SYNTHESIS AND STUDY OF BIOLOGICAL ACTIVITY OF SUBSTITUTED 4-AMINO-2-STYRYLQUINAZOLINES

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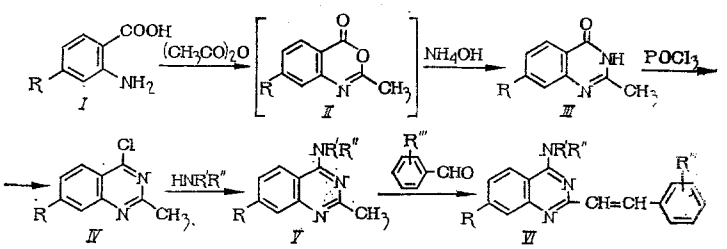
It has been shown by research of Soviet scientists [1] that 2-styrylquinoline derivatives, obtained by condensation of the corresponding substituted 4-aminoquinaldines with aromatic or heterocyclic aldehydes, possess high and diverse chemotherapeutic activity.

The original domestic preparations of trichomonacid [1, 2] [2-(p-nitrostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinoline triphosphate] and aminoquinol [1, 3] [2-(o-chlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline triphosphate] have found use in medical practice as media for curing trichomonad illnesses and lambliasis. These medical preparations have been produced for more than 15 years by the pharmaceutical chemical industry of the USSR. Subsequently it was established that compounds of the 2-styrylquinoline series display not only an expressed antiprotozoic, antimalarial, and antitubercular effect, but also possess antiinflammatory [4] and antiviral [5-7] activity.

In addition, the nearest aza analogs of 4-amino-2-styrylquinolines (4-amino-2-styrylquinazoline derivatives containing a pyrimidine ring in the heterocyclic system instead of a pyridine ring) have not been described in the literature before publication of our research.*



Ia—IVa R=H; Ib—IVb R=Cl

Anthranilic (Ia) or 4-chloroanthranilic (Ib) acid was transformed by the described method [10] of boiling for 3 h with acetic anhydride to 2-methylbenzoxazinones-4 (II), which without separation were transformed by heating for 1 h with boiling 25% aqueous ammonia solution to the corresponding 2-methylquinazolones-4 (III) in a yield of 82-85%, calculated on (I). Transformation of (IIIa) with phosphorus oxy-

*The method proposed in this paper of obtaining 4-amino-2-styrylquinazolines is protected by an author's certificate [8]. Slightly later the American firm Squibb took out a patent in Switzerland [9] on preparing substituted 4-amino-2-styrylquinazolines by another method: reaction of 4-chloro-2-styrylquinazolines with amines.

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TABLE 1. Substituted 4-Amino-2-methylquinazolines

Compound	R	NR'R''	Yield (%)	mp (deg)[1]	Found (%)				Empirical formula	Calculated (%)			
					C	H	Cl	N		C	H	Cl	N
Va	H	$N(C_2H_5)_2$	100	60—2[2]	72,92	7,85	—	19,85	$C_{13}H_{17}N_3$	72,52	7,96	—	19,52
Vb	H	NHC_6H_5	100	161—2,5	76,57	5,83	—	17,65	$C_{15}H_{13}N_3$	76,57	5,57	—	17,86
				286—7 (dec)	—	—	12,91	15,19	$C_{15}H_{13}N_3 \cdot 2HCl$	—	—	13,07	15,46
Vc	H	$NHCH_2C_6H_5$	96	186—7	77,45	6,21	—	16,96	$C_{16}H_{15}N_3$	77,08	6,06	—	16,86
				235—6	—	—	12,27	14,63	$C_{16}H_{15}N_3 \cdot HCl$	—	—	12,40	14,70
Vd	H	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	77	109—110	71,87	9,28	—	18,85	$C_{18}H_{28}N_4$	71,96	9,39	—	18,65
				177—8	36,23	6,33	—	9,58	$C_{18}H_{28}N_4 \cdot 3H_3PO_4$	36,37	6,27	—	9,43
Ve	Cl	$N(C_2H_5)_2$	81	220—1[4]	54,73	6,00	24,72	14,48	$C_{13}H_{16}ClN_3 \cdot HCl$	54,55	5,99	24,78	14,68
Vf	Cl	$N(CH_2)_5$	89	243—4[4]	56,03	5,70	23,60	14,29	$C_{14}H_{16}ClN_3 \cdot HCl$	56,38	5,75	23,78	14,09
Vg	Cl	NHC_6H_5	87	197—8	66,64	4,66	12,93	15,46	$C_{15}H_{12}ClN_3$	66,79	4,48	13,15	15,58
				306—7	—	—	23,06	14,21	$C_{15}H_{12}ClN_3 \cdot HCl$	—	—	23,16	13,72
Vh	Cl	$NHCH_2C_6H_5$	95	165—6	67,55	5,21	12,16	14,74	$C_{16}H_{14}ClN_3$	67,72	4,97	12,50	14,81
				287—8	—	—	22,18	13,13	$C_{16}H_{14}ClN_3 \cdot HCl$	—	—	22,15	13,12
Vi	Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	82	140—1	64,72	8,02	10,30	17,25	$C_{18}H_{27}ClN_4$	64,75	7,84	10,62	16,79
					34,45	5,76	5,54	8,78	$C_{18}H_{27}ClN_4 \cdot 3H_3PO_4$	34,37	5,77	5,64	8,91

1) Bases (Vc) and (Vg) were recrystallized from benzene, base (Vh) was recrystallized from acetone, and the remaining bases were recrystallized from heptane.
2) bp 152-153 deg (1 mm).
3) Base, mp 47-48 deg (from heptane), bp 161-162 deg (4 mm).
4) Base, mp 58-59 deg (from heptane), bp 177-178 deg (4 mm).
5) Found, %: P 15.41. Calc. %: P 15.63.
6) Found, %: P 14.64; Calc. %: P 14.78.

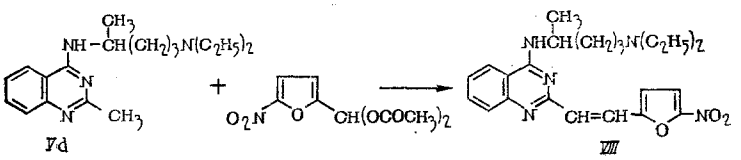
chloride in the presence of dimethylaniline to 2-methyl-4-chloroquinazoline (IVa) is described in the literature [11]. We obtained 2-methyl-4,7-dichloroquinazoline (IVb) by an analogous method.

During the study of chemical properties of (IV) the exclusively high mobility was encountered of the chlorine atom in position 4 of these compounds during their reaction with various nucleophilic agents. Thus, (IVb) upon recrystallization from absolute ethanol, is transformed quantitatively to 2-methyl-4-ethoxy-7-chloroquinazoline hydrochloride (VII). The high mobility of the chlorine atom in position 4 of compounds (IV) upon their reactions with various aliphatic, aromatic, and aliphatic-aromatic amines gave high yields of substituted 4-amino-2-methylquinazolines (V) (Table 1). Therefore, in contrast to the method described almost simultaneously with us in the Swiss patent [12], where analogous reactions are carried out at high temperatures, with lower amines, and under pressure, the indicated transformations could be carried out in boiling benzene with a time of the process of 3 h (only in the case of δ-diethylamino-α-methylbutylamine was it found necessary to increase the reaction time to 7 h to reach optimal yields).

Conditions of carrying out the final step of the synthesis, reaction of compounds (V) with aromatic or heteroaromatic aldehydes, are determined by the character of components introduced into the reaction. A wide variation of parameters of the process (reagent ratios, type of catalysts, temperature, time of reaction, etc.) using thin-layer chromatography for control made it possible to propose three general methods of synthesizing substituted 4-amino-2-styrylquinazolines (VI) (Table 2). A mixture of acetic anhydride and anhydrous sodium acetate is used as the catalyst in methods A and B; piperidine is the catalyst in method C. Method C is used in those cases when the initial compounds are acidophobic or form stable reaction products with acetic anhydride [compounds (VIm) and (VIII)]. In method A, used in the case of compounds (V) having a δ-diethylamino-α-methylbutylamino group, due to which unstable reaction products are evidently formed with aldehydes and the latter are partially removed from the reaction sphere [13], a large excess of aldehyde – a threefold amount in comparison with (V) – is used. This requires separation of excess aldehyde upon further treatment of the hydrochloride salt. In method B, suitable for compounds (V), having residues of simpler amines in position 4, not reacting with aldehydes, such an excess of the carbonyl component is not required and the (V)–aldehyde ratio amounts to 1:1.5. This simplifies further separation of styrylquinazoline derivatives as the hydrochlorides.

From PMR spectral data (taken on a JNM-4H-100 instrument at 100 MHz in various solvents: CD_3OD, CD_3COCD_3, $(CD_3)_2SO$, internal standard tetramethylsilane), all of the synthesized compounds (VI) have the trans configuration of substituents at the double bond in the styryl portion of the molecule; J = 16 Hz for the corresponding protons.

Analogously to compounds (VI), from (Vd) and 5-nitrofurfural diacetate by method C was also obtained 2-[β-(5'-nitrofuryl-2')vinyl]-4-(δ-diethylamino-α-methylbutylamino)quinazoline (VIII).



Vd VIII

Study of salts of compounds (VI) for bacteriostatic activity was carried out in relation to 10 forms of inducers of acute bacterial infections (Staphylococcus aureus, Streptococcus haemolitycus, E. coli, S. typhi abdominalis, Sh. dysenteriae Flexneri, Corynebacterium diphtheriae PW8, Pseudomonas aeruginosa, Proteus vulgaris, Bacillus antracoides, Mycobacterium tuberculosis strain H-37Rv), and five forms of pathogenic fungi (Microsporon lanosum, Trichophyton gypseum, Achorion schönleini Actinomyces albus, Candida albicans).

It was established that compounds (VIf, g, h, k) possess expressed bacteriostatic activity in vitro in relation to Gram-positive bacteria and do not react with Gram-negative bacteria. Compounds (VIg, h) are highly active in relation to tuberculosis mycobacteria; the minimum tuberculostatic concentration of these materials is equal to 0.25 and 0.5 μg/ml, respectively. Compound (VIk) also possesses expressed activity in relation to tuberculosis mycobacteria, the minimum tuberculostatic concentration of which is equal to 4 μg/ml; with respect to pathogenic fungi a weak activity in in vitro experiments was shown by (VIg, h, k).

The antiinflammatory effect of compounds (VI) was studied in addition on noninbred white rats of both sexes during acute exudative and chronic proliferative inflammation. The exudative inflammation was produced by introduction of a 0.2% silver nitrate solution in the pleural (0.3 ml) or abdominal (1 ml) cavity.

TABLE 2. Substituted 4-Amino-2-styrylquinazolines

Compound	R	NR′R″	R‴	Yield	mp (deg)*	Found (%)				Empirical formula	Calculated (%)			
						C	H	Cl	N		C	H	Cl	N
VIa	Cl	$N(C_2H_5)_2$	p -Cl	66	118—9 (M)	64,44	5,08	18,78	11,08	$C_{20}H_{19}Cl_2N_3$	64,52	5,14	19,05	11,29
					245—6	55,95	5,22	24,91	9,74	$C_{20}H_{19}Cl_2N_3 \cdot HCl \cdot H_2O$	56,28	5,20	24,92	9,85
VIb	Cl	$N(C_2H_5)_2$	p -NO_2	55	160—1 (E)	62,90	5,06	9,33	14,43	$C_{20}H_{19}ClN_4O_2$	62,74	5,00	9,26	14,64
					267—8 (dec.)	—	—	16,53	13,12	$C_{20}H_{19}Cl_4NO_2 \cdot HCl$	—	—	16,91	13,36
VIc	Cl	$N(CH_2)_5$	p -Cl	52	148—9 (E)	65,50	5,01	18,43	10,69	$C_{21}H_{19}Cl_2N_3$	65,63	4,98	18,45	10,94
					271—2	—	—	25,19	9,89	$C_{21}H_{19}Cl_2N_3 \cdot HCl$	—	—	25,28	9,99
VId	Cl	$N(CH_2)_5$	p -NO_2	59	174—5 (E—EA)	63,75	4,86	8,81	14,21	$C_{21}H_{19}ClN_4O_2$	63,88	4,85	8,98	14,19
					274—5	—	—	16,06	12,83	$C_{21}H_{19}ClN_4O_2 \cdot HCl$	—	—	16,44	12,99
VIe	Cl	NHC_6H_5	p -NO_2	42	242—3 (EA)	65,45	4,02	—	13,68	$C_{22}H_{15}ClN_4O_2$	65,59	3,75	—	13,91
VIf	Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	p -Cl	48	249—250	45,76	5,80	10,75	8,93	$C_{25}H_{30}Cl_2N_4 \cdot 2H_3PO_4$†	45,96	5,55	10,85	8,57
VIg	Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	o -Cl	52	149—150 (C)	—	—	15,23	12,29	$C_{25}H_{30}Cl_2N_4$	—	—	15,50	12,25
					237—8	45,80	5,69	—	—	$C_{25}H_{30}Cl_2N_4 \cdot 2H_3PO_4$‡	45,96	5,55	—	—
VIh	Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	p -NO_2	54	119—120 (H)	—	—	7,33	14,87	$C_{25}H_{30}ClN_5O_2$	—	—	7,58	14,96
					269—270	55,40	5,85	19,32	12,73	$C_{25}H_{30}ClN_5O_2 \cdot 2HCl$	55,51	5,96	19,66	12,96
VIi	H	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	p -CH_3O	33	131—2 (C)	74,58	7,92	—	13,27	$C_{26}H_{34}N_4O$	74,60	8,19	—	13,39
					277—8	—	—	14,41	11,29	$C_{26}H_{34}N_4O \cdot 2HCl$	—	—	14,43	11,40
VIj	H	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	p -Cl	50	109—110 (H)	70,80	7,42	8,31	13,04	$C_{25}H_{31}ClN_4$	70,97	7,40	8,38	13,25
					223—4 (AN)	50,53	4,40	4,0	15,72	$C_{25}H_{31}ClN_4 \cdot 2C_6H_3N_3O_7$	50,43	4,24	4,03	15,89
					83—2	54,85	5,98	—	6,64	$C_{25}H_{31}ClN_4 \cdot 2C_6H_8O_7$ **	55,05	5,88	—	6,94
VIk	H	$NHCH(CH_2)_3N(C_2H_5)_2$	o -Cl	42	240—1 (I)	—	—	21,44	11,30	$C_{25}H_{31}ClN_4 \cdot 2HCl$	—	—	21,15	11,45
VIl	H	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	p -NO_2	45	269—270	56,38	6,68	13,11	12,83	$C_{23}H_{31}N_5O_2 \cdot 2HCl \cdot 1^1/_2H_2O$	56,27	6,80	13,31	13,12
VIm	Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	p -OH, m-CH_2O	28	238—240	43,50	6,46	5,28	7,88	$C_{26}H_{33}ClN_4O_2 \cdot 2H_3PO_4 \cdot 3H_2O$	43,43	6,31	4,93	7,79

*The crystallization solvent is indicated in parentheses: M is methanol, E is absolute ethanol, EA is ethyl acetate, E—EA is a mixture of equal volumes of absolute alcohol and ethyl acetate, C is cyclohexane, H is heptane, AN is acetonitrile, I is isopropanol.

†Found, %: P 9.29, Calc., %: P 9.48.

‡Found, %: P 9.60, Calc., %: P 9.48.

**Citrate.

After 6 h the exudate was pumped out from the corresponding cavity, the amount of which was an indicator of the intensity of the inflammatory process. Compounds (VI) were introduced 30 min before introduction of silver nitrate. Compounds (VIm) and (VI *l*) were injected subcutaneously; all remaining preparations of (VI) were introduced through a probe into the stomach. The dose amounted to 100 mg/kg.

Chronic inflammation was produced by implantation of sterile felt beads under the skin of the stomach in the animals. The weight of the formed granule served as an index of the inflammatory reaction. Weighing of the granule was carried out 7 days after implantation. During investigation of the effect on chronic inflammation, compounds (VI) were introduced 30 min before the operation and one time per day during the next 6 days. Introduction was achieved by the same method and under the same conditions as during acute exudative inflammation. The highest antiinflammatory activity was shown by compounds (VIa, m, *l*). They are only insignificantly inferior to phenylbutazone in all indices characterizing the antiinflammatory effect. It is interesting to note that the highest chemotherapeutic activity was displayed in 4-amino-2-styrylquinazolines having the δ-diethylamino-α-methylbutylamine chain in position 4 and p-nitro- and o- or p-chloro substituents in the styryl portion of the molecule [compounds (VIf, g, h, k)]. Analogous 4-diethylamino- (VIa, b), 4-piperidino- (VIc, d), and 4-phenylamino derivatives (VIe) of 2-styrylquinazolines did not have a significant chemotherapeutic effect.

On the other hand, no special effect of the 4-δ-diethylamino-α-methylbutylamino group was displayed in relation to the inflammatory process and the highest activity in experiments was displayed by compound (VIa), a derivative of 4-diethylamino-2-styrylquinazoline.

A further study of the connection between the structure and biological effect of substituted 4-amino-2-styrylquinazolines is being continued.

EXPERIMENTAL

2-Methyl-4,7-dichloroquinazoline (IVb). A mixture of 14.2 g of (IIIb), 21.8 g of dimethylaniline, 7.5 g of freshly distilled phosphorus oxychloride, and 250 ml of anhydrous benzene was boiled with stirring for 5 h. The benzene solution was decanted from the tarry residue, washed with water, a 20% sodium hydroxide solution, an additional two times with water, dried with magnesium sulfate, and evaporated; the dimethylaniline was distilled in vacuum.

The crystallized residue was triturated with a small amount of petroleum ether and 10 g of technical (IVb) was filtered, mp 92-94 deg. After recrystallization from 150 ml of petroleum ether 8.5 g (54%) of (IVb) was obtained, mp 95-96 deg: pale-yellow crystals; soluble in ether, acetone, benzene, chloroform, ethyl acetate, alcohols; less soluble in petroleum ether, heptane; and insoluble in water. Found, %: C 51.00; H 3.06; Cl 32.92; N 13.09; $C_9H_6Cl_2N_2$. Calc., %: C 50.75; H 2.85; Cl 33.24; N 13.16.

2-Methyl-4-ethoxy-7-chloroquinazoline (VII). We heated 0.5 g of (IVb) to solution (~15 min) in 10 ml of absolute ethanol. Upon cooling the solution, crystals of the hydrochloride of (VII) separated. Yield was 0.61 g (quantitative): colorless crystals of mp 266-267°. The material is poorly soluble in water and alcohols, insoluble in ether, benzene, chloroform, acetone, and ethyl acetate. Found, %: Cl 27.11; N 10.50. $C_{11}H_{11}ClN_2O \cdot HCl$. Calc., %: Cl 27.37; N 10.81.

General Method of Preparing Substituted 4-Amino-2-methylquinazolines (V). A mixture of 26 mmoles of (IV) and 52 mmoles of the corresponding amines was boiled in 150 ml of anhydrous benzene for 3 h (in the case of δ-diethylamino-α-methylbutylamine it was necessary to increase the reaction time to 7 h). The cooled reaction mass was treated with 70 ml of a 20% sodium hydroxide solution and extracted with benzene. The benzene solution was washed with water, dried with potassium carbonate, and evaporated in vacuum; the residue was subjected to vacuum distillation [in the case of (Va, e, f)] or recrystallized. The corresponding hydrochloric or phosphoric acid salts of compounds (V) were obtained in virtually quantitative yields by addition to the ether solution of base of an alcoholic hydrogen chloride solution or an ether phosphoric acid solution.

Constants, yields, and analyses of the synthesized compounds (bases and salts) are given in Table 1. All bases are colorless, crystalline materials, poorly soluble in heptane and petroleum ether, highly soluble in other usual organic solvents [(Vc, g) are poorly soluble in benzene, (Vh) is poorly soluble in benzene, ethyl acetate, and acetone], and virtually insoluble in water. Salts presented in Table 1 are colorless crystals, soluble in water [with the exception of (Vf)] and alcohols, insoluble in nonpolar organic solvents.

General Method of Synthesizing Substituted 4-Amino-2-styrylquinazolines (VI). Method A. A mixture of 23 mmoles of (V), 70 mmoles of aldehyde, 35 mmoles (2.9 g) of anhydrous sodium acetate, and 30 ml of acetic anhydride was heated for 6-8 h with mixing at a temperature of 148-152 deg. After cooling to 85 deg the reaction mass was poured into 150 ml of 8% hydrochloric acid heated to 80-85 deg, and the excess aldehyde was extracted with ether. Then the hydrochloric acid solution was made basic with 20% aqueous potassium carbonate solution and the separated base was extracted with ether. The ether extract was dried with potassium carbonate and evaporated. The styryl-derivative base was either subjected directly to purification by recrystallization from heptane (VIh) or was subsequently transformed to the salt, differing in solubility from the corresponding salts of the initial compounds (V); the free base was separated from the purified salt by extraction with ether, and was then recrystallized from the solvents presented in Table 2. The salts and solvents used were: picrate in hot methanol for (VIi), picrate in acetonitrile for (VIj), phosphate in methanol for (VIf), m-hydrochloride in isopropanol for (VIk). All substituted 2-styryl-4-(δ-diethylamino-α-methylbutylamino)quinazolines with the exception of (VIm) were obtained by the indicated method.

Method B. A mixture of 23 mmoles of (V), 35 mmoles of aldehyde, 23 mmoles of anhydrous sodium acetate, and 30 ml of acetic anhydride was heated for 5 h with mixing and a temperature of 148-152 deg. After cooling to 85 deg the reaction mass was poured into 150 ml of 8% hydrochloric acid heated to 80-85 deg. The precipitate of (VI) hydrochloride, separating out upon further cooling, was filtered, washed with water, and transformed to the base by treatment with a 20% aqueous potassium carbonate solution. The liberated base was extracted with ether, and after removal of ether, recrystallized from the appropriate solvent (solvents are presented in Table 2). Base (VIa) before crystallization was purified additionally by column chromatography with aluminum oxide; elution was with benzene.

All styrylquinazolines having amine residues in position 4 differing from δ-diethylamino-α-methylbutylamine were synthesized by the indicated method.

Method C. A mixture of 5 g of (Vi), 6.9 g of vanillin, and 30 drops of freshly distilled piperidine was heated for 4 h with stirring at 125-130 deg. The reaction mass was transferred to a chromatographic column (75×2 cm) containing benzene-washed aluminum oxide (250 g, Grade II activity). Elution with 270 ml of ethyl acetate gave 1.7 g of initial (Vi), after which 8 g of a mixture consisting mainly of (Vi) and vanillin was eluted with methanol.

To separate vanillin, the product was dissolved in 50 ml of conc. hydrochloric acid and vanillin was extracted with benzene. The hydrochloric acid solution was neutralized with 40% sodium hydroxide solution to pH 6.0 and made basic by addition of a buffer solution of pH 8.0. At pH 8.0 (VIm) was extracted with chloroform, the solvent was distilled, and the residue was dried by two additions of anhydrous benzene with subsequent distillation. Then the material (4.5 g) was dissolved in anhydrous acetone, the solution was filtered, and orthophosphoric acid was added. The precipitated crystals of (VIm) diphosphate were filtered and washed with methanol and acetone.

In all cases the course of reaction and purity of obtained compounds (VI) were controlled by the method of thin-layer chromatography on aluminum oxide of Grade II activity; Dragendorff reagent or UV light was used to develop the chromatographs. Only one spot remained on the thin-layer chromatograms after purification of the final reaction products of (VI), and spots of side products and starting compounds (V) were absent. Mobile phases used for thin-layer chromatography and R_f of final and initial (in brackets) products are presented below: (VIa), benzene, 0.66 [(Ve) 0.22]; (VIb), benzene–ether (3:1), 0.71 [(Ve) 0.55]; (VIc), benzene–ether (3:1), 0.68 [(Vf) 0.55]; (VId), benzene–ether (6:1), 0.72 [(Vf) 0.41]; (VIe), benzene–ether (3:1), 0.02 [(Vg) 0.55]; (VIf) benzene–ethyl acetate (1:1), 0.42 [(Vi) 0.31]; (VIg), ether–ethyl acetate (3:1), 0.75[(Vi) 0.64]; (VIh), benzene–methanol (9:1), 0.85 [(Vi) 0.74]; (VIi), chloroform, 0.75 [(VIi) 0.15]; (VIj), ethyl acetate, 0.71[(Vd) 0.52]; (VIk), ethyl acetate, 0.70 [(Vd) 0.52]; (VI*l*), ethyl acetate, 0.61 [(Vd) 0.52]; (VIm), methanol, 0.70 [(Vi) 0.99].

Bases (VI) are crystalline materials and of a yellow to intensely yellow color (as a function of the character of substituents), virtually insoluble in water, highly soluble in chloroform, acetone, benzene, and poorly soluble in heptane and cyclohexane. Bases (VIf-j) are highly soluble in ether, ethyl acetate, and alcohols; upon going to bases (VIa-e) the solubility of compounds in ether, ethyl acetate, and alcohols decreases significantly. To transform the synthesized compounds (VI) as the corresponding salts to solutions of bases (VIa, c, i, k) in ether, (VIb, d) in acetone, (VIh, *l*) in isopropanol is added an alcoholic citric acid solution and to solutions of (VIf, g) in methanol is added a methanol orthophosphoric solution. The obtained salts are yellow crystalline materials, soluble in water, less soluble in alcohols, and sparingly

soluble in ether, acetone, ethyl acetate.

Constants, yields, and analyses of the synthesized compounds (VI) are presented in Table 2.

2-[β-5'-Nitrofuryl-2'-vinyl]-4-(δ-diethylamino-α-methylbutylamino)quinazoline (VIII). A mixture of 6 g of (Vd), 14.6 g of 5-nitrofurfural diacetate, 2.8 g of anhydrous sodium acetate, and 30 ml of acetic anhydride was heated for 6 h with stirring and a temperature of 120 deg. The acetic anhydride was distilled, the reaction mass was poured into 150 ml of 6% hydrochloric acid solution heated to 80-85 deg. After cooling, 30 ml of conc. hydrochloric acid was added and unreacted 5-nitrofurfural diacetate was extracted with benzene. The hydrochloric acid solution was made basic with 20% potassium carbonate solution and extracted with ether, the solvent was distilled, and the residue (6.3 g) was recrystallized from cyclohexane. We obtained 2.3 g (27%) of (VIII), mp 116-118 deg. Yellow crystals, soluble in ether, acetone, chloroform, benzene, alcohols; less soluble in heptane, cyclohexane; insoluble in water. Found, %: C 65.36; H 6.73; N 16.28. $C_{23}H_{29}N_5O_3$. Calc., %: C 65.23; H 6.90; N 16.54.

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