SYNTHESIS AND CHEMOTHERAPEUTIC STUDIES OF 2-STYRYL-4-(δ-DIETHYLAMINO-α-METHYLBUTYLAMINO)QUINAZOLINES

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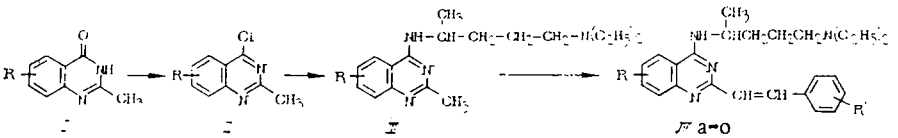
UDC 615.281:547.856].012.1

Previous communications [1-6] have described the synthesis and biological examination of substituted 2-styryl-4-aminoquinazolines, which experimentally exhibit high activity against Gram-positive bacteria, *Mycobacterium tuberculosis*, protozoal infectious agents, pathogenic viruses, and fungi, and also possess pronounced antiinflammatory properties.

In pursuit of these investigations, we have synthesized and studied a new series of 2-styryl-4-(δ-diethylamino-α-methylbutylamino)quinazolines with a variety of substituents in the quinazoline nucleus and in the styryl moiety of the molecule.



The compounds were synthesized by a previously developed general method [7, 8], from the appropriate 2-methyl-4-quinazolones (I), which were converted via the 2-methyl-4-chloroquinazolines (II) into the 2-methyl-4-(δ-diethylamino-α-methylbutylamino)quianazolines (III), followed by condensation with substituted aldehydes to give the 2-styryl-4-(δ-diethylaminomethylbutylamino)quinazolines (IVa-o) (Table 1) required for chemotherapeutic study.

During the course of synthesizing the styrylquinazolines (IV), and preparing some of them in large amounts in order to carry out further biological studies, we found it necessary to improve the method of purification of 7-chloro-4-quinazolone (I, R = 7-Cl).* The use of the general method for the purification of 4-quinazolones described in the literature, involving treatment of the crude product with aqueous sodium hydroxide, heating with charcoal, filtration, and acidification of the cooled filtrate with acetic acid [9], was not suitable in the case of (I). Addition of alkali to an aqueous suspension of this compound up to a pH of 12 did not result in conversion to the water-soluble O-sodium derivative, and further basification up to pH 14 resulted in precipitation of the bulk of the O-sodium derivative in admixture with the charcoal. Attempts to convert this derivative into a soluble form by adding water were unsuccessful, since hydrolysis of the bulk of the O-sodium derivative occurred with precipitation of the difficultly water-soluble 2-methyl-7-chloro-4-quinazolone, which did not enable it to be separated from impurities. Further dilution with water and heating the mixture to boiling did not result in the dissolution of the precipitate but to an increase in its amount as a result of increased hydrolysis.

Our investigations showed that only over a narrow range of pH values (12.0 to 13.0) and at 50-55°C was the quinazolone (I) completely converted into its O-sodium derivative, which dissolved in water and could be purified by filtration with charcoal from water-insoluble impurities. Further neutralization of the filtrate with 20% sulfuric acid to pH 7.0 gave this compound in virtually quantitative yield and a purity of not less than 98%,

*Those participating in this work, in addition to the authors of the paper, included I. S. Tubina and T. Yu. Vinokurova of the VNIKhFI Analytical Laboratory, and O. N. Volzhina and Z. M. Klimonova of the VNIKhFI Pilot Plant.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 2, pp. 183-188, February, 1982. Original article submitted July 31, 1981.

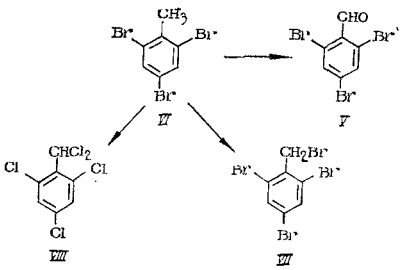
 0091-150X/82/1602-0122$07.50

TABLE 1. Substituted 2-Styryl-4-(δ-diethylamino-α-methylbutylamino)quinazolines (IV)

Compound	R	R″	Yield, %	mp, °C	Found, %					Molecular formula	Calculated, %				
					C	H	Br	Cl	N		C	H	Br	Cl	N
IVa	H	2,4-di-Br	57	116—117[a]	—	—	29,2	—	9,9	$C_{25}H_{30}Br_2N_4$	—	—	29,2	—	10,2
				242—243	—	—	25,5	11,3	9,0	$C_{25}H_{30}Br_2N_4 \cdot 2HCl$	—	—	25,8	11,4	9,0
IVb	6-OCH_3	2,4-di-Br	55	160—161[b]	54,3	5,9	27,5	—	10,1	$C_{26}H_{32}Br_2N_4O$	54,2	5,6	27,7	—	9,7
				256—257	—	—	24,7	10,9	8,7	$C_{26}H_{32}Br_2N_4O \cdot 2HCl$	—	—	24,6	10,9	8,6
IVc	6-NO_2	2,4-di-Br	53	179—180[b]	50,8	4,9	—	—	11,6	$C_{25}H_{29}Br_2N_5O_2$	50,8	4,9	—	—	11,8
				260—261	—	—	23,9	10,6	10,5	$C_{25}H_{29}Br_2N_5O_2 \cdot 2HCl$	—	—	24,0	10,7	10,5
IVd	7-Cl	2,4-di-Br	56	122—123[b]	51,6	4,9		33,3	9,6	$C_{25}H_{29}Br_2ClH_4$	51,7	5,0	33,6		9,6
				267—268	—	—	24,1	15,9	8,6	$C_{25}H_{29}Br_2ClN_4 \cdot 2HCl$	—	—	24,5	16,2	8,6
IVe	H	2,4,6-tri-Br	26	184—185	—	—	34,1	10,1	7,7	$C_{25}H_{29}Br_3N_4 \cdot 2HCl$	—	—	34,3	10,2	8,0
IVf	6-NO_2	2,4,6-tri-Br	51	161—162[a]	44,4	4,2	35,8	—	10,4	$C_{25}H_{28}Br_3N_5O_2$	44,8	4,2	35,8	—	10,4
				234—235[c]	39,2	4,1	—	—	9,1	$C_{25}H_{28}Br_3N_5O_2 \cdot 2HCl$	39,4	4,2	—	—	9,2
IVg	7-Cl	2,4,6-tri-Br	40	155—156[a]	45,1	4,4	36,3	5,4	8,4	$C_{25}H_{28}Br_3ClN_4$	45,5	4,3	36,3	5,4	8,5
				202—204[d]	40,7	4,1	32,3	14,3	7,6	$C_{25}H_{28}Br_3ClN_4 \cdot 2HCl$	40,9	4,1	32,7	14,5	7,6
IVh	H	2,4,6-tri-Cl	56	176—177[a]	56,9	5,4	—	26,9	10,6	$C_{25}H_{28}Cl_4N_4$	57,1	5,3	—	26,9	10,6
				112—113[c]	48,5	4,9	—	34,4	9,0	$C_{25}H_{28}Cl_4N_4 \cdot 2HCl$	48,6	5,2	—	34,5	9,1
IVi	6-OCH_3	2,4,6-tri-Cl	44	174—175[a]	50,8	6,9	—	20,4	10,7	$C_{26}H_{31}Cl_3N_4O$	59,9	5,9	—	20,4	10,7
				237—238	—	—	—	29,6	9,7	$C_{26}H_{32}Cl_3N_4O \cdot 2HCl$	—	—	—	29,8	9,4
IVj	6-NO_2	2,4,6-tri-Cl	74	182—183	55,9	5,4	—	20,0	13,0	$C_{25}H_{28}Cl_3N_5O_2$	55,9	5,3	—	19,8	13,0
				261—262	—	—	—	28,8	11,7	$C_{25}H_{28}Cl_3N_5O_2 \cdot 2HCl$	—	—	—	29,0	11,5
IVk	7-Cl	2,4,6-tri-Cl	56	176—177[a]	56,9	5,4	—	27,0	10,7	$C_{25}H_{28}Cl_4N_4$	57,1	5,3	—	27,0	10,7
				212—213[c]	48,5	4,9	—	34,4	9,0	$C_{25}H_{28}Cl_4N_4 \cdot 2HCl$	48,6	5,2	—	34,5	9,1
IVl	6-OCH_3	penta-F	4	114—115[a]	61,3	5,8	18,8		11,1	$C_{26}H_{29}F_5N_4O$	61,4	5,8	18,7		11,0
				269—270	52,3	5,5	—	11,8	9,4	$C_{26}H_{29}F_5N_4O \cdot 2HCl \cdot H_2O$	52,1	5,5	—	11,8	9,3
IVm	6-NO_2	penta-F	34	169—170[a]	57,1	5,2	17,9		13,4	$C_{25}H_{26}F_5N_5O_2$	57,3	5,0	18,1		13,4
				244—245	50,3	4,7	—	—	11,7	$C_{25}H_{26}F_5N_5O_2 \cdot 2HCl$	50,3	4,7	—	—	11,7
IVn	7-Cl	penta-F	48	248—249[d]	50,1	4,7	—	17,7	9,2	$C_{25}H_{26}ClF_5N_4 \cdot 2HCl \cdot H_2O$	49,8	5,0	—	17,6	9,3

a) From heptane.
b) From heptane—benzene (3:1).
c) From ethanol.
d) From isopropyl alcohol.

permitting normal further synthesis of (II) and (III) (R = 7-Cl). In addition to 2-methyl-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinazoline (III, R = 7-Cl), also used were compounds unsubstituted in the benzene moiety of the quinazoline nucleus, 2-methyl-4-(δ-diethylamino-α-methylbutylamino)quinazoline (III, R = H) and its 6-methoxy derivative (R = 6-OCH_3), and 6-nitro derivative (III, R = 6-NO_2), the synthesis of which has been described [1, 2, 5]. The aldehydes used in the preparation of the styrylquinazolines (IV) were haloaromatic aldehydes, since earlier investigations had shown that the highest chemotherapeutic activity was obtained in styrylquinazolines containing a halogen atom in the styryl moiety of the molecule. In addition to compounds which were available or readily accessible by standard methods (2,4,6-trichloro-, 2,4-dibromo-, and 2,3,4,5,6-pentafluorobenzaldehydes), 2,4,6-tribromobenzaldehyde (V) was also used. The synthesis of the aldehyde (V) has previously been studied [10] from m-nitrobenzaldehyde via 2,4,6-tribromo-3-aminobenzaldehyde in an overall yield of 42%, or from m-toluidine via 2,4,6-tribromo-m-toluidine and 2,4,6-tribromotoluene (VI) in 19.5% yield. It is reported in the literature that 2,4,6-tribromotoluene (VI), as a result of steric hindrance, is not oxidized by selenium dioxide [11], but on heating for 12 h with an excess of bromine at 220°C it is partially converted into 2,4,6-tribromobenzylidene dibromide, hydrolysis of which affords the aldehyde (V) in 24% yield [10].



Our treatment of 2,4,6-tribromotoluene (VI) with an excess of bromine in boiling carbon tetrachloride gave a 94% yield of 2,4,6-tribenzyl bromide (VII), and chlorination of (VI) in the presence of a catalytic amount of PCl_3 with UV irradiation at 180-220°C for 10 h resulted in 75% conversion to 2,4,6-trichlorobenzylidene dichloride (VIII) which forms on hydrolysis 2,4,6-trichlorobenzaldehyde. Despite literature reports [11], oxidation of (VI) with chromic anhydride in acetic anhydride at 0 to +10°C followed by hydrolysis of the diacetoxy derivative afforded a 30% yield of 2,4,6-tribromobenzaldehyde (V).

Condensation of the substituted 2-methyl-4-(δ-diethylamino-α-methylbutylamino)quinazolines (III) with the haloaldehydes was effected in the presence of acetic anhydride and sodium acetate by the general method described in the Experimental section. The constants, yields and analyses of compounds (IVa-o) are given in Table 1.

EXPERIMENTAL CHEMICAL PART

Purification of 2-Methyl-7-chloro-4-quinazolone (I, R = 7-Cl). To a suspension of 300 g of a paste consisting of 50.2% of the quinazolone (I) and 40% of water, obtained by ammonolysis of 2,4-dichlorobenzoic acid, in 300 ml of water was added 40% sodium hydroxide solution until the pH reached 12.0-13.0. The resulting aqueous solution of the O-sodium derivative of (I), containing insoluble impurities, was mixed with 15 g of charcoal at 50-55°C, and filtered. To the filtrate was added 20% sulfuric acid until the pH reached 7.0. The resulting precipitate was filtered off, washed with water, and dried to give 152 g of 98% (I) (R = 7-Cl), mp 270°C (dec.) [11]. Yield 98.7%.

2,4,6-Tribenzyl Bromide (VII). To a solution, heated to boiling, of 3.29 g (10 mmole) of (VI) in 15 ml of CCl_4 was added dropwise over 3 h a solution of 6.55 g (41 mmole) of bromine in 5 ml of CCl_4. Boiling was continued for a further 10 h, after which the mixture was evaporated. The residue was recrystallized from 96% ethanol to give 3.85 g (94%) of (VII), mp 74-75°C [12].

2,4,6-Tribromobenzaldehyde (V). A solution of 46 g (139 mmole) of (VI) in 200 ml of acetic anhydride and 40 ml of concentrated sulfuric acid was cooled to 0°C, and a solution of 50 g (500 mmole) of chromic anhydride in 225 ml of acetic anhydride was added dropwise with vigorous stirring, the temperature of the reaction mixture being kept below 10°C.

TABLE 2. Chemotherapeutic Activities of Substituted 2-Styryl-4-(δ-diethylamino-αmethylbutylamino)quinazolines

Compound	Staph. aureus	Str. haemolyticus	C. diphtheriae	Bac. anthracoides spores	M. tuberculosis no s.	M. tuberculosis w.s.	Microsporum lanosum	Trichophyton	Achorion Schönleim	Actin. albus	Candida albicans	Viricidal activity: concentration of compound, μg/ml	Viricidal activity: no. of neutralized EID_{100}
	minimum inhibitory concentration, μg/ml												
IVa	7,8	7,8	3,9	7,8	0,25	31,2	250	250	500	500	500	1000	10
												100	10
												10	1
												1	0
IVb	3,9	3,9	3,9	3,9	0,5	7,8	15,6	62,2	62,5	31,2	31,2	1000	1
IVc	15,6	3,9	62,5	31,2	0,5	7,8	125	250	62,5	125	500	1000	10
												100	10
												10	1
												1	0
IVd	3,9	3,9	3,9	3,9	0,5	7,8	3,9	62,5	62,5	15,6	7,8	1000	100
												100	10
												10	0
IVe	7,8	2	3,9	3,9	3,9	125	15,6	15,6	7,8	15,6	31,2	1000	10
												100	10
												10	1
												1	0
IVf	7,8	7,8	7,8	7,8	0,06	31,2	31,2	15,6	3,9	2	62,5	1000	1
IVg	7,8	3,9	3,9	3,9	1	31,2	7,8	7,8	1	3,9	15,6	1000	10
												100	10
IVh	7,8	2	31,2	7,8	1	31,2	31,2	62,5	62,5	1000	31,2	1000	100
												100	10
IVi	3,9	3,9	3,9	3,9	0,5	31,2	31,2	62,5	62,5	62,5	62,5	1000	10
												100	10
IVj	3,9	2	15,6	7,8	31,2	—	250	250	250	250	250	1000	1
												100	0
												10	0
IVk	3,9	2	7,8	2	125	—	31,2	62,5	62,5	1000	125	1000	100
IVm	7,8	3,9	7,8	7,8	0,5	31,2	31,2	15,6	15,6	500	500	1000	0
IVn	7,8	2	7,8	2	1	15,6	15,6	15,6	250	500	500	1000	100
												100	1

Following stirring for 3 h, the mixture was poured onto ice, the solid filtered off, washed with water, and dried, to give 34 g of the diacetate (V), containing around 15% of starting material (VI) as impurity. The material was recrystallized from alcohol, and hydrolyzed by boiling for 1 h with a mixture of 100 ml of alcohol, 150 ml of water, and 10 ml of sulfuric acid. The precipitate of the aldehyde (V) which separated on cooling was filtered off, washed with water, and dried to give 14 g (19.2%), mp 98-99°C (from alcohol) [10].

General Method of Synthesis of Substituted 2-Styryl-4-(δ-diethylamino-α-methylbutylamino)quinazolines (IV). A mixture of 15 mmole of the quinazoline (III) (R = H, 6-OCH_3, 6-NO_2, 7-Cl), 45 mmole of the halo-substituted benzaldehyde, 22.6 mmole (1.85 g) of anhydrous sodium acetate, and 30 ml of acetic anhydride was heated with stirring at 160-162°C for 12 h [for (III), R = 6-OCH_3, the reaction was carried out at 139-141°C, and for (III), R = 6-NO_2, at 160-162°C for 6 h]. The reaction mixture was cooled to 60°C and poured into 100 ml of 6% hydrochloric acid heated to 80°C. After cooling, nonbasic material was extracted with ether, the hydrochloric acid solution was basified with potassium carbonate to pH 9.0-10.0, and the free base which separated was extracted with ether (8 × 50 ml). The ether extract was dried over potassium carbonate and evaporated, and the residue was dissolved in 200 ml of anhydrous acetone and acidified with alcoholic hydrogen chloride to pH 4.0-5.0. The resulting precipitate of the hydrochloride was filtered off, recrystallized, and the free base again isolated and extracted with ether. The residue after removal of the ether was recrystallized from the solvent indicated in Table 1 and converted into the dihydrochloride. The dihydrochlorides were yellow powders, readily soluble in water and alcohols, and insoluble in acetone, ethyl acetate, benzene, chloroform, and ether. The bases were readily soluble in the usual organic solvents apart from hexane and heptane, and insoluble in water. According to the PMR data, all the compounds (IV) possessed the trans-configuration for the substituents at the double bond of the styryl moiety of the molecule (for the corresponding protons, J = 16 Hz).

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the compounds was determined by double serial dilution in a liquid nutrient medium [13] using four species of Gram-positive bacteria, acid-resistant *Mycobacterium tuberculosis* strain $H_{37}R_V$, and five species of pathogenic fungi. Table 2 shows that the compounds possess fairly high activity towards Gram-positive microorganisms. The minimum bacteriostatic concentrations (MBC) were generally 2-7.8 μg/ml. No relationship between the MBC values and the positions of the substituents in the quinazoline ring was observed. The compounds had high antituberculosis activity, and on Sutton's medium without protein loading the minimum tuberculostatic concentration for most of the compounds was 1 μg/ml or less. On a medium with 10% of added horse serum, the activity was significantly reduced.

The highest activity against pathogenic fungi was noted in compounds containing three bromine atoms in the styryl moiety of the molecule.

With respect to Gram-negative bacteria (*E. coli, S. typhi, Sh. flexneri, Pr. vulgaris, Ps. aeruginosa*), all the compounds except (IV_i) were virtually inactive, and in concentrations of 250 μg/ml failed to suppress the growth of these microorganisms. Compound (IV_i) was active against *E. coli, S. typhi, Sh. flexneri,* its MBC in these instances being 3.9-7.8 μg/ml. Compound (IVd) was examined using an experimental model of dermal microsporia in guinea pigs, by local application as a 1% emulsified ointment for three weeks, giving a weakly positive effect in this model.

Antiviral activity was studied against influenza virus APR-8 (HON1) and herpes simplex virus, type 1, strain 1-C.

For the determination of viricidal activity, equal volumes of different concentrations of aqueous solutions or suspensions of the test compounds were mixed with a given number (1-100) of 100% embryonic infective doses (EID_{100}) of herpes virus. The mixture was kept for 1 h at 14°C, and introduced into the allantoic cavity of 10-day-old chick embryos in a volume of 0.2 ml. The effects of the compounds were determined by the hemagglutinin reaction, and expressed as the number of neutralized EID_{100} of the virus.

Antiherpes activity was studied in a primary cell culture of chick embryo fibroblasts. The compounds were introduced in the maximum tolerated and smaller doses into test tubes one hour following infection of the monolayer, and their virus-inhibiting activity assessed by the prevention of the cytopathic effects of the virus on the cells.

The greatest viricidal activity towards influenza virus was shown by 2-(2',4',6'-tribromostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-aminoquinazoline, obtained by reduction of (IVf) by a previously-described method [5]. This compound in concentrations of 1000 and 100 μg/ml completely neutralized 100 EDI_{100} of virus, and in concentration of 10 μg/ml neutralized 10 EDI_{100}. The other bromo- or chlorostyryl derivatives (IVa, d, f, g, h, i, and k) were less active (Table 2).

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ADAMANTYLPHENOLS.

II. SYNTHESIS AND ANTIVIRAL ACTIVITY OF BROMINATED HYDROQUINONES AND QUINONES CONTAINING AN ADAMANTYL SUBSTITUENT

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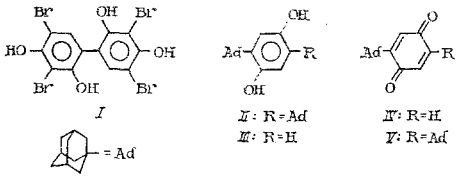
In continuation of a search for antiviral drugs among adamantyl analogs [1] of the drug tebrofen (I) [2], we have studied the synthesis and antiviral activities of adamantylhydroquinones, adamantylquinones, and their bromination products.



I

II: R = Ad
III: R = H

IV: R = H
V: R = Ad

High levels of antiviral activity have been found in hydroquinone itself, and in a number of alkyl, aryl, and halo-derivatives of hydroquinone and p-benzoquinone [3]. Adamantane derivatives, among which are the well-known antiviral drugs remantadine and amantadine, are also of interest in the search for compounds possessing antiviral activity [4]. It therefore appeared to us to be of interest to synthesize compounds which contained in a single molecule an adamantane residue and a hydroquinone or p-benzoquinone residue.

In the adamantylation of hydroquinone, it would be expected that the latter would be less reactive to electrophilic substitution than phenol or resorcinol. It was in fact found to be impossible to synthesize adamantylhydroquinone by boiling adamantyl bromide with hydroquinone in benzene, i.e., under conditions in which phenol and resorcinol are readily adamantylated [1]. Although when the reaction was carried out in molten hydroquinone gaseous hydrogen bromide was evolved and TCL showed that the desired product had been formed, it was not found possible to isolate it in the pure state from the complex reaction mixture. Direct adamantylation of hydroquinone was achieved by reaction of adamantyl bromide with hydroquinone in the presence of trifluoroacetic acid (TFA) [5]. Examination of the conditions for the adamantylation of hydroquinone in the presence of TFA showed that, depending on the ratios of the reagents and TFA, either diadamantylhydroquinone (II) was formed, or a mixture of this compound with adamantylhydroquinone (III), which could be separated by fractional crystallization. Diadamantylhydroquinone was obtained in 76% yield with an adamantyl bromide:hydroquinone:TFA ratio of 3:1:13. Changing this ratio to 1:5:5.25 gave a mixture (57 and 42%) of mono- and diadamantylhydroquinones in an overall yield of 71.2%, calculated on the adamantyl bromide taken. We were unable to achieve preferential formation of adamantylhydroquinone by changing the ratios of the reactants and catalyst, perhaps as a result of the high rate of adamantylation of adamantylhydroquinone in comparison with that of hydroquinone

Quinones containing one or two adamantyl residues were obtained by oxidation of the corresponding hydroquinones. Diadamantylhydroquinone in the presence of potassium periodiate was oxidized to the corresponding quinone (V) in 60% yield, but this oxidant was unsuitable for the synthesis of adamantylquinone (IV). The latter was obtained in 73% yield by using sodium dichromate in sulfuric acid. The use of silver oxide as oxidant afforded the quinone (IV) in quantitative yield. Reaction of (III) with bromine either in carbon tetrachloride

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0091-150X/82/1602-0127$07.50