Preparation of Some N,N'-Bis-(4-quinaldino)/(4-quinazolino)- α,ω -diaminoalkanes (hydrochlorides) as Potential Antibacterial and Antitubercular Compounds

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N,N'-Bis-(4-quinaldino)- α,ω -diaminoalkanes dihydrochloride are found to be highly active (*in vitro*) against *S. aureus*, *E. coli* and *M. tuberculosis* (H37Rv strain) and the corresponding 4-quinazolino compounds inactive.

In continuation of our earlier work¹⁾ on N,N'-bis-(9-acridino)- α,ω -diaminoalkanes (dihydrochloride), with particular reference to their significant antibacterial, antitubercular and antileprotic activities, we have now synthesised some new quinaldine and quinazoline derivative of the above type and studied their antibacterial properties. This was done with a view to study the influence of the size and the basic nature of the carrier moiety on the antibacterial activity in comparison to the acridine nucleus.

The synthesis of these compounds with general structure (I) was accomplished by the condensation of 4-chloroquinazoline and 4-chloroquinaldine with α,ω -diaminoalkanes in phenol²⁾ at 130~135°C. The diamines used here were either prepared by standard method³⁾ or obtained from commercial firms.

where

$n=2$ to 12

R=4-quinaldino, 4-quinazolino

EXPERIMENTAL

4-Chloroquinaldine.⁴⁾ 4-Hydroxyquinaldine^{5,6)} was prepared by a slight modification of the original Conrad Limpach⁷⁾ reaction and interacted with phosphorous oxychloride.

4-Hydroxyquinazoline.⁸⁾ This was obtained by heating anthranilic acid with formamide. It was crystallised from water in fine colourless needles, mp 215~216°C (Reported⁸⁾ mp 215.5~216.5°C).

4-Chloroquinazoline.⁹⁾ It was prepared by the method of Gabriel¹⁰⁾ from 4-hydroxyquinazoline, phosphorous pentachloride and phosphorous oxychloride, mp 95~96°C (Reported¹⁰⁾ mp 96°C).

N,N'-Bis-(4-quinaldino)-ethylenediamine dihydrochloride (I: $n=2$, R=4-quinaldino):

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TABLE I

Compound No.	Structure HN-(CH ₂) _n -NH·2HCl R R		Antibacterial activity		Antitubercular (on H37Rv Strain)			
	n	R	0.1 ml of 10 ⁻² solution of the compound in water by Cup-plate method. Diameter of cup is 10 mm	Growth in Youman's medium at the end of three weeks concentration of drug	10 ⁻⁴	10 ⁻⁵	10 ⁻⁶	Rv Control
1	2	4-Quinaldino	12 mm	-ve	+	‡	‡	‡
2	3	4-Quinaldino	17 mm	11 mm	+	‡	‡	‡
3	4	4-Quinaldino	19 mm	15 mm	0	0	‡	‡
4	5	4-Quinaldino	19 mm	12 mm	0	‡	‡	‡
5	6	4-Quinaldino	14 mm	14 mm	+	‡	‡	‡
6	7	4-Quinaldino	20 mm	15 mm	0	+	‡	‡
7	8	4-Quinaldino	18 mm	16 mm	0	‡	‡	‡
8	9	4-Quinaldino	18 mm	-ve	‡	‡	‡	‡
9	10	4-Quinaldino	-ve	-ve	0	0	‡	‡
10	12	4-Quinaldino	-ve	-ve	0	0	‡	‡
11	2	4-Quinazolino	-ve	-ve	‡	‡	‡	‡
12	3	4-Quinazolino	-ve	-ve	‡	‡	‡	‡
13	4	4-Quinazolino	-ve	-ve	‡	‡	‡	‡
14	5	4-Quinazolino	13 mm	-ve	‡	‡	‡	‡
15	6	4-Quinazolino	-ve	-ve	‡	‡	‡	‡
16	7	4-Quinazolino	-ve	-ve	+	+	‡	‡
17	8	4-Quinazolino	-ve	-ve	‡	‡	‡	‡
18	9	4-Quinazolino	-ve	-ve	‡	‡	‡	‡
19	10	4-Quinazolino	-ve	-ve	‡	‡	‡	‡
20	12	4-Quinazolino	-ve	-ve	‡	‡	‡	‡
5% Phenol control value for compounds 1, 2, 4, 6, 7, 8, 9, 10, 13, 16, 17, 18, 19, 20			17 mm	18 mm	0=No growth + to ‡=various stages of growth Sl=slight growth			
Compounds 3, 11, 12, 14			23 mm	20 mm				
Compounds 5, 15			31 mm	22 mm				

In a 50 ml round-bottomed flask fitted with a reflux condenser and calcium chloride guard tube, ethylenediamine (0.01 mole), 4-chloroquinaldine (0.02 mole) and phenol 10 g were refluxed in an oil bath maintained at 130~135°C for 14~16 hr. After cooling to room temperature the reaction mixture was diluted with ether and desired dihydrochloride was obtained on scratching. Recrystallisation from aqueous ethanol afforded pure material. Other compounds mentioned in Table I were prepared in a similar manner and their properties are given in Table II.

RESULTS

All the compounds were tested against *S.*

aureus, *E. coli* and *M. tuberculosis* (H37Rv strain). The results are recorded in Table I. Practically all quinazoline derivatives are found to be inactive against the above microorganisms; where as almost all the quinaldine derivatives exhibited appreciable activity with a maximum at chain length of $n=7$ and $n=8$. The size of the two carrier heterocyclic moieties, quinaldine and quinazoline being practically identical, the significant inactivity of such quinazoline derivatives may be attributed partly to the less basic character of quinazoline ($pK_a=3.51$) as compared to quinaldine ($pK_a=4.85$).

TABLE II

No. from Table I	Formula	Yield %	Crystallisation solvent	mp °C	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
1	C ₂₂ H ₂₂ N ₄ ·2HCl	85	Aqueous ethanol	275 d	63.61	63.38	5.78	5.62	13.49	13.31
2	C ₂₃ H ₂₄ N ₄ ·2HCl	91	Ethanol	190 d	64.33	64.67	6.06	6.28	13.05	12.88
3	C ₂₄ H ₂₆ N ₄ ·2HCl·H ₂ O	77	Ethanol	170 d	62.47	62.63	6.50	6.38	12.14	11.68
4	C ₂₅ H ₂₈ N ₄ ·2HCl	76	Ethanol & ether	78~79	65.64	65.72	6.56	6.48	12.25	12.06
5	C ₂₆ H ₃₀ N ₄ ·2HCl·H ₂ O	90	Ethanol	155 d	63.80	63.62	6.95	6.61	11.45	11.09
6	C ₂₇ H ₃₂ N ₄ ·2HCl·H ₂ O	78	Ethanol	115 d	64.41	63.98	7.15	6.88	11.11	10.95
7	C ₂₈ H ₃₄ N ₄ ·2HCl	86	Ethanol	310 d	67.33	67.56	7.21	6.81	11.22	11.40
8	C ₂₉ H ₃₆ N ₄ ·2HCl·2H ₂ O	90	Ethanol	73 d	63.38	63.51	7.65	7.55	10.20	9.78
9	C ₃₀ H ₃₈ N ₄ ·2HCl·2H ₂ O	89	Ethanol	75 d	63.94	64.05	7.81	7.90	9.94	9.62
10	C ₃₂ H ₄₂ N ₄ ·2HCl·2H ₂ O	94	Ethanol	70 d	67.01	66.85	8.02	7.70	9.77	9.28
11	C ₁₈ H ₁₆ N ₆ ·2HCl	89	Ethanol	290 d	—	—	—	—	21.59	21.11
12	C ₁₉ H ₁₈ N ₆ ·2HCl	77	Ethanol	255 d	—	—	—	—	20.84	21.13
13	C ₂₀ H ₂₀ N ₆ ·2HCl	86	Ethanol	330	57.55	57.72	5.27	5.28	20.14	20.54
14	C ₂₁ H ₂₂ N ₆ ·2HCl	74	Ethanol & ether	260 d	58.46	58.72	5.56	5.71	19.48	19.24
15	C ₂₂ H ₂₄ N ₆ ·2HCl·H ₂ O	88	Ethanol	295 d	57.02	56.71	6.04	5.91	18.14	17.60
16	C ₂₃ H ₂₆ N ₆ ·2HCl·H ₂ O	83	Ethanol	135 d	57.86	58.02	6.28	6.20	17.19	17.26
17	C ₂₄ H ₂₈ N ₆ ·2HCl	91	Ethanol	298~299	60.88	60.87	6.34	6.38	17.75	17.78
18	C ₂₅ H ₃₀ N ₆ ·2HCl·H ₂ O	84	Ethanol	98 d	59.40	59.32	6.73	7.03	16.63	16.83
19	C ₂₆ H ₃₂ N ₆ ·2HCl	80	Ethanol	193~194	62.27	61.87	6.66	6.96	16.76	16.55
20	C ₂₈ H ₃₆ N ₆ ·2HCl	79	Ethanol	198~199	63.51	63.31	7.18	7.00	15.87	16.17

It is significant here to mention that the optimum size of heterocyclic carrier nucleus required for the production of highly active antibacterial compounds, is that of quinoline (*cf.* acridine derivatives¹¹).

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