SYNTHESIS AND CHEMOTHERAPEUTIC INVESTIGATION OF SUBSTITUTED 2-STYRYL-4-AMINO-6-METHOXYQUINAZOLINES

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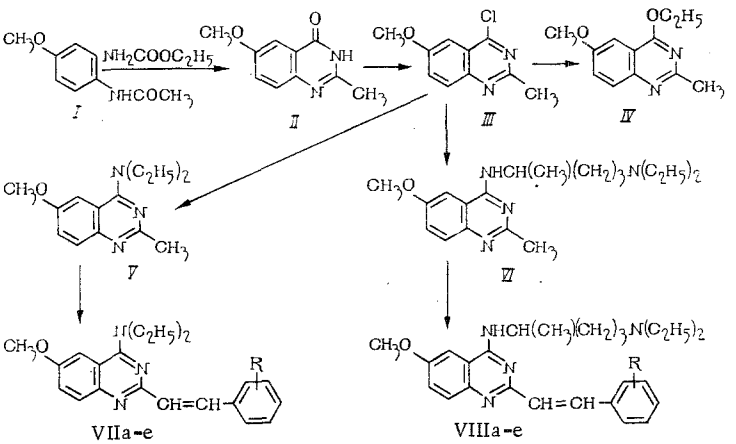
In continuation of our earlier investigations into structure–activity relationships in 4-amino-2-styrylquinazolines, it was thought desirable to change from benzene ring unsubstituted and 7-chloro derivatives to the 6-methoxy derivatives. The chemotherapeutic activity of quinolines is known to be enhanced by a change of this nature.

The 2-styryl-4-amino-6-methoxyquinazolines were synthesized by the following route:



R = o-Cl (a); n-Cl (b); n-Br (c); o-NO_2 (d); n-NO_2 (e).

The starting material employed was 2-methyl-6-methoxy-4-quinazolone (II), obtained by reaction of N-acetyl-p-anisidine (I) with urethane in presence of phosphorus pentoxide. Recrystallization of the quinazolone II from water and alcohol raised its mp 20° above the literature value [1]. The quinazolone II was converted into the corresponding 2-methyl-4-chloro-6-methoxyquinazoline (III) by treatment with phosphoryl chloride in the presence of dimethylaniline, as in the previously described conversion of 2-methyl-7-chloro-4-quinazolone into 2-methyl-4,7-dichloro-quinazoline. The yield of the chloroquinazoline III was 88%. The chlorine atom in the 4 position of III was much less reactive than in the analogous 2-methyl-4-chloroquinazoline (IX) and 2-methyl-4,7-dichloroquinazoline (X). Although chlorine in the 4 position in IX and X was completely replaced on recrystallization from alcohol, in III boiling in alcohol for at least an hour was needed. A similar reduction in reactivity is found in the reaction of III with amines (diethylamine and δ-diethylamino-α-methyl-butylamine), when it was necessary to increase the reaction time from 7 to 16-30 h. More severe conditions than in the case of the similar reactions of N-substituted 2-methyl-4-aminoquinazolines and 2-methyl-4-amino-7-chloroquinazolines with aromatic aldehydes were also required with substituted 2-methyl-4-amino-6-methoxyquinazolines (V and VI). The best results were obtained in the synthesis of 2-styryl-4-amino-6-methoxyquinazolines

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(VII and VIII) by using sodium acetate and acetic anhydride as catalysts and carrying out the reaction for 7-10 h at 150-155° (for VIII) and 168-172° (for VII).

The hydrochlorides of VII and VIII were examined for antimicrobial activity in nine species of organisms causing acute bacterial infections (Staphylococcus aureus, Streptococcus haemolyticus, Escherichia coli, Salmonella typhiabdominalis, Shigella dysenteriae Flexneri, Corynebacterium diphtheriae PW N 8, Pseudomonas aeruginosa, Proteus vulgaris, and Bacillus antracoides), Mycobacterium tuberculosis H-37Rv, and five species of pathogenic fungi (Microsporon lanosum, Trichlophyton gypseum, Achorion schonleini, Actinomyces albus, and Candida albicans). It was shown that high bacteriostatic activity towards Gram-positive bacteria was shown by VIIIa and the previously synthesized 2-(3'-methoxy-4'-hydroxystyryl)-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinazoline (minimum inhibitory concentration 4-30 μg/ml), towards Mycobacterium tuberculosis by VIIa VIIb, VIIIa, and VIIId (minimum inhibitory concentration 0.5-8 μg/ml). The growth of pathogenic fungi was only suppressed by these compounds in high concentrations.

The activity of 2-(4'nitrostyryl)-4-(δ-diethylamino-α-methylbutylamino)quinazoline was further examined in vitro against pathogenic Protozoa. It was shown to inhibit the growth of Trichomonas vaginalis at a concentration of 4 μg/ml, and Entamoeba histolytica at 1 μg/ml. This compound had antilamblia activity in experimental lambliosis in white mice. An internal dose of 500 mg/kg for five days resulted in complete recovery, and a dose of 250 mg/kg gave a partial cure.

EXPERIMENTAL

2-Methyl-6-methoxy-4-quinazolone (II). A mixture of 26.4 g (160 mmole) of p-acetanisidine, 18 g (202 mmole) of urethane, 105 g of phosphorus pentoxide, and 120 ml of anhydrous xylene was stirred for 10 min, then heated. At a temperature of ~120° the mixture became difficult to stir, and the stirrer was therefore disconnected, and heating continued at 150° for 3 h, the mixture being agitated at intervals. The reaction mixture was cooled in ice, and 240 ml of water was added. The acidic aqueous solution was extracted with benzene to remove nonbasic materials, and it was then basified with sodium carbonate to pH 5.0-6.0. The tarry precipitate was filtered off, and basification continued with a 50% solution of potassium carbonate to pH 9.0. The precipitated quinazolone II was filtered off, washed with water, and recrystallized from water and absolute alcohol to give colorless crystals, mp 277-278° (lit. [1] mp 257°). The compound is sparingly soluble in water and the common organic solvents. Yield 17.7 g (53%). Found, %: C 63.15; H 5.28; N 14.62. $C_{10}H_{10}N_2O_2$. Calculated, %: C 63.14; H 5.30; N 14.73.

2-Methyl-4-chloro-6-methoxyquinazoline (III). Quinazoline II (4 g, 20.8 mmole), 2.5 g (16.3 mmole) of freshly distilled phosphoryl chloride, 6.7 g (55.5 mmole) of dimethylaniline, and 120 ml of dry benzene were boiled for 8 h. The resulting solution was washed twice with 50 ml of water, then with 30 ml of 20% aqueous sodium hydroxide, and finally twice with 30 ml of water. The benzene layer was dried over potassium carbonate, evaporated, the excess of dimethylaniline removed under reduced pressure, and the residue recrystallized from heptane. There was obtained 3.9 g (88%) of the chloroquinazoline III as bright yellow crystals, mp 127-128°, readily soluble in ether, benzene, acetone, ethyl acetate, chloroform, and alcohols, moderately soluble in heptane and hexane, and insoluble in water. Found, %: C 57.61; H 4.37; N 13.48; Cl 16.91. $C_{10}H_9ClN_2O$. Calculated, %: C 57.56; H 4.35; N 13.43; Cl 16.99.

2-Methyl-4-ethoxy-6-methoxyquinazoline (IV). The chloroquinazoline III (0.5 g, 2.4 mmole) was boiled for 1 h with 5 ml of absolute ethanol. The resulting solution was evaporated, and the residual hydrochloride of the methoxyquinazoline IV was filtered off, yield 0.5 g (82%). Colorless crystals, mp 270-271°, readily soluble in methanol and water, moderately soluble in acetone and ethanol, and insoluble in ether. Found, %: C 56.38; H 5.96; N 10.99; Cl 13.75. $C_{12}H_{14}N_2O_2 \cdot HCl$. Calculated, %: C 56.57; H 5.93; N 11.00; Cl 13.92.

2-Methyl-4-diethylamino-6-methoxyquinazoline (V). A mixture of 8.5 g (40.6 mmole) of the chloroquinazoline III and 9 g (123 mmole) of freshly distilled diethylamine was boiled for 30 h in 350 ml of benzene. The mixture was treated with 50 ml of a 20% solution of sodium hydroxide, and the benzene layer separated, washed twice with water, and dried over potassium carbonate. The benzene was removed under reduced pressure, the residue dissolved in dry acetone, and the hydrochloride of V was precipitated by adding alcoholic hydrogen chloride to give 9.1 g (83%) of colorless crystals, mp 250-251°. The compound was readily soluble in water, alcohols, and chloroform, moderately soluble in acetone, and insoluble in ether. Found, %: C 59.65; H 6.94; N 14.83; Cl 12.49. $C_{14}H_{19}N_3O \cdot HCl$. Calculated, %: C 59.67; H 7.15; N 14.91; Cl 12.59.

2-Methyl-4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinazoline (VI). A mixture of 8.4 g (25.4 mmole) of the chloroquinazoline III and 19.1 g (121 mmole) of δ-diethylamino-α-methylbutylamine was boiled

TABLE 1. Substituted 2-Styryl-4-amino-6-methoxyquinazolines (VII and VIII) and Their Hydrochlorides

Compound	Melting point* (deg)	Yield (%)	Found (%)					Molecular formula	Calculated (%)				
			C	H	N	Cl (Cl^1)	Br		C	H	N	Cl (Cl^1)	Br
VIIa	105—6	59	68,46	6,00	11,55	9,88		$C_{21}H_{22}ClN_3O$	68,56	6,03	11,42	9,64	
Hydrochloride VIIa	263—4				10,38	17,56		$C_{21}H_{22}ClN_3O \cdot HCl$			10,39	17,54	
VIIb	115—6	61	68,43	6,12	11,42	9,47		$C_{21}H_{22}ClN_3O$	68,56	6,03	11,42	9,64	
Hydrochloride VIIb	242—3				10,16	16,68		$C_{21}H_{22}ClN_3O \cdot HCl \cdot H_2O$			9,95	16,79	
VIIc	112—3	60	61,52	5,45	10,36		19,36	$C_{21}H_{22}BrN_3O$	61,17	5,38	10,19		19,38
Hydrochloride VIIc	260—1				9,49	(7,87)	17,73	$C_{21}H_{22}BrN_3O \cdot HCl$			9,36	(7,90)	17,81
VIIe	129—30	57	66,62	5,86	14,90			$C_{21}H_{22}N_4O_3$	66,65	5,86	14,84		
Hydrochloride VIIe	244—5				13,05	8,41		$C_{21}H_{22}N_4O_3 \cdot HCl \cdot H_2O$			12,95	8,19	
VIIIa	266—7	18	57,29	6,85	10,28	(13,01)		$C_{26}H_{33}ClN_4O \cdot 2HCl \cdot H_2O$	57,37	6,84	10,22	(12,98)	
VIIIb	278—9	30	59,40	6,66	10,92	(13,46)		$C_{26}H_{33}ClN_4O \cdot 2HCl$	59,36	6,72	10,65	(13,48)	
VIIIc	165—6	45	63,11	6,92	11,22		16,15	$C_{26}H_{33}BrN_4O$	62,75	6,70	11,26		16,06
Hydrochloride VIIIc	277—8		54,00	6,18	9,73	(12,50)		$C_{26}H_{33}BrN_4O \cdot 2HCl \cdot {}^1/_2H_2O$	53,89	6,27	9,67	(12,24)	
VIIId	269—70	34	57,27	6,61	13,01	(12,77)		$C_{26}H_{33}N_5O_5 \cdot 2HCl_2 \cdot {}^1/_2H_2O$	57,23	6,66	12,83	(13,00)	
VIIIe	188—9	40	67,31	7,29	15,10			$C_{26}H_{33}N_5O_3$	67,36	7,18	15,11		
Hydrochloride VIIIe	278—9				12,59	12,85		$C_{26}H_{33}N_5O_3 \cdot HCl \cdot H_2O$			12,63	12,79	

*The hydrochlorides were crystallized from acetone, compounds VIIa-c, e, VIIIc and e from heptane, and compounds VIIIa, b, and d from alcohol.

for 16 h in 300 ml of benzene. The reaction mixture was treated with 30 ml of a 20% solution of sodium hydroxide. The benzene layer was separated, washed twice with water, dried over potassium carbonate, and evaporated to dryness under reduced pressure. The residue was recrystallized from heptane to give 11 g (83%) of VI as colorless crystals, mp 150-151°, readily soluble in ether, benzene, acetone, chloroform and alcohols, sparingly soluble in hexane and heptane, and insoluble in water. Found, %: C 69.26; H 9.14; N 17.02. $C_{19}H_{20}N_4O$. Calculated, %: C 69.03; H 9.17; N 16.95.

General Method of Preparation of Substituted 2-Styryl-4-amino-6-methoxyquinazolines VII and VIII. A mixture of 23.1 mmole of the substituted 2-methyl-4-amino-6-methoxyquinazoline V or VI, 69.5 mmole of the substituted benzaldehyde, 2.9 g (35 mmole) of anhydrous sodium acetate, and 30 ml of freshly distilled acetic anhydride was heated for 7-10 h at 150-155° (for VI) or 168-172° (for V), the course of the reaction being followed by thin layer chromatography on unbound grade II alumina (visualization by Dragendorff's reagent in UV light). When the reaction was complete, the hot mixture was poured into 100 ml of 8% hydrochloric acid at 80-85°, and to the cooled hydrochloric acid solution was added a further 50 ml of concentrated hydrochloric acid. The excess of aromatic aldehyde was extracted with ether, and the hydrochloric acid solution was basified with potassium carbonate, and the free base extracted with benzene. After removal of the benzene, the residue was purified to remove traces of the starting materials, methylquinazolines V and VI, from the styrylquinazolines VII and VIII. Purification was effected either by recrystallizing the free base twice from heptane (for stryryl-quinazolines VIIa-c and VIIIe) or by precipitating the styrylquinazoline as the hydrochloride (for VIIe and VIIIa-d) from the acetone solution, followed by recrystallization.

The constants, yields and analyses for the substituted 2-styryl-4-amino-6-methoxyquinazolines VII and VIII are given in Table 1.

All the substituted 2-styryl-4-amino-6-methoxyquinazolines VII and VIII as the free bases were bright yellow crystalline solids, readily soluble in ether, acetone, benzene, acetone, chloroform, and alcohols, moderately soluble in cyclohexane and heptane, and insoluble in water. The hydrochlorides were yellow crystalline solids, soluble in chloroform and alcohols, moderately soluble in acetone, and insoluble in ether.

LITERATURE CITED

1. T. Bhattacharyya, P. K. Bose, and J. N. Ray, J. Ind. Chem. Soc., 6, 279-287 (1929).