SYNTHESIS AND ANTIVIRAL ACTIVITY OF SUBSTITUTED 4-(δ-DIETHYLAMINO-α-METHYLBUTYLAMINO)-2-STYRYLQUINAZOLINES

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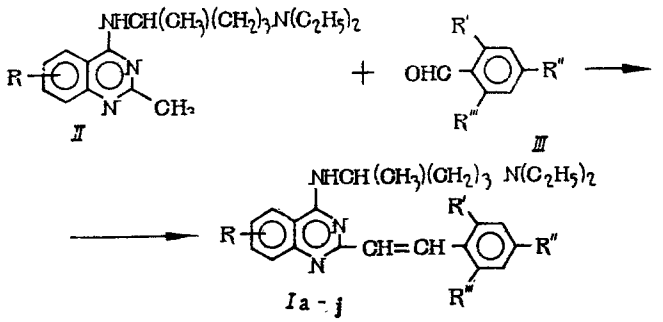
In previous communications in this series [1-3] we have described the synthesis and biological study of substituted 4-amino-2-styrylquinazolines. These compounds exhibited marked experimental activity toward gram-positive bacteria, *Mycobacterium tuberculosis*, infectious protozoa, as well as potent antiinflammatory action. We also found that the greatest chemotherapeutic activity belongs to compounds that have the δ-diethylamino-α-methylbutylamino chain in position 4 and chlorine in the o- or p-positions in the styryl component.

In order to make a further study of the spectrum of the chemotherapeutic activity of 2-styrylquinazoline derivatives and to elucidate the structure–activity relationships of these compounds, we have synthesized several new representatives of substituted 4-(δ-diethylamino-α-methylbutylamino)-2-styrylquinazolines (Ia)-(Ig), (Ik). We tested these and some compounds synthesized earlier (Ih)-(Ij) for *in vitro* virucidal action against influenza A/PR-8/34 virus (HO No. 1).

We synthesized compounds (I) by the general method developed earlier [4, 5] by condensation of 6-methoxy- or 7-chloro-substituted, or unsubstituted 4-(δ-diethylamino-α-methylbutylamino)-2-methylquinazolines (II) with aromatic aldehydes (III)



Ia: R = R″ = R‴ = H, R′ = Cl; b: R = R‴ = H, R′ = R″ = Br;
c: R = 7-Cl, R′ = R″ = Br, R‴ = H; d: R = 7-Cl,
R′ = R″ = R‴ = Cl; e: R = 6-CH_3O, R′ = R″ = Cl, R‴ = H;
f: R = 6-CH_3O, R′ = R″ = R‴ = Cl; g: R = H, R′ = R″ = R‴ = Cl;
h: R = 7-Cl, R′ = R‴ = H, R″ = NO_2; i: R = 6-CH_3O,
R′ = R‴ = H, R″ = NO_2; j: R = 7 = Cl,

where the 5-nitrofuryl residue replaces the substituted aryl group.

II a: R = H; b: R = 6-CH_3O; c: R = 7-Cl;
III a: R′ = Cl, R″ = R‴ = H; b: R″ = Cl, R′ = R‴ = H;
c: R′ = R″ = Cl, R‴ = H; d: R′ = R″ = R‴ = Cl;
e: R″ = NO_2, R′ = R‴ = H; f: R′ = R″ = Br, R‴ = H.

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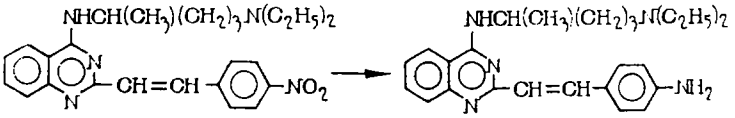
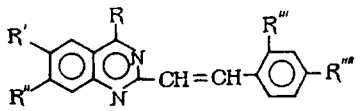
We prepared compound (Ik) (R = R' = R''' = H, R'' = NH_2) by reduction of nitrostyrylquinazoline (Il) [1] with sodium sulfide.



Il Ik

For comparison we examined the substituted 2-styrylquinazolines of the general formula (IV), which we also synthesized earlier [1-3], for activity against this virus; these have other amine residues in position 4 instead of the δ-diethylamino-α-methylbutylamino chain, namely diethylamine (IVa)-(IVd), (IVh), aniline (IVe), and N-piperidine (IVf) and (IVg).



IVa-h

a: R = $N(C_2H_5)_2$, R' = R''' = H, R'' = R'''' = Cl; b: R = $N(C_2H_5)_2$, R' = R'''' = H, R'' = Cl, R''' = NO_2; c: R = $N(C_2H_5)_2$, R' = R'''' = H, R'' = R''' = Cl; d: R = $N(C_2H_5)_2$; R' = CH_3O, R'' = R'''' = H, R''' = Cl; e: R = NHC_6H_5, R' = R''' = H, R'' = Cl, R'''' = NO_2; f: R = N-piperidyl, R' = R''' = H, R'' = R'''' = Cl; g: R = N-piperidyl, R' = R''' = H, R'' = Cl, R'''' = NO_2; h: R = $N(C_2H_5)_2$, R' = CH_3O, R''' = H, R'''' = NO_2.

We evaluated the virucidal activity of compounds (I) and (IV) as the water-soluble hydrochloride salts; when the hydrochlorides were poorly soluble we used a suspension of the salt or the free base in water. We can classify these compounds in three groups on the basis of their substituents and antiviral activity.

The greatest activity toward the virus is displayed by the compounds of the first group, (Ia)-(Ig), the 4-(δ-diethylamino-α-methylbutylamino)-2-styrylquinazoline derivatives in which the styryl component bears one, two, or three halogen atoms, chlorine or bromine (Table 1). Compounds of the second group, the 4-(δ-diethylamino-α-methylbutylamino-2-styrylquinazoline derivatives (Ih)-(Ik) that have nitro or amino groups instead of the halogen atoms in the styryl fragment or where styryl is replaced by 5-nitrofurylvinyl (Ij) have much lower antiviral activity. Compounds of the third group, (IVa)-(IVh), in which the δ-diethylamino-α-methylbutylamino chain in position 4 is replaced by other amine residues, are devoid of any virucidal properties.

Thus, our work has revealed the virucidal activity of 4-(δ-diethylamino-α-methylbutylamino)-2-styrylquinazoline derivatives and the structure—virucidal activity relationships of these compounds in the case of influenza virus. However, these compounds are less active than known virucidal agents.

EXPERIMENTAL CHEMICAL PART

2-(2',4'-Dibromostyryl)-4-(δ-diethylamino-α-methylbutylamino)quinazoline (Ib). A mixture of methylquinazoline (IIa) (6 g, 18.1 mmole), 2,4-dibromobenzaldehyde (IIIg) (16 g, 60.5 mmole), anhydrous sodium acetate (2 g, 24.4 mmole), and acetic anhydride (30 ml) was heated with stirring at 140-142°C for 12 h. The reaction mixture was cooled to 50-60°C and poured into 5% hydrochloric acid (120 ml), previously heated to 80-85°C. The hydrochloric acid solution was extracted with ether to remove unreacted 2,4-dibromobenzaldehyde and the by-product 2,4-dibromocinnamic acid. It was then made alkaline with 50% aqueous potassium carbonate and the liberated base was extracted with chloroform. The chloroform extract was dried over fused potassium carbonate and evaporated. The residue (10.4 g) was twice crystallized from heptane to give styrylquinazoline (Ib) (6.3 g) with mp 116-117°C. The white crystals were highly soluble in common organic solvents, less soluble in heptane and hexane, and virtually insoluble in water. The dihydrochloride of (Ib) was highly soluble in water, alcohols, and chloroform, and insoluble in ether and acetone.

TABLE 1. Substituted 4-Amino-2-styrylquinazolines and Their Antiviral Activity

Compound	Yield, %	Melting point, °C	Found, %					Formula	Calculated, %					Activity	
			C	H	Br	Cl	N		C	H	Br	Cl	N	compound concentration, μg/ml	number of neutralized EID_{50} in 0.2 ml
Ia·2HCl	42	240	—	—	—	21,44	11,30	$C_{25}H_{31}ClN_4 \cdot 2HCl$	—	—	—	21,15	11,45	1000	1000
														100	10
														10	0
Ib	57	116	—	—	29,24	2	9,85	$C_{25}H_{30}Br_2N_4$	—	—	29,24	—	10,26	1000	100
														100	100
Ib·2HCl	—	242	—	—	25,41	11,30	9,05	$C_{25}H_{30}Br_2N_4 \cdot 2HCl$	—	—	25,80	11,45	9,05	10	10
														1	0
Ic	56	122	51,67	4,99	33,31		9,59	$C_{25}H_{29}Br_2ClN_4$	51,70	5,03	33,62	—	9,65	1000	1000
														100	100
Ic·2HCl	—	267	—	—	23,98	15,82	8,58	$C_{25}H_{29}Br_2ClN_4 \cdot 2HCl$	—	—	24,45	16,27	8,57	10	0
Id	56	177	57,10	5,42		29,96	10,67	$C_{25}H_{28}Cl_4N_4$	57,10	5,31	—	26,95	10,64	1000	1000
Ie	47	171	64,26	6,70		14,31	11,54	$C_{26}H_{32}Cl_2N_4O$	64,06	6,62		14,55	11,49	1000	100
														100	100
Ie·2HCl	—	267	—	—		25,15	10,04	$C_{26}H_{32}Cl_2N_4O \cdot 2HCl$	—	—		25,31	10,00	10	0
If	44	175	59,75	5,98		20,40	10,72	$C_{26}H_{31}Cl_3N_4O$	59,89	5,90		20,36	10,73	1000	100
														100	100
If·2HCl	—	238	—	—		29,62 (Cl′ 11,50)	9,79	$C_{26}H_{31}Cl_3N_4O \cdot 2HCl$	—	—		29,80 (Cl′ 11,92)	9,42	10	0
Ig	41	163	61,05	5,76		21,33	11,10	$C_{25}H_{29}Cl_3N_4$	61,10	5,94		21,63	11,39	1000	1000
														100	100
Ig·2HCl	—	227	—	—		Cl′	9,92	$C_{25}H_{29}Cl_3N_4 \cdot 2HCl$	—	—		Cl′	9,92	10	5
				12		12,10						12,55		1	0
Ih	[1]	—	—	—	—	—	—	—	—	—	—	—	—	1000	5
														100	5
														10	0
Ii	[2]	—	—	—	—	—	—	—	—	—	—	—	—	1000	100
														100	100
														10	0
Ij	[1]	—	—	—	—	—	—	—	—	—	—	—	—	1000	100
														100	100
														10	0
Ik	41	137	74,26	8,00	—	—	17,29	$C_{25}H_{33}N_5$	74,40	8,24	—	—	17,36	1000	10
														100	5
														10	0

Note. Square brackets enclose literature references.

2-(2',4',6'-Trichlorostyryl)-4-(δ-diethylamino-α-methylamino)-6-methoxyquinazoline (If). A mixture of methylquinazoline (IIb) (3.56 g, 10.8 mmole), 2,4,6-trichlorobenzaldehyde (IIIc) (6.25 g, 32.4 mmole), sodium acetate (1.32 g, 16.1 mmole), and acetic anhydride (20 ml) was heated with stirring at 140-142°C for 10 h. It was then poured into 5% hydrochloric acid (85 ml), previously heated to 80°C. After cooling, the mixture was diluted with concentrated hydrochloric acid (35 ml) and extracted with ether (6 × 150 ml). The aqueous solution was made alkaline with 50% potassium carbonate solution and extracted with ether (8 × 100 ml). The ethereal extract was dried over potassium carbonate and evaporated to give styrylquinazoline (If) (4.09 g). The white yellowish crystals were highly soluble in common organic solvents and insoluble in water. The dihydrochloride of (If) formed light yellow crystals, soluble in water, alcohols, and chloroform and insoluble in ether and acetone.

The other 2-styrylquinazoline derivatives (I) were synthesized in the same way. Their physical constants, elemental analyses, and yields are summarized in Table 1. The PMR spectra (recorded on a JNM-4H-100 at 100 MHz in various solvents, internal standard tetramethylsilane) imply that in the synthetic compounds (I) the substituents on the double bond in the styryl component have the trans-configuration; J = 16 Hz for the relevant protons.

2-(4'-Aminostyryl)-4-(δ-diethylamino-α-methylbutylamino)quinazoline (Ik). To a solution of (Iℓ) (3.6 g, 8.3 mmole) [1] in a mixture of alcohol (160 ml) and water (70 ml) was added a solution of sodium sulfide (10 g, 41.7 mmole) in water (50 ml). The reaction mixture was left at room temperature for 3 days. The end of the reduction was verified by thin-layer chromatography on aluminum oxide (grade II) with chloroform as mobile phase and UV detection [R_f 0.77 (Iℓ), 0.64 (Ik)]. After the end of the reaction the mixture was evaporated to a volume of 70 ml, made alkaline with 50% potassium carbonate solution, and extracted with chloroform. The chloroform extract was dried over potassium carbonate and evaporated. The residue (3.5 g) was crystallized from heptane (600 ml) to give aminostyrylquinazoline (Ik) (2 g) as yellow crystals, insoluble in water, and highly soluble in common organic solvents apart from heptane and hexane. The yield, physical constants, and analysis of the compounds are included in Table 1.

EXPERIMENTAL CHEMOTHERAPEUTIC PART

Equal volumes of aqueous solutions or aqueous suspensions of the test compounds were mixed in test tubes (various concentrations) with various quantities (1-1000) of the embryonic infectious doses (EID_{50}) of influenza A/PR-8/34 virus (HO No. 1). The mixture was left at 14°C for 1 h; a volume of 0.2 ml was then used for infection of the allantoic cavity of ten-day chick embryos. After 48 h in a thermostat at 37°C, the chick embryos were dissected; the allantoic cavity was removed and used to determine the titer of the virus by the hemagglutination reaction. The activity of the compounds was expressed as the number of neutralized EID_{50} of the virus.

Our results are summarized in Table 1. Compounds (IVa)-(IVh), which do not appear in the table and whose synthesis we described in [1-3], had EID_{50} of zero at a concentration of 1000 μg/ml.

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