with stirring below 10° 196 g (0.99 mole) of Ia. Stirring was continued in the cold for 3 hr, and then at room temperature overnight. Dilution with 2 vol of anhydrous ether precipitated the product. The crude product was filtered, taken up in 100 ml of boiling methanol, and treated with charcoal, and the mixture was filtered. Dilution of the cooled filtrate with ether gave VI as pale yellow crystals melting at 192–193° in a yield of 149 g (72.7%).

Anal. Calcd for $C_5H_8N_2O_3 \cdot HCl$: C, 29.06; H, 3.42; Cl, 17.16; N, 27.12. Found: C, 28.72; H, 3.48; Cl, 17.12; N, 27.01.

Acknowledgments.—We wish to thank Mr. Grant Gustin and Mr. Marvin Tefft for elemental analysis, and Mr. R. A. Dobson for the testing data.

Nitrofuryl Heterocycles. IV[1]. 4-Amino-2-(5-nitro-2-furyl)quinazoline Derivatives

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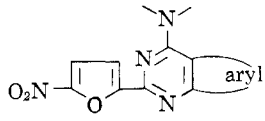
Thirty-five 4-(substituted amino)-2-(5-nitro-2-furyl)quinazolines were prepared and found to possess broad *in vitro* antibacterial activity against a variety of organisms. Several compounds were also active *in vivo* against *Staphylococcus aureus* infections. The most active compound contained the 4-bis(2-hydroxyethyl)amino group. A new molecular grouping responsible for enhancing the antibacterial activity of nitrofurans is postulated.

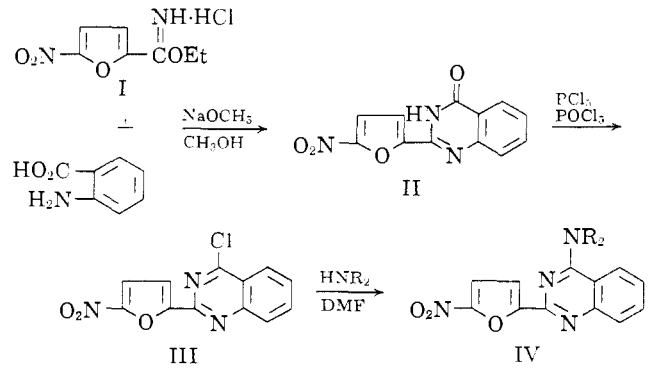
In the previous papers of this series[1] it was shown that the attachment of a heterocyclic ring system to the 2-position of the 5-nitrofuran nucleus frequently gave antimicrobial agents. It is the intent of this and a succeeding paper to demonstrate that the attachment of a condensed pyrimidine ring system to the 2-position of the nitrofuran ring will also give derivatives possessing exceptional antibacterial activity. This ring system is represented by the following general formula. This paper is concerned with the synthesis



and biological evaluation of 4-amino-2-(5-nitro-2-furyl)quinazoline derivatives.

Chemistry.—The general procedure of Dymek and Berezowski[2] was followed to prepare quinazolinone (II) from ethyl 5-nitro-2-furimidate (I).[3] Chlorination of II with phosphorus pentachloride solution gave the 4-chloro derivative III in an over-all yield of about 72% from I. Displacement of the chloro group in III with a variety of amines proceeded smoothly in dimethylformamide (DMF) solution to give the amino derivatives IV listed in Table I. These reactions are summarized in Scheme I.

SCHEME I



Screening Results.—The 4-amino derivatives IV were screened for *in vitro* and *in vivo* antibacterial activity according to the procedures described previously.[4] It can be seen in Table II that the 35 derivatives of IV herein reported possess broad *in vitro* activity against both gram-positive and gram-negative organisms. The activity of several of the derivatives (**13–16**, **18**, **19**, **22–26**, **28–31**, and **33**) against both *Pseudomonas aeruginosa* and *Proteus vulgaris* is particularly noteworthy. The most active compounds contain the 2-hydroxyethylamino group, $NRCH_2CH_2OH$, in which R is H (**7**), alkyl (**13–16**), or hydroxyalkyl (**18** and **19**). These compounds also demonstrated good activity *in vivo* against *Staphylococcus aureus* infections in mice. The *in vivo* data are summarized in Table III. The next most active group of compounds contain the dialkylaminoalkylamino grouping (**22–33**). Except for compound **33** (γ-morpholinopropylamino) this group demonstrated good *in vitro* activity but failed to show *in vivo* activity at the levels tested. The toxicity of several compounds described in Table II is being investigated.

Experimental Section

All melting points were taken on a hot stage (Mel-Temp) melting apparatus and are corrected.

2-(5-Nitro-2-furyl)-4(3H)-quinazolinone (II).—To a stirred solution of 27.0 g (0.5 mole) of sodium methoxide in 500 ml of methanol was added 110 g (0.5 mole) of ethyl 5-nitro-2-furimidate hydrochloride[3] and then 68.5 g (0.5 mole) of anthranilic acid. The mixture was refluxed for 4 hr and concentrated to dryness *in vacuo* on a steam bath, and the residue was shaken with 500 ml of ice–water. The mixture was acidified with acetic acid. The crude product was filtered, washed with water, and dried to give 114 g (89%) of II. Recrystallization of a sample from DMF (charcoal) gave the product as yellow micro needles decomposing above 300°.

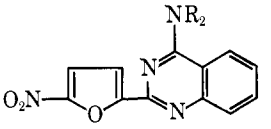
(1) For the previous paper in this series see H. A. Burch and W. O. Smith, *J. Med. Chem.*, **9**, 405 (1966).

(2) W. Dymek and L. Berezowski, *Dissertationes Pharm.* **15**, 23 (1963); *Chem. Abstr.*, **59**, 11491b (1963).

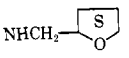
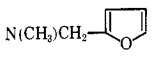
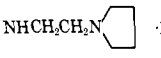
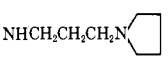
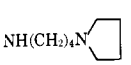
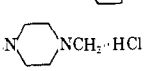
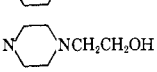
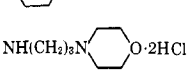
(3) W. R. Sherman and A. Von Esch, *J. Med. Chem.*, **8**, 25 (1965).

(4) F. F. Ebetino, W. F. Carey, and B. F. Stevenson, *ibid.*, **6**, 633 (1963).

TABLE I



IV

No.	NR_2	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	$NHCH_2CH_2OCH_3$	160–162	57	$C_{15}H_{14}N_4O_4$	57.32	4.49	17.83	57.30	4.61	17.74
2	$NHCH_2CH_2CH_2OCH_3$	145–146	82	$C_{16}H_{16}N_4O_4$	58.53	4.91	17.07	58.61	4.80	16.87
3		218–219.5	86	$C_{15}H_{14}N_4O_4$	58.89	4.32	17.17	58.81	4.28	17.22
4	$N(CH_2CH_2OC_2H_5)_2$	61.5–62.5	79	$C_{20}H_{24}N_4O_6$	59.99	6.04	13.99	60.03	5.80	14.13
5		213–214	75	$C_{17}H_{16}N_4O_4$	59.99	4.74	16.46	59.99	4.78	16.48
6		119–120	90	$C_{18}N_{14}N_4O_4$	61.71	4.03	16.00	61.83	4.03	15.94
7	$NHCH_2CH_2OH$	221.5–223	94	$C_{14}H_{12}N_4O_4$	56.00	4.03	18.66	56.05	4.26	18.48
8	$NHCH_2CH(CH_3)OH$	203–204	78	$C_{15}H_{14}N_4O_4$	57.32	4.49	17.83	57.09	4.40	17.94
9	$NHC(CH_3)_2CH_2OH$	248–249	84	$C_{16}H_{16}N_4O_4$	58.53	4.91	17.07	58.69	5.07	17.02
10	$NHCH_2CH_2CH_2OH$	181–183	55	$C_{15}H_{14}N_4O_4$	57.32	4.49	17.83	57.55	4.50	17.81
11	$NHCH_2CHOHCH_2OH$	216–217	81	$C_{15}H_{14}N_4O_5$	54.54	4.27	16.96	54.66	4.19	16.89
12	$N(CH_3)CH_2(CHOH)_4CH_2OH$	132.5–133.5	53	$C_{19}H_{22}N_4O_8$	52.53	5.10	12.90	52.24	5.31	12.64
13	$N(CH_3)CH_2CH_2OH$	151–152	70	$C_{15}H_{14}N_4O_4$	57.32	4.49	17.83	57.25	4.56	18.01
14	$N(C_2H_5)CH_2CH_2OH$	185.5–186.5	72	$C_{16}H_{16}N_4O_4$	58.53	4.91	17.07	58.64	4.79	17.01
15	$N(CHMe_2)CH_2CH_2OH$	157–158	48	$C_{17}H_{18}N_4O_4$	59.64	5.30	16.37	59.70	5.38	16.36
16	$N(C_4H_9)CH_2CH_2OH$	120–121	75	$C_{18}H_{20}N_4O_4$	60.66	5.66	15.72	60.76	5.76	15.76
17	$N(CH_2Ph)CH_2CH_2OH$	153–154	80	$C_{21}H_{18}N_4O_4$	64.60	4.65	14.35	64.64	4.63	14.12
18	$N(CH_2CH_2OH)_2$	167–168	58	$C_{16}H_{16}N_4O_5$	55.81	4.68	16.27	55.89	4.59	16.34
19	$N(CH_2CH_2OH)CH_2CH(CH_3)OH$	164–165	46	$C_{17}H_{18}N_4O_5$	56.98	5.06	15.64	57.14	5.25	15.65
20	$N[CH_2CH(CH_3)OH]_2$	170–171	73	$C_{18}H_{20}N_4O_5$	58.06	5.41	15.05	57.94	5.55	14.92
21	$NH(CH_2)_3O(CH_2)_2O(CH_2)_2OH$	131–132	79	$C_{19}H_{22}N_4O_6$	56.71	5.51	13.92	56.64	5.38	13.92
22	$NHCH_2CH_2N(CH_3)_2 \cdot HCl$	271–272	57	$C_{16}H_{17}N_5O_3 \cdot HCl$	52.82	4.99	(9.75)[a]	52.83	5.00	(9.65)
23	$NHCH_2CH_2CH_2N(CH_3)_2 \cdot HCl$	243–244	56	$C_{17}H_{19}N_5O_3 \cdot HCl$	54.04	5.34	(9.38)	54.06	5.24	(9.38)
24	$N(CH_3)CH_2CH_2N(CH_3)_2 \cdot HCl$	260–262	60	$C_{17}H_{19}N_5O_3 \cdot HCl$	54.04	5.34	(9.38)	54.17	5.34	(9.30)
25	$NHCH_2CH_2N(C_2H_5)_2 \cdot HCl$	264–266	60	$C_{18}H_{21}N_5O_3 \cdot HCl$	55.17	5.66	(9.05)	55.16	5.86	(9.03)
26	$NHCH_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$	154–155	43	$C_{19}H_{23}N_5O_3 \cdot HCl$	56.22	5.96	(8.74)	55.96	5.73	(8.82)
27	$N(CH_3)CH_2CH_2N(C_2H_5)_2HCl$	224–225	58	$C_{19}H_{23}N_5O_3 \cdot HCl \cdot 0.5H_2O$	55.00	6.07	(8.54)	55.18	6.02	(8.53)
28		272–273	77	$C_{18}H_{19}N_5O_3 \cdot HCl$	55.45	5.17	(9.10)	55.54	5.22	(9.00)
29		199–202	58	$C_{19}H_{21}N_5O_3 \cdot HCl \cdot 0.5H_2O$	55.27	5.62	16.96	55.47	5.60	17.19
30		213–215	43	$C_{20}H_{23}N_5O_3 \cdot HCl$	57.48	5.79	16.76	57.44	5.80	16.60
31		284–285	68	$C_{17}H_{17}N_5O_3 \cdot HCl$	54.33	4.83	18.64	54.18	4.81	18.63
32		177–179	84	$C_{18}H_{19}N_5O_4$	58.53	5.19	18.96	58.54	5.18	18.91
33		204–205	64	$C_{19}H_{21}N_5O_4 \cdot 2HCl$	50.00	5.08	(15.34)	50.07	5.02	(15.07)
34	$N(NH_2)CH_3$	228–229	51	$C_{13}H_{11}N_5O_3$	54.73	3.89	24.55	54.75	3.90	24.74
35	$N(NH_2)CH_2CH_2OH$	190–191	94	$C_{14}H_{13}N_5O_4$	53.33	4.16	22.22	53.46	4.26	22.43

[a] Analysis for chlorine.

TABLE II

ANTIBACTERIAL ACTIVITY OF 4-SUBSTITUTED AMINOQUINAZOLINES (IV)

No.	*Escherichia coli* Es-2[b]	*Escherichia coli* Es-L	*Salmonella typhosa* SaD-13	*Pseudomonas aeruginosa* Ps-10	*Proteus vulgaris* Pr-12	*Aerobacter aerogenes* Ae-6	*Erysipelothrix insidiosa* Er-4	*Staphylococcus aureus* Mi-5	*Streptococcus pyogenes* StA-1	*Streptococcus agalactiae* StB-12
	Minimal inhibitory concentration, μg/ml[a]									
1	0.38	3	0.75	>50	>50	12.5	0.38	0.38	0.75	3
2	0.19	3	0.75	>50	>50	12.5	0.38	0.38	0.75	1.5
3	0.3	>50	1	>50	>50	>50	0.2	1	1	6
4	3	>50	12.5	>50	>50	>50	0.38	3	12.5	25
5	0.38	1.5	1.5	>50	>50	6	0.095	0.75	1.5	3
6	0.38	3	0.75	>50	>50	>50	0.095	0.38	1.5	1.5
7	0.048	0.75	0.095	>50	50	1.5	0.048	0.19	0.024	0.095
8	0.38	1.5	0.38	>50	>50	3	0.19	0.19	0.19	0.75
9	1.5	25	3	>50	>50	>50	0.38	1.5	12.5	>50
10	0.095	1.5	0.38	>50	>50	6	0.095	0.19	0.095	0.19
11	0.095	1.5	0.38	>50	>50	6	0.012	0.75	0.024	0.095
12	1.5	50	25	>50	>50	>50	0.19	25	1.5	1.5
13	0.024	0.75	0.19	6	12	0.75	0.048	0.75	0.19	0.38
14	0.048	1.5	0.38	12.5	25	3	0.095	0.75	0.38	1.5
15	0.095	1.5	0.38	25	50	6	0.095	0.75	0.19	1.5
16	0.048	0.75	0.38	12.5	50	3	0.048	0.38	1.5	0.38
17	0.095	0.75	0.19	>50	>50	3	0.048	0.38	0.38	1.5
18	0.012	0.19	0.048	3	6	3	0.012	0.38	0.024	0.19
19	0.048	0.38	0.19	12.5	25	0.75	0.19	0.75	0.095	0.38
20	0.19	3	0.75	>50	>50	12.5	0.38	0.75	3	6
21	0.75	12.5	1.5	>50	>50	12.5	0.19	0.75	0.19	0.38
22	0.095	1.5	0.38	25	50	6	0.095	1.5	0.048	0.75
23	0.048	1.5	0.38	25	50	3	0.048	0.75	0.024	0.38
24	0.19	6	1.5	25	200	25	0.38	6	0.75	6
25	0.19	6	0.75	25	50	6	0.19	1.5	0.19	0.75
26	0.095	3	0.75	100	50	6	0.095	0.75	0.024	0.38
27	0.38	25	3	100	>200	25	0.38	6	1.5	6
28	0.095	1.5	0.38	25	50	3	0.095	0.75	0.095	0.38
29	0.09	1.5	0.4	12	50	6	0.09	0.75	0.05	0.4
30	0.02	1.5	0.4	25	50	0.1	0.02	0.4	0.02	0.2
31	0.048	1.5	0.19	25	100	0.75	0.095	1.5	0.38	1.5
32	0.095	0.75	0.19	>50	>50	1.5	0.48	0.38	0.095	0.75
33	0.095	0.75	0.19	50	50	1.5	0.095	0.38	0.019	0.75
34	0.048	1.5	0.19	>50	25	3	0.024	0.38	0.19	0.38
35	0.38	1.5	0.38	>50	>50	6	0.048	0.75	0.38	0.75
Nitrofurazone[c]	3	12.5	3	>100	100	100	12.5	12.5	6	12.5

[a] Minimum inhibitory concentration is the lowest concentration of compound that prevents visible growth after 24 hr of incubation. [b] Eaton Laboratories strain number. [c] Furacin®, for comparison.

TABLE III

In Vivo ACTIVITY OF SOME 4-SUBSTITUTED AMINOQUINAZOLINES (IV) AGAINST *Staphylococcus aureus* INFECTIONS

No.	ED_{50} (mice), mg/kg, Route: Oral	Ip
1	32	—
2	200	—
3	>200	14
4	45	—
5	>100	8
7	50	—
10	50	6
11	>200	1
13	54	—
14	>200	8
15	200	—
16	88	—
17	>200	8
18	76	—
19	42	—
20	33	—
21	44	2
33	50	—
34	>200	12
35	38	—

Anal. Calcd for $C_{12}H_7N_3O_4$: C, 56.03; H, 2.74; N, 16.34. Found: C, 55.90; H, 3.00; N, 16.31.

4-Chloro-2-(5-nitro-2-furyl)quinazoline (III).—To a stirred suspension of 159 g (0.77 mole) of PCl_5 in 790 ml of $POCl_3$ was added in small portions at 25–30° 198 g (0.77 mole) of II. After completing the addition the mixture was refluxed for 4 hr during which time solution became complete. The chilled solution was diluted with 3 l. of anhydrous ether and filtered, and the residue was washed with ether. The yield of crude III after air drying was 106 g (80.5%). This material was used without further purification. Recrystallization of a sample from toluene (charcoal) gave the product as yellow needles melting at 196–197.5°.

Anal. Calcd for $C_{12}H_6ClN_3O_3$: C, 52.28; H, 2.19; Cl, 12.86. Found: C, 52.31; H, 2.14; Cl, 12.79.

4-[Bis(2-hydroxyethyl)amino]-2-(5-nitro-2-furyl)quinazoline (IV-18).—A stirred solution of 30.2 g (0.11 mole) of III and 26.3 g (0.25 mole) of diethanolamine in 300 ml of DMF was heated on a steam bath for 2 hr. The mixture was diluted with 300 ml of water, chilled, and filtered. Recrystallization of the residue from aqueous ethanol (or aqueous DMF) (charcoal) gave the product as yellow platelets. The remaining derivatives in Table I were prepared from III and the appropriate amine.

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