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Synthesis and Biological Activity of Some New Furan Quaternary Salts

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A series of new *N*-(5-substituted 2-furfuryl)-*N*,*N*-dimethyl-*N*-aryloxyalkyl quaternary ammonium salts relating to general structure IV has been synthesized by reacting 5-substituted 2-(*N*,*N*-dimethylaminomethyl)furans IIa–d with appropriate aryloxyalkyl bromides III. The resulting compounds are tested for in vitro antimicrobial activity. A simpler synthesis of 5-nitro-2-(*N*,*N*-dimethylaminomethyl)furan (IId) involving the reduction of *N*,*N*-dimethyl-5-nitro-2-furamide (Ib) with diborane is described. A new compound, 5-bromo-2-(*N*,*N*-dimethylaminomethyl)furan (IIc), is prepared in a similar way. Many of these compounds (**22**, **28**, **34**, **37–42**, **44**, and **45**) indicate high activity against *Staphylococcus aureus*, *Streptococcus faecalis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* and are more active than nitrofurantoin. Compounds **22**, **34**, and **41** exhibit the highest in vitro antibacterial activity in the series. Some of these quaternary salts (**22**, **25**, **37**, **39–41**, and **60**) possess appreciable activity against *Mycobacterium tuberculosis* $H_{37}Rv$. None of these compounds show significant antifungal activity. Eight compounds (**18**, **21**, **22**, **26–28**, **32**, and **34**) having high in vitro antibacterial activity were inactive when tested for anthelmintic activity in rats against *Nippostrongylus brasiliensis* and *Hymenolepis nana*.

The chemotherapeutic applications of quaternary ammonium salts have gained importance since World War II. Many members of this class are known to possess antibacterial[1] and antifungal[2] activities and have found general utility in skin disinfectants as well as in the formulation of creams, ointments, lotions, powders, etc. Quaternary ammonium salts such as biphenium 3-hydroxy-2-naphthoate and thenium 4-chlorobenzenesulfonate containing a substituted phenolic ether moiety are claimed to possess anthelmintic properties.[3] 5-Nitrofuran derivatives are well known to possess antibacterial activity. In our previous paper,[4] we described the synthesis and antimicrobial activity of a series of aryl- and aryloxyalkyl-*N*-(5-nitro-2-furyl)carbamates. Aryloxyalkyl esters derived from different hydroxybenzoic acids also exhibited significant antimicrobial activity.[5] It was considered of interest to synthesize and study the antimicrobial action of several new furan quaternary salts which contain the features of appropriately substituted furan and phenolic ethers. Hence, a series of new *N*-(5-substituted 2-furfuryl)-*N*,*N*-dimethyl-*N*-aryloxyalkyl quaternary ammonium bromides IV has been prepared. In certin cases where the quaternary ammonium bromides could not be isolated owing to their hygroscopic nature, corresponding tosylates V have been prepared and tested for antimicrobial activity.

During the course of our work it came to our notice that analogous 5-substituted furan quaternary compounds find a mention in a British patent[6] and are claimed to possess anthelmintic activity. However, none of the claimed furan quaternary salts have been described in the complete specification of this patent.

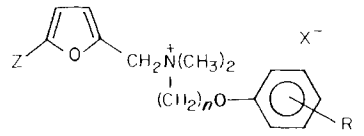
Chemistry. Various new furan quaternary ammonium bromides IV were made by reacting 5-substituted 2-(*N*,*N*-dimethylaminomethyl)furans IIa–d with appropriate aryloxyalkyl bromides III in acetone at reflux temperature or by leaving at room temperature without any solvent. The various steps leading to the synthesis of these new furan quaternary salts are represented in Scheme I.

2-(*N*,*N*-Dimethylaminomethyl)furan[7] (IIa) and 5-methyl-2-(*N*,*N*-dimethylaminomethyl)furan[8] (IIb) were prepared by the known methods. 5-Nitro-2-(*N*,*N*-dimethylaminomethyl)furan[9] (IId) was previously prepared from 5-nitro-2-furfuryl chloride by reacting with dimethylamine in an autoclave at 40 °C. We have now prepared this amine by a more convenient method by reducing the corresponding amide Ib with diborane in situ according to the method of Brown.[10] 5-Bromo-2-(*N*,*N*-dimethylaminomethyl)furan (IIc) which has not been reported so far was also prepared in a similar way. The intermediate aryloxyalkyl bromides III were prepared following the method of Marvel[11] by heating the corresponding phenols with an excess of appropriate dibromoalkane in the presence of aqueous sodium hydroxide.

The 5-substituted furan quaternary ammonium tosylates V (compounds **35**, **43**, **45**, **49**, and **51–54**) were prepared by treating the aqueous solution of the corresponding crude quaternary ammonium bromides with sodium *p*-toluenesulfonate solution in water. However, compound **5** was prepared differently by treating 5-nitro-2-(*N*,*N*-dimethylaminomethyl)furan (IId) with 4-chlorothymyloxyethyl tosylate (VI). All the compounds were characterized by elemental analyses and are listed in Table I.

Biological Results and Discussion. Many of the new furan quaternary salts reported in this paper possess broad spectrum in vitro antibacterial activity against representative bacteria as shown in Table II. The highest activity is shown against gram-negative bacteria, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, with MIC values as low as 1.5 μg/ml. Only a few compounds show activity against *Escherichia coli* and *Salmonella typhi* but of a low order (50–100 μg/ml). In the case of gram-positive bacteria, some of these compounds show fairly high activity (2–10 μg/ml) against *Staphylococcus aureus* and *Streptococcus faecalis*. Many of these compounds possess appreciable activity against *Mycobacterium tuberculosis*

Table I. Furan Quaternary Salts

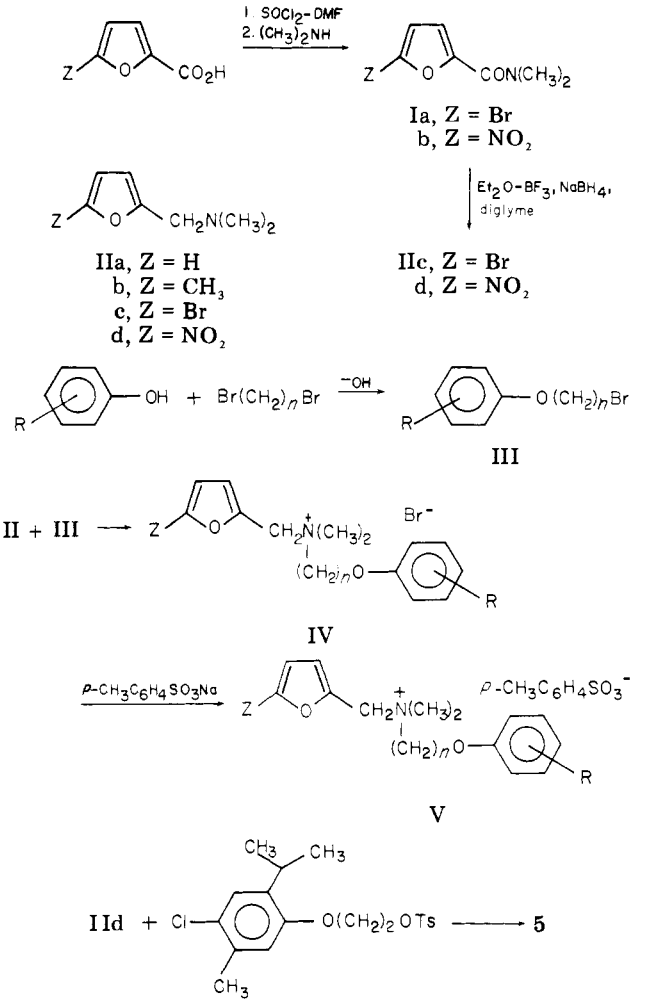


Compd no.	Z	R	n	X	Method[a]	Mp, °C[b]	Yield,[c] %	Formula	Analyses[d]
1	NO_2	H	2	Br	B	184–185	33	$C_{15}H_{19}BrN_2O_4$	C, H, N
2	NO_2	4-Cl	2	Br	A	182–183	42	$C_{15}H_{18}BrClN_2O_4$	C, H, N
3	NO_2	2,4-Cl_2	2	Br	B	141–143	38	$C_{15}H_{17}BrCl_2N_2O_4$	C, H, N
4	NO_2	2-CH_3	2	Br	A	172–174	50	$C_{16}H_{21}BrN_2O_4$	C, H, N
5	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	2	*p*-$CH_3C_6H_4SO_3$	D	184–185 dec	37	$C_{26}H_{33}ClN_2O_7S$	C, H, N
6	Br	H	2	Br	B	144–146	68	$C_{15}H_{19}Br_2NO_2$	C, H, N
7	Br	2-Cl	2	Br	B	158–160	74	$C_{15}H_{18}Br_2ClNO_2$	C, H, N
8	Br	4-Cl	2	Br	B	133–135	91	$C_{15}H_{18}Br_2ClNO_2$	C, H, N
9	Br	2,4-Cl_2	2	Br	B	72–74	92	$C_{15}H_{17}Br_2Cl_2NO_2$	H, N; C[e]
10	Br	2-CH_3	2	Br	B	88–90	97	$C_{16}H_{21}Br_2NO_2$	C, H, N
11	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	2	Br	B	161–163	80	$C_{19}H_{26}Br_2ClNO_2$	C, H, N
12	Br	2,4,6-Br_3	2	Br	B	175–177	88	$C_{15}H_{16}Br_5NO_2$	C, H, N
13	NO_2	2,4,6-Br_3	3	Br	B	177–179	45	$C_{16}H_{18}Br_4N_2O_4$	H, N; C[f]
14	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	3	Br	B	71–73	73	$C_{20}H_{28}BrClN_2O_4$	C, H, N
15	Br	2,4,6-Br_3	3	Br	B	170–171	78	$C_{16}H_{18}Br_5NO_2$	C, H, N
16	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	3	Br	B	130–132	86	$C_{20}H_{28}Br_2ClNO_2$	C, H, N
17	NO_2	2,4,6-Br_3	4	Br	B	166–168	78	$C_{17}H_{20}Br_4N_2O_4$	C, H, N
18	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	4	Br	B	130–132	85	$C_{21}H_{30}BrClN_2O_4$	C, H, N
19	NO_2	2-Cl	4	Br	B	124–125	84	$C_{17}H_{22}BrClN_2O_4$	C, H, N
20	NO_2	4-Cl	4	Br	B	172–174	79	$C_{17}H_{22}BrClN_2O_4$	C, H, N
21	Br	2,4,6-Br_3	4	Br	B	158–160	93	$C_{17}H_{20}Br_5NO_2$	C, H, N
22	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	4	Br	B	88–90	94	$C_{21}H_{30}Br_2ClNO_2$	C, H, N
23	Br	2-Cl	4	Br	B	112–114	83	$C_{17}H_{22}Br_2ClNO_2$	C, H, N
24	Br	4-Cl	4	Br	B	133–135	91	$C_{17}H_{22}Br_2ClNO_2$	C, H, N
25	NO_2	2,4,6-Br_3	5	Br	B	138–140	90	$C_{18}H_{22}Br_4N_2O_4$	C, H, N
26	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	5	Br	B	168–170	90	$C_{22}H_{32}BrClN_2O_4$	C, H, N
27	Br	2,4,6-Br_3	5	Br	B	164–166	82	$C_{18}H_{22}Br_5NO_2$	C, H, N
28	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	5	Br	B	78–80	92	$C_{22}H_{32}Br_2ClNO_2$	C, H, N
29	Br	2-Cl	5	Br	B	118–120	71	$C_{18}H_{24}Br_2ClNO_2$	C, H, N
30	Br	4-Cl	5	Br	B	152–154	71	$C_{18}H_{24}Br_2ClNO_2$	C, H, N
31	Br	2,4-Cl_2	5	Br	B	97–99	87	$C_{18}H_{23}Br_2Cl_2NO_2$	H, N; C[g]
32	NO_2	2,4,6-Br_3	6	Br	B	151–153	80	$C_{19}H_{24}Br_4N_2O_4$	C, H, N
33	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	6	Br	A	100–102	61	$C_{23}H_{34}BrClN_2O_4$	C, H, N
34	Br	2,4,6-Br_3	6	Br	B	91–93	80	$C_{19}H_{24}Br_5NO_2$	C, H, N
35	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	6	*p*-$CH_3C_6H_4SO_3$	C	99–101	14	$C_{30}H_{41}BrClNO_5S\cdot H_2O$	C, H, N
36	NO_2	2,4,6-Br_3	7	Br	B	152–154	70	$C_{20}H_{26}Br_4N_2O_4$	H, N; C[h]
37	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	7	Br	B	142–144	52	$C_{24}H_{36}BrClN_2O_4$	C, H, N
38	Br	2,4,6-Br_3	7	Br	B	113–115	75	$C_{20}H_{26}Br_5NO_2$	C, H, N
39	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	7	Br	B	85–87	84	$C_{24}H_{36}Br_2ClNO_2$	C, H, N
40	NO_2	2,4,6-Br_3	8	Br	B	132–134	70	$C_{21}H_{28}Br_4N_2O_4$	C, H, N
41	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	8	Br	B	*i*	82	$C_{25}H_{38}BrClN_2O_4\cdot H_2O$	C, H, N
42	Br	2,4,6-Br_3	8	Br	B	110–112	80	$C_{21}H_{28}Br_5NO_2$	C, H, N
43	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	8	*p*-$CH_3C_6H_4SO_3$	C	155–156	47	$C_{32}H_{48}BrClNO_5S$	C, H, N

44	NO_2	2,4,6-Br_3	10	Br	B	96–98	90	$C_{23}H_{13}Br_4N_2O_4$	C, H, N
45	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	10	*p*-$CH_3C_6H_4SO_3$	C	105–107	13	$C_{34}H_{49}ClN_2O_7S$	C, H, N
46	Br	2,4,6-Br_3	10	Br	B	115–117	62	$C_{23}H_{32}Br_5NO_2$	C, H, N
47	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	10	Br	B	57–59	92	$C_{27}H_{42}Br_2ClNO_2 \cdot H_2O$	C, H, N
48	NO_2	2,4,6-Br_3	12	Br	B	120–121	40	$C_{25}H_{36}Br_4N_2O_4$	H, N; C[j]
49	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	12	*p*-$CH_3C_6H_4SO_3$	C	133–135	43	$C_{36}H_{53}ClN_2O_7S$	C, H, N
50	Br	2,4,6-Br_3	12	Br	B	155–156	35	$C_{25}H_{36}Br_5NO_2$	C, H, N
51	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	12	*p*-$CH_3C_6H_4SO_3$	C	100	36	$C_{36}H_{53}BrClNO_5S$	C, H, N
52	NO_2	3,4,6-CH_3,Cl,$CH(CH_3)_2$	14	*p*-$CH_3C_6H_4SO_3$	C	120	30	$C_{38}H_{57}ClN_2O_7S$	C, H, N
53	Br	2,4,6-Br_3	14	*p*-$CH_3C_6H_4SO_3$	C	*i*	35	$C_{34}H_{47}Br_4NO_5S \cdot H_2O$	C, H, N
54	Br	3,4,6-CH_3,Cl,$CH(CH_3)_2$	14	*p*-$CH_3C_6H_4SO_3$	C	*i*	28	$C_{38}H_{57}BrClNO_5S$	C, H, N
55	H	3,4,6-CH_3,Cl,$CH(CH_3)_2$	4	Br	B	67–69	64	$C_{21}H_{31}BrClNO_2$	C, H, N
56	H	2,4,6-Br_3	5	Br	B	178–180	58	$C_{18}H_{23}Br_4NO_2$	C, H, N
57	H	2,4,6-Br_3	6	Br	B	124–126	53	$C_{19}H_{25}Br_4NO_2$	C, H, N
58	CH_3	2,4,6-Br_3	2	Br	B	152–153	49	$C_{16}H_{10}Br_4NO_2$	C, H, N
59	CH_3	3,4,6-CH_3,Cl,$CH(CH_3)_2$	4	Br	B	105–107	47	$C_{22}H_{33}BrClNO_2$	C, H, N
60	CH_3	2,4,6-Br_3	5	Br	B	159–160	59	$C_{19}H_{25}Br_4NO_2$	C, H, N
61	CH_3	2,4,6-Br_3	6	Br	B	117–118	62	$C_{20}H_{27}Br_4NO_2$	H, N; C[k]

[a] The letters relate to the general procedures given in the Experimental Section. [b] Melting points were determined in closed capillary tubes in a sulfuric acid bath and are uncorrected. [c] The yield of analytically pure compounds is given and no attempts were made to optimize the yield. [d] The compounds were analyzed for C, H, and N. Analytical results are within ±0.4% of the theoretical values except where indicated. The compounds were dried in vacuo (5–10 mm) for 8 h in the presence of P_2O_5 over boiling $CHCl_3$. [e] C: calcd, 37.97; found, 38.77. [f] C: calcd, 30.87; found 31.39. [g] C: calcd, 41.87; found, 42.63. [h] C: calcd, 35.40; found, 36.10. [i] Isolated as sticky solids and are hygroscopic. [j] C: calcd, 40.11; found, 40.74. [k] C: calcd, 37.91; found, 37.09.

Scheme I



$H_{37}Rv$ (5–50 μg/ml). Several of these furan quaternary salts tested are more active than nitrofurantoin against both gram-positive and gram-negative bacteria.

From the data presented in Table II, it is difficult to find any definite structure–activity relationship which is valid for all the compounds that show in vitro antibacterial activity against various bacteria tested. However, from the data presented some correlations can be observed.

Among the compounds which exhibit high in vitro antibacterial activity, several do not necessarily possess a nitro group attached to C_5 of the furan ring. Highly active compounds **28** and **34** contain a 5-bromo-substituted furan ring. These two compounds especially show the highest antibacterial activity against *K. pneumoniae* and *P. aeruginosa* inhibiting the growth of these two organisms at a concentration of 1.5–2.5 μg/ml. Thus, the presence of a nitro group attached to C_5 of the furan ring is not an essential factor for the high in vitro antibacterial activity of these new furan quaternary salts. The activity exhibited by these compounds could possibly be attributed to their molecular structures as a whole. This is further confirmed by the fact that some furan quaternary salts without any substituent (compounds **55–57**) or with a methyl substituent attached to C_5 of the furan ring (compounds **58–61**) possess appreciable in vitro antibacterial activity and are more active than many of the 5-nitrofuran quaternary salts.

Although no real trend is apparent, Table II shows that compounds with 4-chlorothymyl and 2,4,6-tribromophenyl groups as aryl moieties appear to be the most active and

Table II. Antibacterial and Antifungal Activities of *N*-(5-Substituted 2-furfuryl)-*N*,*N*-dimethyl-*N*-aryloxyalkyl Quaternary Ammonium Salts

	Minimum inhibitory concentration, μg/ml														
	Bacteria[a]								Fungi[b]						
Compd no.	*S.a.*	*S.f.*	P.s.	*K.p.*	*S.t.*	*A.t.*	*E.c.*	*M.t.*	*C.a.*	*Cr.n.*	*T.m.*	*T.r.*	*M.c.*	*M.g.*	*H.c.*
3	200	>200	100	100	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
5	100	200	25	25	>200	100	>200	50	>200	100	>200	>200	>200	>200	>200
9	100	>200	50	100	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
11	9	25	5	25	100	25	>200	10	>200	50	100	>200	100	>200	50
12	25	25	25	25	>200	100	>200	NT	>200	50	100	>200	100	>200	100
13	50	200	25	25	>200	100	>200	50	>200	200	>200	>200	>200	>200	200
14	25	25	2	5	100	25	>200	>200	>200	>200	>200	>200	>200	>200	>200
15	10	25	4	7.5	100	50	>200	10	>200	50	>200	>200	>200	>200	>200
16	10	10	4	7.5	100	25	>200	10	>200	50	>200	100	100	>100	100
17	25	50	8	10	>200	50	>200	25	>200	50	>200	>200	>200	>200	50
18	7.5	25	1.5	5	>200	25	>200	10	>200	25	>200	>200	>200	>200	>200
19	100	>200	100	100	>200	>200	>200	NT	>200	>200	>200	>200	>200	>200	>200
20	100	>200	100	100	>200	>200	>200	NT	>200	>200	>200	>200	>200	>200	>200
21	5	25	5	7.5	100	50	>200	50	>200	25	>200	>200	>200	>200	50
22	2.5	7.5	2.5	2.5	>200	25	>200	7.5	50	25	50	>200	75	50	>200
23	100	>200	100	100	>200	>200	>200	NT	>200	>200	>200	>200	>200	>200	>200
24	100	100	50	100	100	100	100	NT	>200	>200	>200	>200	>200	>200	>200
25	25	25	7.5	5	>200	25	>200	7.5	>200	25	>200	>200	>200	>200	>200
26	10	10	2.5	2.5	50	25	>200	5	>200	25	>200	100	100	100	100
27	2	7.5	2	1.5	50	25	100	10	>200	25	>200	>200	>200	>200	100
28	2.5	5	2.5	2.5	50	10	100	10	>200	10	100	>200	100	>200	100
29	50	>200	50	100	>200	>200	>200	NT	>200	>200	>200	>200	>200	>200	>200
30	50	100	25	50	>200	>200	>200	NT	>200	>200	>200	>200	100	>200	>200
31	25	50	10	25	>200	50	>200	NT	>200	50	>200	>200	50	>200	100
32	10	25	2.5	5	100	25	>200	10	>200	100	>200	100	100	100	25
33	>200	>200	>200	>200	>200	>200	>200	NT	>200	25	>200	200	100	>200	>200
34	2	5	1.5	1.5	50	7.5	100	10	>200	25	>200	>200	100	>200	25
35	50	50	10	25	>200	100	>200	10	>200	100	200	200	100	200	>200
36	7.5	7.5	3	5	>200	25	>200	10	>200	5	>200	>200	>200	>200	>200
37	4	3	2	3	>200	7.5	>200	5	>200	4	>200	>200	>200	>200	>200
38	3	4	2	2	>200	7.5	>200	25	>200	5	>200	>200	>200	>200	>200
39	10	7.5	3	7.5	>200	7.5	>200	7.5	50	25	>200	>200	>200	>200	>200
40	4	4	2	2	>200	10	>200	7.5	>200	4	>200	>200	>200	>200	>200
41	2	3	1	2	>200	4	>200	7.5	>200	4	>200	>200	>200	>200	>200
42	3	4	2	4	>200	7.5	>200	50	>200	4	>200	>200	>200	>200	>200
43	100	100	25	100	>200	100	>200	25	>200	50	200	200	100	200	>200
44	2	4	3	4	>200	10	>200	7.5	>200	4	>200	>200	>200	>200	>200
45	200	100	50	200	>200	>200	>200	25	>200	100	200	>200	>200	>200	>200
46	10	4	2	3	>200	7.5	>200	50	>200	4	>200	>200	>200	>200	>200
47	25	50	25	>200	>200	>200	>200	NT	>200	100	>200	>200	100	>200	100
48	200	200	50	200	>200	>200	>200	100	>200	200	>200	>200	>200	>200	>200

49	200	200	50	200	>200	>200	100	>200	100	>200	>200	>200	>200	>200	>200	>200	>200
50	200	200	50	200	>200	>200	100	>200	200	>200	>200	200	>200	>200	>200	>200	>200
51	200	>200	50	200	>200	>200	200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
53	100	100	50	100	200	>200	200	>200	200	>200	>200	200	>200	>200	>200	>200	>200
54	>200	>200	200	200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200	>200
55	25	25	7.5	10	>200	>200	10	100	25	>200	>200	>200	>200	>200	>200	>200	>200
56	25	50	25	25	>200	>200	25	100	25	100	>200	100	>200	100	100	100	50
57	25	25	5	7.5	>200	50	25	50	25	100	>200	100	>200	100	100	100	50
58	50	50	25	50	>200	100	25	>200	50	>200	>200	50	>200	25	>200	>200	>200
59	25	25	5	5	100	50	10	>200	25	50	>200	50	>200	25	>200	>200	100
60	7.5	25	5	5	100	25	5	>200	25	25	>200	25	>200	>200	>200	>200	100
61	5	7.5	2.5	5	75	25	10	>200	10	>200	>200	10	>200	>200	>200	>200	75
Nitrofurantoin	25	100	2.5	5	25	25	25										
Amphotericin B								2.5	0.5	10	10		5	10			0.5

[a] *S.a.* = *Staphylococcus aureus* (ATCC 6538), *S.f.* = *Streptococcus faecalis* (ATCC 10541), *P.s.* = *Pseudomonas aeruginosa* (ATCC 10145), *K.p.* = *Klebsiella pneumoniae* (ATCC 10031), *S.t.* = *Salmonella typhi* (115), *A.t.* = *Agrobacterium tumefaciens* (NRRL B 36), *E.c.* = *Escherichia coli* (114), *M.t.* = *Mycobacterium tuberculosis*, $H_{37}Rv$. [b] *C.a.* = *Candida albicans* (SKF 2270), *Cr.n.* = *Cryptococcus neoformans* (103), *T.m.* = *Trichophyton mentagrophytes* (A 280 USPHS), *T.r.* = *Trichophyton rubrum* (252 CSTM), *M.c.* = *Microsporum canis* (VM 200 USPHS), *M.g.* = *Microsporum gypseum* (153 CSTM), *H.c.* = *Histoplasma capsulatum* (RNSH Hi $70^1/_2$). NT, not tested.

those compounds without these two groups are either totally inactive or possess only very low activity against all the bacteria tested. In the case of 5-nitrofuran quaternary salts, enhanced activity is noticed with increase in length of alkyl chain, $(CH_2)_n$ (except compound **33**), leading to the highest activity with compounds containing $n = 8$ (compounds **40** and **41**) while in the case of 5-bromofuran quaternary salts, maximum activity is noticed with compounds containing alkyl chains having $n = 5$ and 6 (compounds **27**, **28**, and **34**). Furan quaternary ammonium tosylates are not as active as the bromides, although they show moderate antibacterial and antifungal activity.

These quaternary salts do not exhibit significant antifungal activity (Table II) though many compounds possess appreciable activity against *Cryptococcus neoformans* inhibiting the growth of this organism at concentrations as low as 4 μg/ml.

Eight compounds (**18**, **21**, **22**, **26–28**, **32**, and **34**) showing high antibacterial activity were also tested for their anthelmintic activity against *Nippostrongylus brasiliensis* and *Hymenolepis nana* and were found to be inactive at test concentrations (250 mg/kg) in rats. Acute toxicity studies in mice indicate these eight compounds to be highly toxic (LD_{50} in mice, 25–75 mg/kg ip) and hence further screening for their in vivo activity was not undertaken.

Experimental Section

Melting points were determined in closed capillary tubes in a sulfuric acid bath and are uncorrected. Microanalyses were performed using the Hosli Micro-Combustion apparatus MK 101. Analytical data are given as defined in footnote *d*, Table I. All the quaternary salts reported in Table I were purified by precipitation from $CHCl_3$ solution (activated carbon) using either petroleum ether (bp 40–60 °C) or dry Et_2O.

***N*,*N*-Dimethyl-5-bromo-2-furamide (Ia).** To 5-bromo-2-furoic acid (48 g, 0.25 mol) in freshly distilled $SOCl_2$ (50 ml) was added DMF (1 ml). The solution was refluxed for 3 h. Excess $SOCl_2$ was removed and the crude acid chloride (50 g) was taken in Et_2O (200 ml). The ethereal solution was cooled to 0 °C. To this was added dropwise dimethylamine solution (35%, 125 ml) with shaking and maintaining the temperature below 10 °C. *N*,*N*-Dimethyl-5-bromo-2-furamide separated out as a pale-brown solid which was filtered, washed thoroughly with H_2O, and dried over $CaCl_2$: yield 38 g (70%). This product was practically pure. An analytical sample was obtained by recrystallizing from MeOH as white crystals, mp 84–86 °C. Anal. ($C_7H_8BrNO_2$) C, H, N.

5-Bromo-2-(*N*,*N*-dimethylaminomethyl)furan (IIc). To a stirred and cooled suspension of Ia (35.75 g, 0.164 mol) in anhydrous diglyme (125 ml) was added $NaBH_4$ (6.25 g, 0.164 mol) followed by boron trifluoride etherate (32 g, 0.225 mol) in diglyme (75 ml) below 10 °C. The resulting clear solution was heated on a steam bath for 3 h when the partially insoluble boron complex separated out. Diglyme (150 ml) was removed under reduced pressure. The residue was poured in ice-water and the solid was filtered off. This was added slowly to boiling HCl (15%, 200 ml) and heating continued for further 0.5 h. The acid solution was cooled to 0 °C and basified with NaOH solution (20%) below 10 °C. The amine was extracted with Et_2O (5 × 75 ml). The ethereal layer was dried over KOH pellets. Removal of Et_2O yielded 5-bromo-2-(*N*,*N*-dimethylaminomethyl)furan as a yellow oil which was distilled under reduced pressure: yield 19 g (57%); bp 46–48 °C (1 mm); bp 108 °C (40 mm). Anal. ($C_7H_{10}BrNO$) C, H, N.

5-Nitro-2-(*N*,*N*-dimethylaminomethyl)furan (IId). This compound was prepared from *N*,*N*-dimethyl-5-nitro-2-furamide[12] (20 g, 0.108 mol) in anhydrous diglyme (125 ml), $NaBH_4$ (4.1 g, 0.108 mol), and boron trifluoride etherate (21 g, 0.15 mol) in diglyme (75 ml) as described for IIc. 5-Nitro-2-(*N*,*N*-dimethylaminomethyl)furan distilled as pale yellow liquid: yield 9 g (50%); bp 80–82 °C (1 mm). Anal. ($C_7H_{10}N_2O_3$) C, H, N.

***N*-(5-Nitro-2-furfuryl)-*N*,*N*-dimethyl-*N*-(4-chlorophenoxyethyl) Quaternary Ammonium Bromide (2, Table I).** **Method A.** A mixture of 1.46 g (0.006 mol) of 4-chlorophen-

oxyethyl bromide and 1.1 g (0.006 mol) of 5-nitro-2-(*N*,*N*-dimethylaminomethyl)furan was taken in dry Me_2CO (20 ml) and heated under reflux for 12 h. The solvent was removed in vacuo and the residue was treated with dry Et_2O (50 ml). The semisolid mass became a fine powder on trituration and was filtered. It was dissolved in $CHCl_3$, clarified with activated carbon, and filtered. The $CHCl_3$ solution on dilution with petroleum ether (bp 40–60 °C) afforded the title compound as white powder which was filtered and washed with dry Et_2O (2 × 20 ml): yield 1.1 g (42%); mp 182–183 °C. Anal. ($C_{15}H_{18}BrClN_2O_4$) C, H, N.

***N*-(5-Bromo-2-furfuryl)-*N*,*N*-dimethyl-*N*-(2,4,6-tribromophenoxyhexyl) Quaternary Ammonium Bromide (34, Table I). Method B.** A mixture of 2.47 g (0.005 mol) of 2,4,6-tribromophenoxyhexyl bromide and 1.02 g (0.005 mol) of 5-bromo-2-(*N*,*N*-dimethylaminomethyl)furan was taken in a conical flask. It was mixed thoroughly and left at room temperature for 36 h. To the viscous reaction mass was added dry Et_2O (50 ml) and the gummy solid so obtained was triturated. The resulting pale-brown solid was filtered, washed with Et_2O (3 × 25 ml), and purified as in the previous experiment: yield 3.2 g (80%); mp 91–93 °C. Anal. ($C_{19}H_{24}Br_5NO_2$) C, H, N.

***N*-(5-Nitro-2-furfuryl)-*N*,*N*-dimethyl-*N*-(4-chlorothymyloxydecyl) Quaternary Ammonium *p*-Toluenesulfonate (45, Table I). Method C.** A mixture of 4.0 g (0.01 mol) of 4-chlorothymyloxydecyl bromide and 1.72 g (0.01 mol) of 5-nitro-2-(*N*,*N*-dimethylaminomethyl)furan was taken in dry methyl ethyl ketone (20 ml) and the reaction mixture was heated under reflux for 12 h. The solvent was removed in vacuo. The resulting gummy mass was washed with excess dry Et_2O. The Et_2O insoluble product (3 g) was dissolved in H_2O (15 ml) to which a solution of sodium *p*-toluenesulfonate (prepared by neutralizing 2.5 g of *p*-toluenesulfonic acid with $NaHCO_3$ solution) was added. The reaction mixture which became turbid was allowed to stand at room temperature for 12 h. The solid that separated out was filtered, washed with H_2O, dried and purified by dissolving in $CHCl_3$, clarified (activated carbon), and precipitated by adding dry Et_2O. The solid was filtered and dried (vacuum desiccator over P_2O_5): yield 0.8 g (13%); mp 105–107 °C. Anal. ($C_{34}H_{49}ClN_2O_7S$) C, H, N.

***N*-(5-Nitro-2-furfuryl)-*N*,*N*-dimethyl-*N*-(4-chlorothymyloxyethyl) Quaternary Ammonium *p*-Toluenesulfonate (5, Table I). Method D.** A mixture of 3.82 g (0.01 mol) of 4-chlorothymyloxyethyl tosylate and 1.7 g (0.01 mol) of 5-nitro-2-(*N*,*N*-dimethylaminomethyl)furan was taken in methyl ethyl ketone (25 ml). The reaction mixture was heated to reflux for 12 h. The solvent was removed in vacuo. The residue was washed with dry Et_2O and triturated. The white solid so obtained was purified by dissolving in $CHCl_3$, clarified (activated carbon), and precipitated with dry Et_2O. The resulting solid was filtered, washed with dry Et_2O, and dried (in vacuum desiccator over P_2O_5): yield 0.9 g (15%); mp 184–185 °C dec. Anal. ($C_{26}H_{33}ClN_2O_7S$) C, H, N.

Biological Evaluation (in Vitro). Antibacterial Activity. The dilution tube method[13] was employed using Tryptone Soya Broth (Oxoid). The highest dilution of the test compound which inhibited the visible growth of the organism was taken as the minimum inhibitory concentration (μg/ml). Duplicates were maintained for all the concentrations. For comparative purposes, the inhibitory activities of nitrofurantoin and amphotericin B for antibacterial and antifungal, respectively, were determined under the same assay conditions and included in Table II. *M. tuberculosis* $H_{37}Rv$ was maintained on Lowenstein–Jensen medium. Antitubercular activity of the compounds was tested in Youman's medium following the serial dilution method.[14]

Antifungal Activity. The compounds were tested for activity by the agar dilution assay method.[15] The lowest concentration of the antifungal agent that inhibited the growth of the fungus was taken as minimum inhibitory concentration.

Anthelmintic Activity. Selected compounds were screened for anthelmintic activity in vivo against *N. brasiliensis* and *H. nana* following the technique of Whitlock and Bliss[16] as described by Steward[17] with slight modifications. For this purpose, young male rats (25–30 g) of the University of Freigburg strain were used.

Antihookworm screening was carried out in rats infected with 500 infective larvae of *N. brasiliensis* followed by the administration of the compound on the eighth day at a 250 mg/kg single oral dose. For each compound three infected rats were used. The worm loads of control and treated groups were compared and the activities were determined. Compounds causing 90% deparasitization were considered active.

For antitapeworm screening, rats were infected with 200 viable ova of *H. nana* followed by administration of a single oral dose (250 mg/kg) of the compound. The worms from the small intestine of each individual rat were collected on the third day and scored. Compounds bringing down the average score to 0–10% of the control were considered active.

Acute Toxicity. LD_{50} was determined by injecting the compounds intraperitoneally (ip) into mice and the values for the eight selected compounds (**18**, **21**, **22**, **26–28**, **32**, and **34**) were found to be 75, 37.5, 25, 50, 25, 37.5, 75, and 25 mg/kg, respectively.

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