Acute toxicity, and antimicrobial and antifungal activity *in vitro* were determined as previously described.[5]

Urinary Excretion of the Drug.—A single oral dose of 20 mg/kg of the drug was administered by intubation and the urine of each rat was collected (in metabolic cage) after 6 hr. The urinary level was determined according to the standard cylinder plate assay[6a] modified by Degen, *et al.*[6] *B. subtilis* ATCC 9466 was used as test organism. Each drug was used as its own standard.

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

(6) (a) "The Pharmacopeia of the United States of America," 17th revision, U. S. P., Bethesda, Md., 1965; (b) L. Degen, M. Salvaterra, and S. Vella, *Chemotherapy*, in press.

Antibacterial Nitrofuran Derivatives. 3. 5-Nitro-2-furaldehyde Piperazinoacylhydrazones

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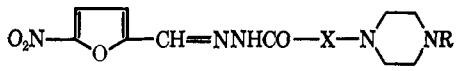
As a part of our investigations on nitrofuran derivatives we recently described[1] a series of water-soluble mono- and disubstituted aminoacethydrazones of 5-nitro-2-furaldehyde active as antibacterial agents.

The 5-nitro-2-furaldehyde *N'*-methylpiperazinoacethydrazone **19**[2] showed the highest urinary excretion and exhibited antibacterial activity in systemic infection of mice with *Streptococcus pyogenes* and *Salmonella typhimurium*, in im infection of mice with *Staphylococcus aureus*, and on urinary *Proteus vulgaris* infection of rats. These activities were comparable to or sometimes better than that of nitrofurantoin.[3-5]

The purpose of this paper was to synthesize a series of compounds with the following structure



to determine the effect of various substituents at the N atom of piperazine and the effect of the modification of the X group.

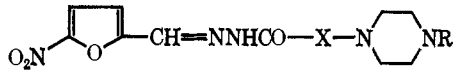
Chemistry.—The synthetic steps leading to the formation of 5-nitro-2-furaldehyde piperazinoacylhydrazones are outlined in Scheme I and are described in the Experimental Section.

The *N*-(β-hydroxyethyl)-, *N*-benzyl-, *N*-(*p*-nitrophenyl)-, *N*-acetyl-, and *N*-(diethylcarbamoyl)piperazines were prepared according to other methods previously reported.[6]

Biological Results (Table I).—The acute toxicity was determined ip in mice. All compounds were tested for bacteriostatic activity *in vitro* on the following microorganisms: *Escherichia coli* 100, *Salmonella typhimurium* 1090, *Pseudomonas aeruginosa* H2, *Proteus vulgaris* OX, *Micrococcus pyogenes* SG511, *Streptococcus pyogenes* A88, *Bacillus subtilis* ATCC 9466, *Myco-*

TABLE I

ANTIMICROBIAL ACTIVITY OF 5-NITRO-2-FURALDEHYDE N'-SUBSTITUTED PIPERAZINOACYLHYDRAZONES



No.	*E. coli*	*S. typhi murium*	*Ps. aeruginosa*	*P. vulgaris*	*M. pyogenes*	*Strep- pyogenes*	*B. subtilis*	*M. tuberculosis*	Drug urinary excre- tion	LD_{50}, mg/kg ip
1	80	160	>160	160	40	160	40	40	0	300
2	20	40	>160	>160	10	20	10	10	0	300
3	10	40	>160	40	10	40	5	80	18.5	260
4	10	10	>160	40	5	10	5	40	20	120
5	20	20	160	80	5	20	5	20	11.5	300
6	10	20	>160	80	5	10	5	10	18	350
7	10	40	>160	80	10	20	5	>160	0	150
8	10[c]	>160	>160	>160[c]	0.625[c]	>160	>160	>160	0	1300
9	10	>160	>160	>160	80	10	5	1.25	0	200
10	10	>160	>160	>160	10	20	5	20	0	180
11	80	>160	>160	>160	160	20	>160	40	*d*	210
12	40	160	>160	>160	10	1.25	5	20	0	270
13	20	80	160	160	10	80	10	2.5	0	180
14	80	80	80	80	20	40	5	40	0	500
15	>160	>160	>160	>160	20	2.5	40	0.31	0	>3000
16	20	80	>160	160	10	5	20	40	0	350
17	80	>160	>160	>160	10	5	10	40	0	80
18	>160	>160	>160	>160	160	>160	>160	>160	*d*	>3000
19[a]	40	40	160	80	20	2.5	20	>160	24	315
20[b]	5	40	160	80	10	5	10	>160	37	96

[a] 5-Nitro-2-furaldehyde *N'*-methylpiperazinoacethydrazone. [b] Nitrofurantoin. [c] In Difco nutrient broth. [d] Not tested.

(1) E. Massarani, D. Nardi, A. Tajana and L. Degen, *J. Med. Chem.*, **14**, 633 (1971).

(2) Nonproprietary name, nifurpipone.

(3) L. Degen, M. Salvaterra, S. Vella, D. Nardi, and E. Massarani, *Chemotherapy*, in press.

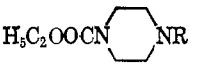
(4) L. Degen, M. Salvaterra, and S. Vella, *ibid.*, in press.

(5) L. Degen, M. Salvaterra, and S. Vella, *ibid.*, in press.

(6) (a) J. Kitchen and C. B. Pollard, *J. Org. Chem.*, **8**, 338 (1943); (b) J. C. Craig and R. J. Young, *Org. Syn.*, **42**, 19 (1962); (c) V. Prelog, G. J. Driza, *Collect. Czech. Chem. Commun.*, **5**, 497 (1933); *Chem. Abstr.*, **28**, 1348 (1934); (d) R. L. Bent, J. C. Dessloch, F. C. Duennebier, D. W. Fassett, D. B. Glass, T. H. James, D. B. Julian, W. R. Ruby, J. M. Snell, J. H. Sterner, J. R. Thirtle, P. W. Vittum, and A. Weissberger, *J. Amer. Chem. Soc.*, **73**, 3100 (1951); (e) G. Schorsch, U. S. Patent 2,973,362, Feb 28, 1961; *Chem. Abstr.*, **55**, 14488c (1961); (f) K. Fujii, K. Tomino, and H. Watanabe, *Yakugaku Zasshi*, **74**, 1049 (1954).

TABLE II

N'-CARBETHOXY-SUBSTITUTED PIPERAZINES

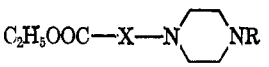


R	Yield, %	Bp, °C (mm)	Recrystn solvent	Mp, °C	Formula[c]
n-$C_{12}H_{25}$	73	154 (0.1)			$C_{19}H_{38}N_2O_2$[a]
Citronellyl	75	138 (0.4)			$C_{17}H_{32}N_2O_2$[b]
			EtOAc	182–183	$C_{17}H_{32}N_2O_2 \cdot HCl$[d]
Geranyl	75		EtOAc	133–135	$C_{17}H_{30}N_2O_2 \cdot HCl$[d]
$CH_2CH_2C_6H_5$	75	140 (0.2)			$C_{15}H_{22}N_2O_2$
			i-PrOH	203–205	$C_{15}H_{22}N_2O_2 \cdot HCl$[d]

[a] This substance was obtained by reaction of *n*-$C_{12}H_{25}Br$ with *N*-carbethoxypiperazine (R. Baltzly, S. W. Blackman, and W. S. Ide, *J. Amer. Chem. Soc.*, **76**, 1164 (1954)]. [b] The pure base was obtained from the hydrochloride. [c] All compds were analyzed for C, H, N. [d] Cl anal. also.

TABLE III

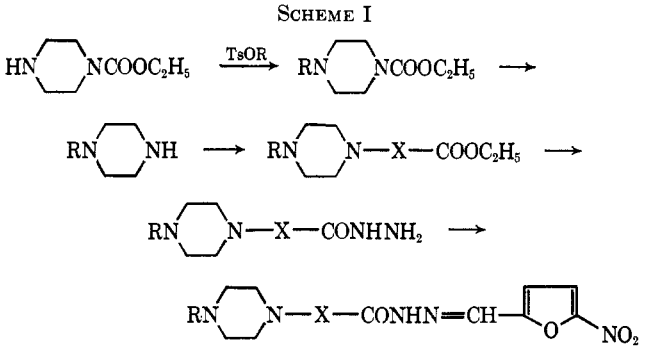
ETHYL N'-SUBSTITUTED PIPERAZINOACETATES AND PROPIONATES



X	R	Yield, %	Bp, °C (mm)	Recrystn solvent	Mp, °C	Formula[e]
$CHCH_3$	Me	68[a]	116 (14)			$C_{10}H_{20}N_2O_2$
CH_2	Et	67[b]	137–138 (22)			$C_{10}H_{20}N_2O_2$
CH_2	*n*-Pr	70[b]	136–137 (18)			$C_{11}H_{22}N_2O_2$
				i-PrOH	178–179	$C_{11}H_{22}N_2O_2 \cdot 2HCl$[f]
CH_2	*i*-Pr	75[b]	137 (15)			$C_{11}H_{22}N_2O_2$[g]
				i-PrOH	192–193	$C_{11}H_{22}N_2O_2 \cdot 2HCl$[f]
CH_2	*n*-Bu	70[b]	145 (12)			$C_{12}H_{24}N_2O_2$[g]
				i-PrOH	191–193	$C_{12}H_{24}N_2O_2 \cdot 2HCl$[f,h]
CH_2	*n*-$C_{12}H_{25}$	80	160 (0.2)			$C_{20}H_{40}N_2O_2$
CH_2	Citronellyl					$C_{18}H_{34}N_2O_2$[c]
CH_2	Geranyl					$C_{18}H_{32}N_2O_2$[c]
CH_2	CH_2CH_2OH	80	115–116 (0.4)			$C_{10}H_{20}N_2O_3$[c]
CH_2	$CH_2CH_2C_6H_5$	50	147–148 (0.3)			$C_{16}H_{24}N_2O_2$
				i-PrOH	215–217	$C_{16}H_{24}N_2O_2 \cdot 2HCl$[f]
CH_2	C_6H_4-4-NO_2	75[d]		*i*-PrOH	122–123	$C_{14}H_{19}N_3O_4$
CH_2	$COCH_3$	70	125–127 (0.1)	Et_2O	40–42	$C_{10}H_{18}N_2O_3$
				i-PrOH	164–166	$C_{10}H_{18}N_2O_3 \cdot HCl$[f]
CH_2	$CON(C_2H_5)_2$	69	138 (0.5)			$C_{13}H_{25}N_3O_3$
				EtOAc	136–137	$C_{13}H_{25}N_3O_3 \cdot HCl$[f]

[a] The reaction was carried out in EtOH with K_2CO_3. [b] N-Substituted piperazine·2HCl was used and to the reaction mixt was added 0.5 ml of H_2O and 0.02 mole of $NaHCO_3$. [c] The crude product was used in the next step. [d] The reaction was carried out in EtCOMe. The compd crystd from the reaction mixt on cooling. [e] See Table II, footnote *c*. [f] See Table II, footnote *d*. [g] Not analyzed. [h] H: calcd, 8.70; found, 9.18.

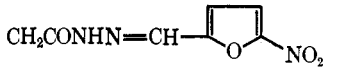
SCHEME I



bacterium tuberculosis $H_{37}Ra$, *Trichophyton mentagrophytes* 1236, and *Candida albicans* 28.

The urinary excretion of all compounds was determined in rats. All compounds were compared for their activity with **19** and nitrofurantoin **20**.

The biological data in Table I showed that **18**, in which two



groups are bound to the piperazine moiety, was inactive.

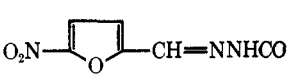
The removal of the Me group from **19** or the substitution with a hydroxyalkyl group (**11**) resulted in a lowering of antibacterial activity *in vitro* and in a loss of urinary excretion.

The lengthening of the alkyl group bounded at the N atom of piperazine resulted in an increase of the activity in *vitro*, whereas we observed an appreciable rate of urinary excretion only for the compounds with an alkyl up to 3 C atoms (**3–6**).

When R was an aralkyl or aryl group (**12–15**) the antibacterial activity *in vitro* was more pronounced against Gram-positive bacteria.

The *N*-acetyl and the *N*-diethylcarbamoyl derivatives (**16**, **17**) exhibited an activity *in vitro* comparable to **19** but were not excreted in the urine.

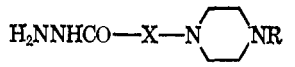
It is also of interest that **3** and **19** with one C atom between the



and the *N*-methylpiperazine moieties were excreted in the urine whereas **2** with X = CH_2CH_2 was not ex-

TABLE IV

N'-SUBSTITUTED PIPERAZINOACYLHYDRAZINES



X	R	Yield, %	Recrystn solvent	Mp, °C	Formula[d]
CH_2	H	70		145–147[a]	$C_6H_{14}N_4O$[f]
			EtOH	167–169	$C_6H_{14}N_4O \cdot 3HCl \cdot H_2O$
CH_2CH_2	Me	78[b]	MeOH–Et_2O	200–201	$C_8H_{18}NO \cdot 3HCl$[e] $\cdot H_2O$[g]
$CHCH_3$	Me	90		120–125[a]	$C_8H_{18}N_4O$
CH_2	Et	80	Ligroin	73–74	$C_8H_{18}N_4O$
CH_2	*n*-Pr	79	C_6H_6–ligroin	97	$C_9H_{20}N_4O$
CH_2	*i*-Pr	79	Ligroin	75–76	$C_9H_{20}N_4O$
CH_2	*n*-Bu	85	Hexane	75–76	$C_{10}H_{22}N_4O$
CH_2	*n*-$C_{12}H_{25}$	66	*i*-PrOH	85–86	$C_{18}H_{38}N_4O$
CH_2	Citronellyl	90			$C_{16}H_{32}N_4O$[c]
CH_2	Geranyl	70			$C_{16}H_{30}N_4O$[c]
CH_2	CH_2CH_2OH	85			$C_8H_{18}N_4O_2$[c]
CH_2	$CH_2C_6H_5$	73	Cyclohexane	103–104	$C_{13}H_{20}N_4O$
CH_2	$CH_2CH_2C_6H_5$	80	*i*-PrOH	143–145	$C_{14}H_{22}N_4O$
CH_2	C_6H_4-4-NO_2	80	MeOH	165–167	$C_{12}H_{17}N_5O_3$
CH_2	$COCH_3$	75	*i*-PrOH–petr ether	103–105	$C_8H_{16}N_4O_2$
CH_2	$CON(C_2H_5)_2$	80	C_6H_6–ligroin	80–81	$C_{11}H_{23}N_5O_2$
CH_2	$CH_2CONHNH_2$	50	MeOH–H_2O	229–231	$C_8H_{18}N_6O_2$

[a] Bp (0.2 mm). [b] The hydrochloride was prepd in a conventional way from the crude hygroscopic base. [c] The crude product was used in the next step. [d] See Table II, footnote *c*. [e] See Table II, footnote *d*. [f] Not analyzed. [g] N: calcd, 17.86; found, 18.30.

creted. Almost all compounds were active *in vitro* against *M. tuberculosis;* only **7**, **8**, **18**, and **19** were inactive. No *in vivo* activity was exhibited by the most active compound *in vitro* (**15**).

The compounds **3–6**, which had better rates of urinary excretion, were tested in systemic infection of mice with *Strep. pyogenes*, *S. typhimurium* and in subacute im *Staphylococcus aureus* infection of mice.

No activity was exhibited by **3**. Compds **4** and **6** were active against *Strep. pyogenes* sepsis, **5** against *S. typhimurium* peritonitis, whereas **19** was active against all three test infections.

Experimental Section[7]

Geranyl *p*-Toluenesulfonate.—To a soln of 100 ml of geraniol in 50 ml of pyridine was added at −5° in small amts 57.18 g (0.30 mole) of *p*-TsCl, and the mixt was stirred at −5 to 0° for 7 hr. Then it was poured into cooled dil HCl, and the oil was extd with Et_2O. After drying (Na_2SO_4), the solvent was evapd and the residue was distd under a stream of N_2. The fraction of bp 90–100° (14 mm) was collected; yield 47 g (68%).

***N'*-Carbethoxy-*N*-geranylpiperazine.**—A mixt of 9.7 g (0.05 mole) of *N*-carbethoxypiperazine·HCl, 20.6 g (0.067 mole) of geranyl *p*-toluenesulfonate, 6.5 g (0.061 mole) of Na_2CO_3, and 30 ml of geraniol was stirred at 100° for 20 hr. Then 140 ml of 0.5 *N* NaOH was added and the mixt was extd with Et_2O. After drying (Na_2SO_4), the solvent was evapd and the crude oil was distd under stream of N_2. The geraniol distd at 65–75° (0.6 mm); the product distd at 135–140° (0.4 mm); yield 11.1 g (75%). Tlc showed nonbasic impurities. The pure hydrochloride was obtd by acidification of Et_2O soln of the base with gaseous HCl. The pptd hydrochloride was collected and crystd. Table II summarizes pertinent data for these products.

***N*-*n*-Dodecylpiperazine.**[8]—*N'*-Carbethoxy-*N*-*n*-dodecylpiperazine (16.3 g, 0.05 mole) was refluxed for 20 hr with 50 ml of 10 *N* HCl. After cooling, the soln was made alkaline by adding NaOH and the oily layer was extd with Et_2O. After drying (Na_2SO_4), the solvent was evapd and the residue was distd: bp 139° (0.6 mm); yield 18.8 g (75%). *Anal.* ($C_{16}H_{34}N_2$) C, H, N.

***N*-Phenethylpiperazine**[9] was prepd from *N'*-carbethoxy-*N*,β-phenethylpiperazine by the above method: bp 94–96° (0.2 mm); yield 75%. *Anal.* ($C_{12}H_{18}N_2$) C, H, N.

***N*-Citronellylpiperazine.**—A mixt of 3.32 g (0.01 mole) of *N'*-carbethoxy-*N*-citronellylpiperazine, 2.34 g (0.04 mole) of KOH, and 10 ml of EtOH was refluxed for 12 hr. Then EtOH was evapd and H_2O was added to the residue. The oily layer was extd with Et_2O. After drying (Na_2SO_4) the solvent was evapd and the residue was distd: bp 93–96° (0.4 mm); yield 1.54 g (70%). *Anal.* ($C_{14}H_{28}N_2$) C, H, N. The HCl salt was prepd in a conventional way. It crystd from EtOH: mp (235) 261–263°. *Anal.* ($C_{14}H_{28}N_2 \cdot 2HCl$) C, H, N, Cl.

***N*-Geranylpiperazine** was prepd by alkaline hydrolysis of *N'*-carbethoxy-*N*-geranylpiperazine as described for the *N*-citronellylpiperazine: bp 105–108° (0.4 mm); yield 80%. This product was used directly in the next step.

Ethyl *N*-Substituted *N*-piperazinoacetates (or -propionates).—To a stirred mixt of 0.01 mole of N-substituted piperazine, 0.01 mole of $NaHCO_3$, and 5 ml of acetone was added 0.01 mole of ethyl chloroacetate (or chloropropionate). The mixt was refluxed for 2–10 hr. The reaction time was determined by tlc on silica gel G (developed in MeOH–C_6H_6, 95:5, and sprayed with Dragendorff's reagent). The esters showed R_f values higher than the N-substituted piperazines. The hot mixt was evapd *in vacuo* and the crude oil was distd. These bases decomposed after a while; their HCl salts, prepd by conventional ways, were stable (Table III).

Ethyl *N'*-Citronellyl-*N*-piperazinoacetate.—To a stirred mixt of 2.24 g (0.01 mole) of *N*-citronellylpiperazine, 0.69 g (0.005 mole) of K_2CO_3, and 5 ml of EtCOMe was added 1.67 g (0.01 mole) of ethyl bromoacetate. The mixt was refluxed for 12 hr and filtered while hot, and the residue was washed with hot EtCOMe. The solvent was evapd *in vacuo* and the residue was distd: bp 135–140° (4 mm); yield 2 g, 65%. This product was used directly for the next step.

Ethyl *N'*-Geranyl-*N*-piperazinoacetate was prepd as the corresponding *N*-citronellyl derivative. The reaction took 20 hr: bp 150–155° (0.6 mm); yield 70%. This product was used directly for the next step.

***N'*-Substituted *N*-Piperazinoacylhydrazines. General Procedure.**—To a soln of 0.01 mole of ethyl *N'*-substituted-*N*-piper-

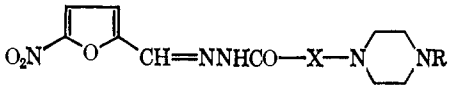
(7) Melting points are uncorrected and were determined in open glass capillaries on a Büchi apparatus. When analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

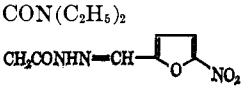
(8) This substance was obtd by reaction of *n*-$C_{12}H_{25}Br$ with piperazine [R. Baltzly, J. S. Buck, E. Lorz, and W. Schön, *J. Amer. Chem. Soc.*, **66**, 263 (1944)], and by heating the *N*,*N*-bis(β-oxyethyl)-*n*-dodecylamine at 240° with NH_4OH in an autoclave with a Cu–Ni–Cr catalyst [N. B. Godfrey, U. S. Patent 3,120,524, Feb 4, 1964; *Chem. Abstr.*, **60**, 9293*d* (1964)].

(9) This substance was obtd by reaction of phenethyl bromide with piperazine.[8]

TABLE V

5-NITRO-2-FURALDEHYDE PIPERAZINOACYLHYDRAZONES



No.	X	R	Recrystn solvent	Mp, °C	Yield, %	Formula[f]
1	CH_2	H	70% EtOH	269–271	85[a]	$C_{11}H_{15}N_5O_4 \cdot 2HCl$[g]
2	CH_2CH_2	Me	EtOH	135–137	60	$C_{13}H_{19}N_5O_4 \cdot H_2O$
3	$CH(CH_3)$	Me	*i*-PrOH–H_2O	117–119	80	$C_{13}H_{19}N_5O_4 \cdot 2H_2O$[i]
			i-PrOH–H_2O	212–214		$C_{13}H_{19}N_5O_4 \cdot 2HCl \cdot H_2O$[h]
4	CH_2	Et	EtOAc	152	85	$C_{13}H_{19}N_5O_4$
			EtOAc	145–147		$C_{13}H_{19}N_5O_4 \cdot CH_3COOH$
5	CH_2	*n*-Pr		164–166	65	$C_{14}H_{21}N_5O_4$
			EtOH	98–101		$C_{14}H_{21}N_5O_4 \cdot 2CH_3COOH$
			90% EtOH	223–224		$C_{14}H_{21}N_5O_4 \cdot 2HCl \cdot 3H_2O$[h]
6	CH_2	*i*-Pr	Me_2CO	156–158	50	$C_{14}H_{21}N_5O_4$
			80% EtOH	237–239		$C_{14}H_{21}N_5O_4 \cdot 2HCl \cdot H_2O$[h]
7	CH_2	*n*-Bu	*i*-PrOH	158–159	90	$C_{15}H_{23}N_5O_4$
			95% EtOH	226–227		$C_{15}H_{23}N_5O_4 \cdot 2HCl$[h]
8	CH_2	n-$C_{12}H_{25}$	EtOAc	144–145	65[b]	$C_{23}H_{39}N_5O_4$
			MeOH	211–212		$C_{23}H_{39}N_5O_4 \cdot 2HCl$[h]
9	CH_2	Citronellyl	70% EtOH	139–141	50	$C_{21}H_{33}N_5O_4$
			EtOH	140 dec		$C_{21}H_{33}N_5O_4 \cdot 2HNO_3$[e]
10	CH_2	Geranyl	70% EtOH	110–112	65[c]	$C_{21}H_{31}N_5O_4$
			MeOH	138–140		$C_{21}H_{31}N_5O_4 \cdot 2HNO_3$
11	CH_2	CH_2CH_2OH	EtOAc	181–183	37	$C_{13}H_{19}N_5O_5$
12	CH_2	$CH_2C_6H_5$	EtOAc	200–201	50	$C_{18}H_{21}N_5O_4$
			95% EtOH	185–187		$C_{18}H_{21}N_5O_4 \cdot 2HCl \cdot 2H_2O$[h]
13	CH_2	$CH_2CH_2C_6H_5$	*i*-PrOH	166–168	80	$C_{19}H_{23}N_5O_4$
			60% EtOH	239–240		$C_{19}H_{23}N_5O_4 \cdot 2HCl$[j]
14	CH_2	C_6H_5	EtOH	200–201	80	$C_{17}H_{19}N_5O_4$
			70% EtOH	228–230		$C_{17}H_{19}N_5O_4 \cdot HCl$[h]
15	CH_2	C_6H_4-4-NO_2	Dioxane–H_2O	229–230	90	$C_{17}H_{18}N_6O_6$
16	CH_2	$COCH_3$	MeOH	193–195	60	$C_{13}H_{17}N_5O_5$
17	CH_2	$CON(C_2H_5)_2$	EtOAc	171–172	65	$C_{16}H_{24}N_6O_5$
18	CH_2			260–261	94[d]	$C_{18}H_{20}N_8O_8$

[a] The reaction mixt was treated with Et_2O and the oil was dissolved in MeOH and acidified with anhyd HCl to give the HCl salt. [b] The base was pptd with H_2O from the reaction mixt. [c] The pptd base must be washed quickly to avoid decompn. [d] The reaction was carried out with 0.02 mole of 5-nitro-2-furaldehyde and 7.5 ml of AcOH. The reaction mixt was treated with hot EtOAc and the ppt was washed with hot aq dioxane. [e] The HNO_3 salt was prepd by acidifying of the MeOH soln of the base with dil HNO_3. [f] See Table II, footnote *c*. [g] O anal. also. [h] See Table II, footnote *d*. [i] H: calcd, 6.71; found, 7.20. [j] Cl: calcd, 15.47; found 14.94.

azinoacetates (or -*N*-propionates) in 2 ml of EtOH was added 0.02 mole of hydrazine hydrate. The mixt was refluxed for 2–12 hr. The reaction time was detd by tlc on silica gel G (developed in MeOH–C_6H_6, 95:5, and sprayed with Dragendorff's reagent). The esters showed R_f values higher than the acylhydrazines. Then EtOH was evapd and the residue was distd or crystd (Table IV).

5-Nitro-2-furaldehyde *N*-Piperazinoacylhydrazones. General Procedure.—To a soln of 0.01 mole of *N*-piperazinoacylhydrazine in 4 ml of AcOH was added a soln of 0.01 mole of 5-nitro-2-furaldehyde in 1 ml of AcOH. The reaction was exothermic. The mixt was stirred for 1 hr below 40°, poured into Et_2O, and stirred until a solid, which was filtered and crystd, pptd. Some products pptd as acetates (**4**, **5**), other as bases (**12**–**17**). When an oil was obtd, it was dissolved in H_2O and the base was pptd by making the soln alkaline with Na_2CO_3 (**2**, **3**, **5**, **6**, **7**, **9**, **10**, **11**). The HCl salts were obtd by conventional ways in EtOH. (Table V).

Pharmacological Methods. For acute toxicity NMRI albino mice (18–20 g) and for urinary excretion Wistar albino rats (200–250 g) were used. Acute toxicity, antimicrobial and antifungal activity *in vitro*, and urinary excretion were determined as previously described.[5,10]

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Synthetic Antibacterials. 3.[1] Nitrofurylvinyl-1,8-naphthyridine Derivatives

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Our interest in nitrofuran derivatives,[2,3] bolstered by the finding that certain nitrofurylvinyl-1,8-naphthyridines[3] possess outstanding activity against *Pseudomonas aeruginosa*, led us to investigate the synthesis

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