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Studies on Antibacterial Agents. III. Synthesis of N,N'-Bis(4-quinolyl-, 4-quinaldinyl-, 4-quinazolinyl-, or 9-acridinyl)polymethylenediamines and Their Sulfonamides

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Polymethylene bis-amines, with heterocycle as a carrier moiety, and their sulfonamides were synthesized and tested against *S. aureus*, *E. coli* and *M. tuberculosis* (H37Rv strain). Structure-activity relationship has been discussed.

Sulfonamides[2–10] are known to exhibit antibacterial properties. Though a large number of sulfonamides have been synthesized, compounds derived from bis-amines have not been reported so far. Our interest in synthetic antibacterials[11,12] prompted us to synthesize bis-amines (I) and their sulfonamides (II), and to evaluate their scope as antibacterial agents, particularly with reference to the heterocycle, *i.e.*, the carrier moiety and the size of the side chain.

Sulfonylation of the bis-amines with aromatic sulfonyl chloride in dry pyridine gave the corresponding sulfonamides which were characterized by elemental and spectral analyses.

Biological assay of the bis-amines and their sulfonamides were carried out *in vitro* against *S. aureus* and *E. coli* following Humphrey and Lightbrown's method,[13] and against *M. tuberculosis* (H37Rv strain) following the procedure of Youman.[14] The results are tabulated in Tables II and IV respectively.

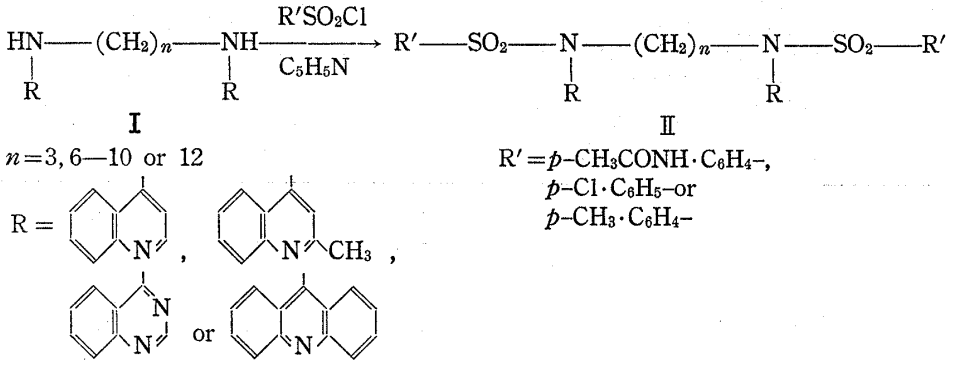

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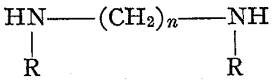
TABLE I.



Compound No.	n	R	Formula[a]	Yield (%)	mp[b] (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	6	4-quinolyl	$C_{24}H_{26}N_4$	78	195—196	77.82	7.02	15.13	78.00	7.00	14.98
2	7	4-quinolyl	$C_{25}H_{28}N_4$	71	102—103	78.12	7.29	14.58	78.20	7.16	14.38
3	8	4-quinolyl	$C_{26}H_{30}N_4$	77	164—165	78.39	7.53	14.07	78.18	7.48	13.69
4	9	4-quinolyl	$C_{27}H_{32}N_4$	80	91—92	78.64	7.76	13.59	78.52	7.68	13.28
5	10	4-quinolyl	$C_{28}H_{34}N_4$	82	156—157	78.87	7.98	13.14	78.66	7.89	13.00
6	12	4-quinolyl	$C_{30}H_{38}N_4$	76	122—123	79.29	8.37	12.33	79.08	8.40	12.26
7	3	4-quinaldinyl	$C_{23}H_{24}N_4$	80	254—255	77.52	6.74	15.81	77.30	6.66	15.66
8	6	4-quinaldinyl	$C_{26}H_{30}N_4$	77	191—192	78.39	7.53	14.07	78.28	7.50	14.10
9	7	4-quinaldinyl	$C_{27}H_{32}N_4$	71	137—138	78.64	7.78	13.59	78.48	7.72	13.38
10	8	4-quinaldinyl	$C_{28}N_{34}N_4$	76	210—211	78.87	7.98	13.14	78.68	7.69	12.98
11	9	4-quinaldinyl	$C_{29}H_{36}N_4$	70	172—173	79.09	8.18	12.72	79.00	8.06	12.48
12	10	4-quinaldinyl	$C_{30}H_{38}N_4$	70	150—151	79.29	8.37	12.33	79.18	8.26	12.28
13	12	4-quinaldinyl	$C_{32}H_{42}N_4$	75	115—116	79.66	8.71	11.61	79.44	8.70	11.46
14	9	4-quinazolinyl	$C_{25}H_{30}N_6$	75	174—175	72.46	7.24	20.28	72.38	7.18	20.10
15	10	4-quinazolinyl	$C_{26}H_{32}N_6$	82	69—70	76.47	7.84	20.58	76.38	7.68	20.42
16	8	9-acridinyl	$C_{34}H_{34}N_4$	69	165—166	81.92	6.82	11·24	81.69	6.70	11.16

a) IR (Nujol) for all the compounds recorded absorption at 3300 cm^{-1} (NH group).
b) crystallizationsolvent: chloroform

TABLE II[a]

No. from Table I	Antibacterial activity 0.1 ml of a 10^{-2}M solution of the compound in water or alcohol by cup-plate method Diameter of cup is 10 mm: *S. aureus*	Antibacterial activity: *E. coli*	Antitubercular activity tested against *M. tuberculosis* (H37Rv strain) Growth in Youman's medium at the end of three weeks Concentration of drugs: 10^{-4}M	10^{-5}M	10^{-6}M	Rv control
1	26	31	−Ve	3+	4+	4+
2	28	28	−Ve	2+	4+	4+
3	24	27	−Ve	+	4+	4+
4	24	27	−Ve	Sl	4+	4+
5	22	26	−Ve	+	4+	4+
6	19	24	−Ve	+	4+	4+
7	28	27	Sl	3+	4+	4+
8	34	27	Sl	3+	4+	4+
9	27	27	−Ve	2+	4+	4+
10	27	28	−Ve	2+	4+	4+
11	27	34	−Ve	+	3+	4+
12	25	30	−Ve	−Ve	4+	4+
13	22	26	−Ve	−Ve	4+	4+
14	15	22	+	3+	4+	4+
15	14	20	+	2+	4+	4+
16	20	22	0	2+	4+	4+
5% Phenol control value	23	34	0	=no growth		
			+to 4+	=various stages of growth		
Ethanol	−Ve	−Ve	Sl	=slight growth		

a) All the compounds were tested *in vitro*.
−Ve: negative result
Sl : slight growth

TABLE III. $R'-SO_2-\underset{\underset{R}{|}}{N}-(CH_2)_n-\underset{\underset{R}{|}}{N}-SO_2-R'$

Compound No.	n	R	R′	Formula	Yield (%)	mp[a] (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR data ν cm^{-1} (m[b])
1	6	4-quinolyl	*p*-Cl·C$_6$H$_4$-	$C_{36}H_{32}O_4N_4S_2Cl_2$	88	180—181	60.08	4.45	7.78	60.10	4.42	7.60	760(C–Cl), 1600(aromatic)
2	7	4-quinolyl	*p*-Cl·C$_6$H$_4$-	$C_{37}H_{34}O_4N_4S_2Cl_2$	76	194—195	60.57	4.63	7.63	60.46	4.48	7.48	750(C–Cl), 1600(aromatic)
3	8	4-quinolyl	*p*-Cl·C$_6$H$_4$-	$C_{38}H_{36}O_4N_4S_2Cl_2$	80	215—216	61.04	4.81	7.49	64.20	4.66	7.36	760(C–Cl), 1600(aromatic)
4	10	4-quinolyl	*p*-Cl·C$_6$H$_4$-	$C_{40}H_{40}O_4N_4S_2Cl_2$	82	209—210	61.93	5.16	7.22	61.68	5.08	7.08	760(C–Cl), 1600(aromatic)
5	12	4-quinolyl	*p*-Cl·C$_6$H$_4$-	$C_{42}H_{44}O_4N_4S_2Cl_2$	78	234—235	62.76	5.47	6.97	62.66	5.48	6.66	760(C–Cl), 1610(aromatic)
6	8	4-quinolyl	*p*-CH$_3$CONH·C$_6$H$_4$-	$C_{42}H_{44}O_6N_6S_2$	74	113—114	63.63	5.55	10.60	63.48	5.60	10.48	1600(aromatic), 1685(CO), 3320(NH)
7	10	4-quinolyl	*p*-CH$_3$CONH·C$_6$H$_4$-	$C_{44}H_{48}O_6N_6S_2$	76	91— 92	64.39	5.85	10.24	64.18	5.66	10.33	1610(aromatic), 1680(CO), 3310(NH)
8	12	4-quinolyl	*p*-CH$_3$CONH·C$_6$H$_4$-	$C_{46}H_{52}O_6N_6S_2$	83	88— 89	65.09	6.13	9.90	64.98	6.08	9.68	1610(aromatic), 1680(CO), 3320(NH)
9	6	4-quinolyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{38}H_{38}O_4N_4S_2$	80	134—135	67.25	5.60	8.25	66.98	5.45	8.08	1600(aromatic)
10	7	4-quinolyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{39}H_{40}O_4N_4S_2$	92	171—172	67.63	5.78	8.09	67.48	5.62	7.88	1600(aromatic)
11	8	4-quinolyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{40}H_{42}O_4N_4S_2$	91	185—186	67.98	5.94	7.93	67.67	5.78	7.80	1600(aromatic)
12	9	4-quinolyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{41}H_{44}O_4N_4S_2$	89	82— 83	68.33	6.11	7.77	68.18	6.00	7.40	1600(aromatic)
13	10	4-quinolyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{42}H_{46}O_4N_4S_2$	85	170—171	68.66	6.26	7.62	68.40	6.30	7.28	1610(aromatic)
14	12	4-quinolyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{44}H_{50}O_4N_4S_2$	74	210—211	69.29	6.56	7.34	68.98	6.46	7.38	1610(aromatic)
15	6	4-quinaldinyl	*p*-Cl·C$_6$H$_4$-	$C_{38}H_{36}O_4N_4S_2Cl_2$	70	111—112	61.04	4.81	7.49	61.18	4.66	7.40	760(C–Cl), 1610(aromatic)
16	8	4-quinaldinyl	*p*-Cl·C$_6$H$_4$-	$C_{40}H_{40}O_4N_4S_2Cl_2$	82	115—116	61.93	5.16	7.22	61.68	5.08	7.30	750(C–Cl), 1610(aromatic)
17	9	4-quinaldinyl	*p*-Cl·C$_6$H$_4$-	$C_{41}H_{42}O_4N_4S_2Cl_2$	84	157—158	62.35	5.32	7.09	62.08	5.38	6.82	750(C–Cl), 1610(aromatic)
18	10	4-quinaldinyl	*p*-Cl·C$_6$H$_4$-	$C_{42}H_{44}O_4N_4S_2Cl_2$	75	204—205	62.76	5.47	6.97	62.60	5.45	6.66	760(C–Cl), 1610(aromatic)
19	6	4-quinaldinyl	*p*-CH$_3$CONH·C$_6$H$_4$-	$C_{42}H_{44}O_6N_6S_2$	80	310 (deconp.)	63.63	5.55	10.60	63.48	5.62	10.48	1615(aromatic), 1680(CO), 3310(NH)
20	8	4-quinaldinyl	*p*-CH$_3$CONH·C$_6$H$_4$-	$C_{44}H_{48}O_6N_6S_2$	72	229—230	64.39	5.85	10.24	64.40	5.66	10.08	1600(aromatic), 1680(CO), 3310(NH)
21	10	4-quinaldinyl	*p*-CH$_3$CONH·C$_6$H$_4$-	$C_{46}H_{52}O_6N_6S_2$	81	129—130	65.09	6.13	9.90	65.20	6.08	9.88	1600a(romatic), 1680(CO), 3310(NH)
22	12	4-quinaldinyl	*p*-CH$_3$CONH·C$_6$H$_4$-	$C_{48}H_{56}O_6N_6S_2$	90	110—111	65.75	6.39	9.58	65.58	6.28	9.28	1610(aromatic), 1690(CO), 3340(NH)
23	3	4-quinaldinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{37}H_{36}O_4N_4S_2$	74	122—123	66.86	5.42	8.43	66.66	5.33	8.18	1615(aromatic)
24	6	4-quinaldinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{40}H_{42}O_4N_4S_2$	79	221—222	67.98	5.94	7.92	67.88	5.88	8.29	1600(aromatic)
25	7	4-quinaldinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{41}H_{44}O_4N_4S_2$	75	139—140	68.33	6.11	7.77	68.30	6.08	7.47	1600(aromatic)
26	8	4-quinaldinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{42}H_{46}O_4N_4S_2$	77	125—126	68.66	6.26	7.62	68.48	6.18	7.20	1600(aromaiic)
27	9	4-quinaldinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{43}H_{48}O_4N_4S_2$	84	101—102	68.98	6.41	7.48	68.88	6.28	7.54	1610(aromatic)
28	10	4-quinaldinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{44}H_{50}O_4N_4S_2$	84	175—176	69.29	6.56	7.36	69.08	6.48	7.56	1610(aromatic)
29	12	4-quinaldinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{46}H_{54}O_4N_4S_2$	91	208—209	69.87	6.83	7·08	69.66	6.66	6.75	1600(aromatic)
30	9	4-quinazolinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{39}H_{42}O_4N_6S_2$	80	202—203	64.81	5.81	11.63	64.66	5.68	11.48	1610(aromatic)
31	10	4-quinazolinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{40}H_{44}O_4N_6S_2$	76	229—230	65.21	5.97	11.41	65.18	5.78	11.18	1600(aromatic)
32	8	9-acridinyl	*p*-CH$_3$·C$_6$H$_4$-	$C_{48}H_{46}O_4N_4S_2$	80	220—221	71.46	5.70	6.94	71.28	7.68	6.80	1615(aromatic)

a) crystallizationsolvent: hot water; *b*) m=medium intensity

Table IV[a)]

No. from Table III	Antibacterial activity 0.1 ml of a 10^{-2}M solution of the compound in water or alcohol by cup-plate method Diameter of cup is 10 mm		Antitubercular activity tested against *M. tuberculosis* (H37Rv strain) Growth in Youman's medium at the end of three weeks Concentration of drugs			
	S. aureus	*E. coli*	10^{-4}M	10^{-5}M	10^{-6}M	Rv control
1	19	18	−Ve	4+	4+	4+
2	16	16	−Ve	4+	4+	4+
3	16	20	−Ve	2+	4+	4+
4	13	19	−Ve	−Ve	4+	4+
5	15	18	−Ve	−Ve	4+	4+
6	18	20	−Ve	+	4+	4+
7	16	18	−Ve	2+	4+	4+
8	14	17	+	2+	4+	4+
9	20	22	−Ve	2+	4+	4+
10	20	16	0	3+	4+	4+
11	20	16	0	3+	4+	4+
12	17	20	−Ve	2+	4+	4+
13	16	16	0	3+	4+	4+
14	−Ve	−Ve	+	3+	4+	4+
15	21	18	Sl	4+	4+	4+
16	19	16	−Ve	4+	4+	4+
17	18	28	−Ve	4+	4+	4+
18	16	28	−Ve	4+	4+	4+
19	15	15	+	4+	4+	4+
20	17	17	−Ve	4+	4+	4+
21	15	18	−Ve	−Ve	4+	4+
22	16	17	−Ve	−Ve	4+	4+
23	17	18	+	2+	4+	4+
24	21	16	0	4+	4+	4+
25	20	16	0	4+	4+	4+
26	20	16	0	4+	4+	4+
27	18	16	0	4+	4+	4+
28	−Ve	−Ve	0	+	4+	4+
29	−Ve	−Ve	0	+	4+	4+
30	−Ve	−Ve	+	2+	4+	4+
31	−Ve	−Ve	3+	3+	4+	4+
32	−Ve	−Ve	0	+	4+	4+
5% Phenol control			0	=no growth		
value	26	20	+to 4+	=various stages of growth		
Ethanol	−Ve	−Ve	Sl	=slight growth		

a) All the compounds were tested *in vitro*.

It is apparent from the results (Tables II and IV) that, with reference to carrier moiety, the activity increases in the following order:

quinazoline<acridine<quinoline<quinaldine.

The size of the side chain does not seem to influence the activity profoundly, and its effect is not of much significance. It is noteworthy that the bis-amines are more active against *S. aureus* and *E. coli* than against *M. tuberculosis*, however, the corresponding sulfonamides exhibit more antitubercular activity. The nature of the substitution in the aromatic sulfonyl group, in the case of sulfonamides, influences the antitubercular property and replacement of a hetero group, such as acetamido or chlorine in the *para* position by a methyl group enhances the antitubercular activity.

Experimental

Infrared spectrum was determined by Perkin-Elmer-257 spectrophotometer, using a nujol film. Melting points are uncorrected.

N,N′-Bis(4-quinolyl-, 4-quinaldinyl-, 4-quinazolinyl-, or 9-acridinyl)polymethylenediamine (I)——Bis-amine dihydrochloride[11,12] was basified with 10—15% NaOH and the precipitated oil was taken up in chloroform, washed with distilled water, dried over anhydrous potassium carbonate, stripped of solvent to afford a pasty mass, which solidified on scratching. It was recrystallized from chloroform. Yields and melting points of the respective compounds are given in Table I. IR (Nujol): 3300 cm^{-1} (NH).

N,N′-Bis(4-quinolyl-, 4-quinaldinyl-, 4-quinazolinyl-, 9-acridinyl-, or arenesulfonyl)polymethylenediamine (II)——Bis-amine and aromatic sulfonyl chloride, taken in the molar proportion of 1: 2, were dissolved in dry pyridine using 10 ml of pyridine/g of the bis-amine, and the mixture was gently heated for 3—4 hr, at 130—135°. After the reaction was over, solvent was removed under reduced pressure, and the residue was triturated with cold water to get a solid, which on crystallization from hot water gave analytical sample. Yields and physical constants are given in Table III.

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Synthesis of Methylpyridine Derivatives. XXX.[1] Reaction of Active Methylene Compounds with 6-Methyl-2-phenyl-4H-1,3-oxazin-4-one and 2-Ethoxy-2,6-dimethyl-2H-1,3-oxazin-4(3H)-one to give 3-Acetylpyridone Derivatives[2]

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Reaction of 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (I) with active methylene compounds, such as diethyl malonate (IIIa), acetylacetone (IIIb), cyclohexane-1,3-dione (IIIc), malononitrile (IIId), ethyl acetoacetate (IIIe), ethyl cyanoacetoacetate (IIIf), and cyanoacetophenone (IIIg) afforded pyridone derivatives, such as 3-acetyl-5-ethoxycarbonyl-4-hydroxy-6-phenyl-2(1H)-pyridone (IVa), 3,5-diacetyl-4-methyl-6-phenyl-2(1H)-pyridone (IVb), 4-acetyl-1-phenyl-6,7-dihydro-3,8-(2H, 5H)-isoquinolinedione (IVc), 3-acetyl-4-amino-5-cyano-6-phenyl-2(1H)-pyridone (IVd), 3-acetyl-5-ethoxycarbonyl-4-methyl 6-phenyl-2(1H)-pyridone (IVe), 3-acetyl-5-cyano-4-hydroxy-6-phenyl-2(1H)-pyridone (IVf), and 3-acetyl-5-cyano-4,6-diphenyl-2(1H)-pyridone (IVg), respectively.

Similarly, 2-ethoxy-2,6-dimethyl-2H-1,3-oxazin-4(3H)-one (II) reacted with IIIa—f under the same conditions to give the corresponding pyridone derivatives (Va—f).

We have previously reported that diketene reacted with imidates to give 1,3-oxazin-4-one derivatives.[4,5] The present paper reports a continuation of our study of those products related to the reaction with active methylene compounds to give pyridine derivatives.

Oxazines used in this reaction are 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (I) and 2-ethoxy-2,6-dimethyl-2H-1,3-oxazin-4(3H)-one (II), prepared by the reaction of diketene with ethyl benzimidate and ethyl acetimidate, respectively.

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