¢
<b>2</b>	10	10	40	<b>20</b>	5	20	1.25	10	1430
3	20	20	40	40	20	40	2.5	$^{2}$	1720
4	20	20	40	40	5	20	1.25	3.5	170°
5	10	10	80	80	10	10	5	0	1200
6	10	20	80	40	5	10	<b>5</b>	0	1130
7	10	10	40	40	2.5	5	0.625	0	130¢
14 <sup>a,b</sup>	10	10	<b>40</b>	40	5	40	5	4.5	300*
150,0	10	20	80	80	20	160	20	0	$109^{h}$
8	2.5	<b>40</b>	80	80	10	80	10	0	150
$16^{a,d}$	<b>20</b>	40	80	80	10	80	5	0	390
9	5	80	>160	>160	20	80	5	0	700
10	10	40	>160	>160	2.5	40	2.5	0	900
11	<b>20</b>	>160	>160	>160	<b>20</b>	80	10	0	800
12	<b>20</b>	20	80	80	20	1.25	<b>5</b>	2.5	$250^{h}$
170,0	80	80	80	80	40	10	2.5	0	$120^{h}$
18 <sup>a, f</sup>	80	160	>160	160	20	2.5	2.5	0	$420^{h}$
13	<b>4</b> 0	40	160	80	20	2.5	20	24	315
$19^{i}$	5	40	160	80	10	5	10	37	96

 TABLE I

 Antimicrobial Activity of 5-Nitro-2-furaldehyde Aminoacethydrazones

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<sup>a</sup> While our study was in progress, A. Jujita, S. Minami, and H. Takamatsu, Yakugaku Zasshi, 84, 890 (1964), reported the synthesis and antimicrobial data of these products. <sup>b</sup> R = N(CH<sub>3</sub>)<sub>2</sub>. <sup>c</sup> R = N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>. <sup>d</sup> R = N(*i*-C<sub>3</sub>H<sub>7</sub>)<sub>2</sub>. <sup>e</sup> R = piperidino. / R = morpholino. <sup>e</sup> AcOH salt. <sup>b</sup> HCl salt. <sup>i</sup> Nitrofurantoin.

**Biological Results** (**Table I**).—The acute toxicity was determined ip in mice. All compounds were tested for bacteriostatic activity *in vitro* on the following micro-

(1) Nonproprietary name, nifurpipone.

<sup>(2)</sup> L. Degen, M. Salvaterra, S. Vella, D. Nardi, and E. Massarani, Chemotherapy, in press.

<sup>(3)</sup> L. Degen, M. Salvaterra, and S. Vella, *ibid.*, in press.