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Derivatives of 2-Styrylquinoline

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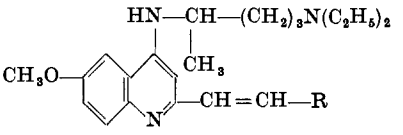
Derivatives of 4-aminoquinoline have, as is well known, considerable antimalarial activity. The first representative of this series, 4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinoline, obtained by one of us in collaboration with O. Y. Magidson in 1937[1] possessed antimalarial activity very similar to that of quinine.[2]

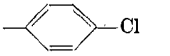
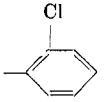
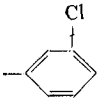
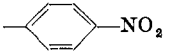
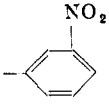
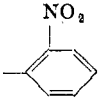
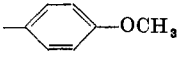
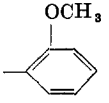
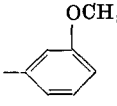
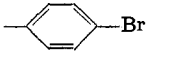
Later, 4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline (chloroquine)[3] was synthesized, which is even more active and can be used not only in malaria but also in the treatment of lupus erythematosus and of amœbal liver abscesses.

In contrast to the derivatives of 4-aminoquinoline, the corresponding derivatives of 4-aminoquinaldine have no antimalarial properties.[1] Thus, the introduction of a methyl group into the 2-position of the quinoline nucleus abolishes chemotherapeutic activity in these compounds. However, as it was shown by our studies, conversion of 4-aminoquinaldines to the corresponding 2-styrylquinolines re-established and even increased antimalarial properties. Furthermore, we observed that such 2-styrylquinoline derivatives have pronounced activity not only against protozoa but also against bacteria, actinomycetes and fungi. This latter observation prompted us to extend the investigation of compounds of this class and to synthesize series of derivatives of 6-methoxy- and 7-chloro-2-styrylquinolines, with different substituents in the styryl group and in position 4 of the quinoline nucleus. The compounds obtained are listed in Tables I, II, and III.

The styrylquinolines were prepared by condensation of the

Table I. Derivatives of 4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinoline



No.	Number in Text	R		m.p. °C	Analysis		Yield %
					Calcd.	Found	
1	I		.2HCl	245–247	N, 8·01 Cl, 20·28	N, 7·90 Cl, 20·58	
2	II		.3H$_3$PO$_4$	98–100	N, 5·63	N, 5·59	70
3	III		.3H$_3$PO$_4$	195–197	N, 5·63	N, 5·78	77·6
4	IV		.3H$_3$PO$_4$	110–112	N, 7·40 P, 12·30	N, 6·94 P, 12·15	90
5	V		.3H$_3$PO$_4$	190–193	N, 7·4	N, 7·54	72
6	VI		.3H$_3$PO$_4$	110–111	N, 7·4	N, 7·54	
7	VII		.3H$_3$PO$_4$	75–76	P, 12·55	P, 12·84	71
8	VIII		.3H$_3$PO$_4$	96–98	N, 5·67 P, 12·55	N, 5·72 P, 12·00	67·2
9	IX		.3H$_3$PO$_4$	196–198	N, 5·67	N, 5·77	66
10	X		.3H$_3$PO$_4$	130–132	N, 5·32 P, 11·78	N, 5·05 P, 11·2	66·3

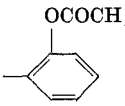
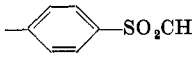
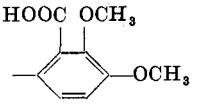
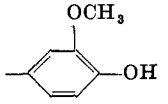
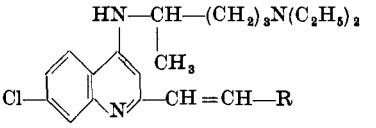
No.	Number in Text	R	m.p. °C	Analysis Calcd.	Analysis Found	Yield %
11	XI	 .$3H_3PO_4$	172–175	N, 5·82 P, 10·75	N, 5·71 P, 10·61	70
12	XII	$-CH_2CH_2CH_3$.$3H_3PO_4$	94–96	N, 6·20 P, 13·74	N, 6·21 P, 13·41	
13	XIII	 .$3H_3PO_4$	98–100	N, 5·33 P, 11·78	N, 5·49 P, 11·95	
14	XIV	 .$3H_3PO_4$	168–170	N, 5·15	N, 5·15	35·2
15	XV	 .$3H_3PO_4$	262–263	N, 5·55	N, 5·24	56·7

Table II. Derivatives of 4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline



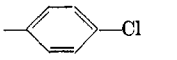
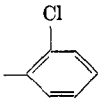
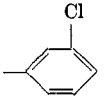
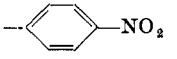
No.	Number in Text	R	m.p. °C	Analysis Calcd.	Analysis Found	Yield %
1	XVI	 .2HCl	260–261	N, 7·95 Cl, 26·84	N, 7·71 Cl, 27·13	
2	XVII	 .$3H_3PO_4$	196–198	N, 5·6	N, 5·64	89
3	XVIII	 .$3H_3PO_4$	210–212	N, 5·6	N, 5·56	64
4	XIX	 .$3H_3PO_4$	245–246	P, 12·22	P, 12·52	75·5

Table II—*cont.*

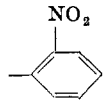
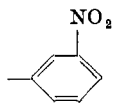
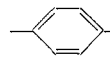
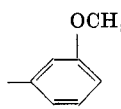
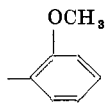
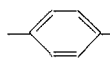
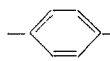
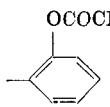
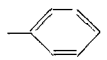
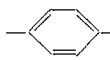
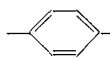
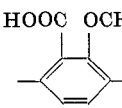
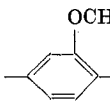
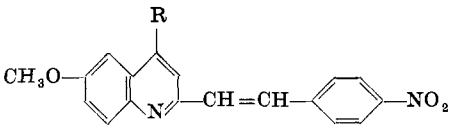
No.	Number in Text	R	m.p. °C	Analysis		Yield %
				Calcd.	Found	
5	XX	 .$3H_3PO_4$	220–222	N, 7·36	N, 7·39	90
6	XXI	 .$3H_3PO_4$	248–250	N, 7·36	N, 7·00	69
7	XXII	 .$3H_3PO_4$	153–155	P, 12·48	P, 12·57	60
8	XXIII	 .$3H_3PO_4$	160–163	N, 5·63	N, 5·46	77·2
9	XXIV	 .$3H_3PO_4$	143–145	N, 5·63 P, 12·48	N, 5·44 P, 12·3	95
10	XXV	 .$3H_3PO_4$	185–187	N, 5·28 P, 11·7	N, 5·11 P, 11·56	64·3
11	XXVI	 .$3H_3PO_4$	165–167	N, 5·29 P, 11·72	N, 5·16 P, 11·64	
12	XXVII	 .2HCl	257–260	N, 7·60 Cl, 19·27	N, 8·04 Cl, 19·02	
13	XXVIII	 .2HCl	167·5–169	N, 8·49 Cl, 21·53	N, 8·26 Cl, 21·30	38
14	XXIX	 .3HCl	127–129	N, 9·75 Cl, 24·74	N, 9·75 Cl, 24·88	
15	XXX		138–140	N, 11·70 Cl, 7·41	N, 11·72 Cl, 7·33	21·6
16	XXXI		180	N, 5·12	N, 5·26	74
17	XXXII		212–215	N, 5·52	N, 5·21	63·2

Table III. Derivatives of 2-(4-nitrostyryl)-6-methoxyquinoline



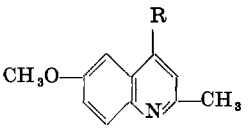
No.	Number in Text	R	m.p. °C	Analysis Calcd.	Analysis Found	Yield %
1	XXXIII	—Cl	184–185	N, 8·45	N, 8·05	80
2	XXXIV	—NH—C$_6$H$_4$— .H$_3$PO$_4$	253–255	N, 8·48	N, 8·20	60·7
3	XXXV	—NHCH$_2$—C$_6$H$_4$— .H$_3$PO$_4$	303·5–305	N, 8·24 P, 6·08	N, 7·85 P, 6·31	
4	XXXVI	—NH(CH$_2$)$_2$N(C$_2$H$_5$)$_2$ .2H$_3$PO$_4$	229–231	N, 9·08	N, 9·10	50
5	XXXVII	—OCH$_3$	181–183	N, 8·32	N, 8·66	90·6
6	XXXVIII	—OC$_2$H$_5$	164–166	N, 7·99	N, 7·76	77
7	XXXIX	—OCH$_2$—C$_6$H$_5$	206–208	N, 6·79	N, 6·93	60·5
8	XL	—O—C$_6$H$_5$	177–179	N, 7·03	N, 6·87	75

corresponding substituted quinaldines with aldehydes in the presence of piperidine (method A),[4,5] or of acetic anhydride[6] (methods B and C).* The necessary 4-substituted quinaldines were obtained by the condensation of 4-chloro-6-methoxyquinaldine[7] or 4,7-dichloroquinaldine[8] with the corresponding amines, sodium alkoxides and phenoxides.[4,7,9]

In Table IV are given data of 4,6-disubstituted quinaldines not previously described in the literature.

* Acetic anhydride was used in the case of 4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinaldines with *p*-nitrobenzaldehyde, salicylaldehyde, and butyraldehyde, as well as of 4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinaldine with salicylaldehyde.

Table IV. 4,6-Substituted quinaldines



No.	R	Constants	Yield %	Analysis, N	
				Calcd.	Found
1	$-OC_2H_5$	b.p. 128°/0·2 mm	93	6·45	6·46
2	$-OCH_2C_6H_5$	b.p. 186°/0·3 mm	66	5·02	5·19
3	$-OC_6H_5$	m.p. 110–112°	75	5·28	5·26
4	$-NHC_6H_5$	m.p. 205–206°	78	10·68	10·82
5	$-NHCH_2C_6H_5$	m.p. 207–208°	64	10·06	10·70

Experimental

Method A. 2-(2-Chlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline triphosphate (XVII). A mixture of 390 g of 4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinaldine, 335 g of *o*-chlorobenzaldehyde, 15 ml of piperidine and 30 ml of xylene was heated at 170–175° for 5 h. The water formed in the reaction was azeotroped off with xylene. After the end of the reaction the product was cooled to 50°, dissolved in 3 l. of acetone and poured with stirring into a solution of 370 g of *ortho*phosphoric acid in 4 l. of acetone. The precipitated triphosphate salt was filtered off, washed with acetone, and dissolved in 16 l. of water at 50–55°. The solution was cleared with activated charcoal, filtered, and the filtrate was made alkaline to phenolphthalein by addition of 50 per cent potassium hydroxide solution. The precipitated base was extracted with ether, the ether extract dried over anhydrous potassium carbonate and the solvent removed. The residue (423 g) was dissolved in 2·5 l. of acetone and then poured into a solution of 290 g of 89·3 per cent *ortho*phosphoric acid in 4 l. of acetone. The yield was 690 g (89 per cent). The yellow powder melted at 196–198° (d.).

Method B. 2-(4-Nitrostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinoline triphosphate (IV). A mixture of 6·38 g of 4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinaldine, 12·1 g of *p*-nitrobenzaldehyde and 5·5 ml of acetic anhydride was heated at 155–160° for 1·5 h. After cooling, 36 ml of 10 per cent hydrochloric acid was added to the reaction mixture, and heating was continued at 103–104° for 2·5 h. The contents of the flask were diluted with water to a volume of 150 ml, the resulting suspension was heated to boiling with charcoal, and the hot solution was filtered and cooled to room temperature. Gradually, over a period of 10 min, and with energetic stirring, it was made alkaline with a 10 per cent solution of sodium hydroxide until basic to phenolphthalein. The precipitated base was filtered off, and was separated from unreacted starting materials by conversion to the hydrochloride, and successive treatments of the latter with 100 ml of acetone and 100 ml of isopropyl alcohol. The yield of 2-(4-nitrostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinoline dihydrochloride was 9·44 g (91 per cent), m.p. 256–258° (d.). This salt was then converted to the base which was dissolved in dichloroethane. The solution was dried over anhydrous potassium carbonate, the solvent was removed, the residue was dissolved in acetone and treated with the stoichiometric amount of 80 per cent *ortho*phosphoric acid. The triphosphate salt was filtered and washed with acetone. The yield was 11·9 g (90 per cent) of a yellow powder, m.p. 110–112° (d.).

Method C. 2-(2-Acetoxystyryl)-4-(δ-diethylamino-α-methylbutylamino-6-methoxyquinoline triphosphate (XI). A mixture of 3·3 g of 4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinaldine, 2·5 g of salicylaldehyde and 5 ml of acetic anhydride was heated in a sealed tube for 5 h at 180–190°. After completion of the reaction the mixture was treated with 15 per cent aqueous base and extracted with chloroform. The chloroform extract was dried over anhydrous potassium carbonate, the solvent removed, and the residue dissolved in 20 ml of methanol. After cooling, the solution was treated with 3 g of *ortho*phosphoric acid in 10 ml of methanol, the mixture was diluted with 50 ml of acetone, the precipitate was filtered off and washed with acetone and ether. The yield was 5·1 g (70 per cent) of a yellow powder, m.p. 172–175° (d.).

Antimicrobial Activities of Derivatives of 2-Styrylquinolines

I. Action of Derivatives of 2-Styrylquinolines on Pathogenic Cocci and Bacteria

Bacteriostatic concentrations were determined *in vitro* for *Staphylococcus aureus*, *Streptococcus hemolyticus* Type A, *Escherichia coli*, *Bacterium typhi*, *Shigella paradysenteriae* Flexner, *Corynebacterium diphtheriae*, *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Bacillus antiracoides*. The bacteria were grown on Hottinger's meat bouillon except the hemolytic streptococci and the diphtheria bacilli which were cultured in the same medium but with addition of 0·5 per cent of glucose and 1 per cent of normal horse serum. The substances to be tested were dissolved in the nutrient medium at an initial dilution of 1 : 2,000. Subsequent dilutions differed from the preceding ones by a factor of 2. Activity was designated as zero if the compound was inactive at a dilution of 1 : 2,000. The results are listed in Table V.

The data in Table V indicate that the derivatives of 2-styryl-6-methoxy-and 2-styryl-7-chloroquinoline which contain a diethylaminoalkylamino group in position 4 have bacteriostatic activity, but if the 4-substituent is a chlorine, alkoxyl, aryloxyl, aralkoxyl or benzylamino group, they are inactive bacteriostatically.

The compounds studied exerted their greatest effect on Gram-positive bacteria (staphylococci, streptococci, diphtheria and anthrax bacilli). The compounds exhibited either no action or had activity only at very high concentrations against Gram-negative bacteria (*E. coli*, *B. typhi*, *S. paradysenteriae*, *Ps. aeruginosa* and *Proteus vulgaris*).

II. Mycobacteriostatic Action of 2-Styrylquinoline Derivatives

In our experiments two strains of *Mycobacterium tuberculosis* were used, namely, *M. tuberculosis* $H_{37}R_v$ which grows in submerged cultures, and the Academia strain which grows as a surface film. We also used one strain of avian tubercle bacilli, and the acid-fast saprophyte B_5 (a new type isolated by Professor Y. K. Veisfeiler from soil in the vicinity of Verchoiansk). *In vitro* experiments were carried out in Soton medium which contained in place of asparagine, an enzymatic hydrolysate of casein.

The test compounds were diluted with this nutrient medium; the initial dilution was 1 : 1,000, and subsequent dilutions differed by a factor of 2. The compounds were considered inactive (designated as 0) if they did not stop the growth of the bacteria at a dilution of 1 : 1,000. Parallel to these tests, the activity of the compounds against *M. tuberculosis* $H_{37}R_v$ was determined in the same medium but with addition of 10 per cent of normal human serum. Compounds found to be active *in vitro* were examined *in vivo* in white mice infected with a strain of bovine tubercle bacilli according to the technique used in this laboratory.[10] The compound was considered active if it prevented or strongly inhibited the murine infection. In Table VI, the activity of the compound was classified as low if the compounds retarded the progress of the disease only little in comparison with controls. The results of these experiments are listed in Table VI.

The data in Table VI show that many representative chemicals of this class have mycobacteriostatic action, but are not selective for different species of mycobacteria. The presence of blood serum in the nutrient reduces their activity in most cases. From a structure-activity point of view, a secondary amino group in position 4 can be regarded as necessary for activity. The most active compounds had a diethylaminoalkylamino chain in the 4-position of the quinoline nucleus. Substances which are highly mycobacteriostatic *in vitro* also have a chemotherapeutic effect on the experimental tuberculosis of white mice. One of these compounds, 2-(4-chlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline dihydrochloride (XVI) was tried clinically in pulmonary tuberculosis. It had a positive therapeutic action in a series of cases, but its medicinal qualities are less favourable than those of streptomycin and isonicotinoyl hydrazine. Therefore the drug was of no practical use.

III. The Effect of Derivatives of 2-Styrylquinoline on Pathogenic Fungi and Actinomycetes

Fungistatic activity was determined *in vitro*. The micro-organisms used were *Microsporum lanosum*, *Trichophyton gypseum*, *Achorion Schönleini*, *Candida albicans*, and *Actinomyces sp.* (obtained from a patient). The pathogenic fungi were seeded into

Table V. Bacteriostatic activities of 4-(δ-diethylamino-α-methylbutylamino)-6-methoxy- and -7-chloroquinolines (*The compounds in this Table, I–XL, are the same as those listed in Tables I–III*)

Number of compound in Text	Bacteriostatic Dilutions (1:×)								
	Staph. aureus	*Strept. hemolyticus* Type A	*E. coli*	*B. typhi*	*Shigella paradysenteriae*	*Corynebacterium diphtheriae*	*Ps. aeruginosa*	*Proteus vulgaris*	*Bc. anthracoides*
I	—	—	—	—	—	—	—	—	—
II	60,000	30,000	8,000	8,000	4,000	30,000	2,000	0	30,000
III	0	16,000	0	0	0	16,000	0	0	16,000
IV	16,000	30,000	0	0	0	0	0	0	16,000
V	16,000	8,000	0	2,000	0	16,000	0	0	8,000
VI	8,000	2,000	0	0	0	4,000	0	0	2,000
VII	16,000	8,000	2,000	2,000	0	16,000	0	0	8,000
VIII	16,000	2,000	0	0	0	0	0	0	8,000
IX	16,000	4,000	0	0	0	0	0	0	16,000
X	8,000	2,000	4,000	0	0	0	0	0	0
XI	30,000	30,000	2,000	4,000	0	4,000	8,000	16,000	16,000
XII	—	—	—	—	—	—	—	—	—
XIII	8,000	4,000	2,000	2,000	0	0	0	0	0
XIV	4,000	0	0	0	0	2,000	0	0	0
XV	4,000	2,000	0	0	0	2,000	0	0	8,000

XVI	—	—	—	—	—	—	—	—	—
XVII	60,000	16,000	2,000	4,000	2,000	30,000	0	0	8,000
XVIII	30,000	16,000	0	2,000	0	8,000	0	0	60,000
XIX	30,000	16,000	0	0	0	0	0	0	4,000
XX	60,000	8,000	2,000	0	0	8,000	0	0	8,000
XXI	32,000	8,000	0	0	0	16,000	0	0	4,000
XXII	32,000	16,000	4,000	4,000	0	30,000	0	0	30,000
XXIII	—	—	—	—	—	—	—	—	—
XXIV	8,000	4,000	0	0	0	0	0	0	8,000
XXV	8,000	2,000	0	0	0	0	0	0	4,000
XXVI	8,000	8,000	2,000	2,000	0	8,000	0	0	8,000
XXVII	—	—	—	—	—	—	—	—	—
XXVIII	—	—	—	—	—	—	—	—	—
XXIX	—	—	—	—	—	—	—	—	—
XXX	—	—	—	—	—	—	—	—	—
XXXI	8,000	8,000	0	0	8,000	0	0	4,000	64,000
XXXII	8,000	2,000	0	0	2,000	0	0	8,000	64,000
XXXIII	0	0	0	0	0	0	0	0	0
XXXIV	4,000	4,000	0	0	0	8,000	0	0	4,000
XXXV	0	0	0	0	0	0	0	0	0
XXXVI	60,000	30,000	0	0	0	60,000	0	0	60,000
XXXVII	0	0	0	0	0	0	0	0	0
XXXVIII	0	0	0	0	0	0	0	0	0
XXXIX	0	0	0	0	0	0	0	0	0
XL	0	0	0	0	0	0	0	0	0

Table VI. Mycobacteriostatic activity of 4-(δ-diethylamino-α-methylbutylamino)-6-methoxy- and -7-chloroquinoline derivatives

No. of compound	Bacteriostatic dilutions (1:×)						Activity on experimental tuberculosis of white mice
	M. tuberculosis $H_{37}R_v$		Academia strain		*M. avium*	*Mycobacterium* B_5	
	Without serum	With serum	Without serum	With serum			
I	1,024,000	256,000	256,000	128,000	—	—	Active
II	256,000	64,000	128,000	128,000	1,000,000	500,000	Inactive
III	512,000	128,000	128,000	128,000	250,000	1,000,000	Low activity
IV	256,000	512,000	256,000	512,000	120,000	250,000	—
V	1,000,000	128,000	64,000	32,000	32,000	120,000	Inactive
VI	128,000	32,000	16,000	16,000	16,000	32,000	Inactive
VII	64,000	32,000	2,000,000	32,000	64,000	64,000	—
VIII	32,000	—	256,000	128,000	128,000	128,000	Inactive
IX	128,000	32,000	32,000	64,000	64,000	128,000	Inactive
X	200,000	100,000	200,000	100,000	500,000	500,000	Inactive
XI	—	—	—	—	30,000	120,000	—
XII	32,000	16,000	16,000	8,000	—	—	Inactive
XIII	—	—	—	—	8,000	32,000	—
XIV	128,000	8,000	8,000	8,000	8,000	32,000	—
XV	8,000	4,000	2,000	2,000	8,000	64,000	—
XVI	8,000,000	1,024,000	256,000	256,000	—	—	Active

XVII	512,000	64,000	128,000	128,000	500,000	250,000	Low activity
XVIII	2,000,000	128,000	256,000	512,000	2,000,000	1,000,000	Low activity
XIX	1,000,000	512,000	2,000,000	512,000	250,000	250,000	Low activity
XX	8,000,000	128,000	512,000	64,000	120,000	250,000	Inactive
XXI	8,000,000	512,000	512,000	256,000	250,000	1,000,000	Inactive
XXII	256,000	128,000	256,000	128,000	120,000	250,000	—
XXIII	—	—	—	—	—	—	—
XXIV	400,000	100,000	800,000	200,000	250,000	250,000	Low activity
XXV	200,000	100,000	100,000	100,000	250,000	500,000	Low activity
XXVI	60,000	—	—	—	60,000	60,000	—
XXVII	—	—	—	—	—	—	—
XXVIII	—	—	—	—	—	—	—
XXIX	—	—	—	—	—	—	—
XXX	—	—	—	—	—	—	—
XXXI	32,000	8,000	16,000	16,000	64,000	0	—
XXXII	64,000	8,000	16,000	8,000	64,000	0	—
XXXIII	1,000	—	—	—	1,000	0	—
XXXIV	128,000	32,000	128,000	64,000	128,000	32,000	—
XXXV	1,000,000	32,000	—	—	60,000	0	—
XXXVI	256,000	128,000	—	—	500,000	120,000	—
XXXVII	1,000	—	—	—	1,000	0	—
XXXVIII	0	—	—	—	0	0	—
XXXIX	0	—	—	—	0	0	—
XL	0	—	—	—	0	0	—

liquid Sabouraud's medium, and the pathogenic actinomycetes were grown on Hottinger's meat bouillon. Fungistatic activity was determined at the maximum dilution at which growth was no longer observed. If the compound did not prevent the growth of fungi at a dilution of 1 : 1,000, it was considered inactive (activity zero). The results of these tests are listed in Table VII.

From the data in this table it can be seen that the fungistatic action of the compounds studied is not great. Substitution with amino groups in position 4 produces higher activity than for substances with other substituents in this position. It should be emphasized that 2-(2-chlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline (XVII) ('Aminochinol') was found to be very active against actinomycetes. True, its activity was somewhat lowered by the presence of blood serum. Aminochinol was studied clinically as a drug for actinomycosis and in a series of cases was found to give good therapeutic effects.

IV. The Effect of Derivatives of 2-Styrylquinolines on Pathogenic Protozoa

Since many of the 2-styryl-4-aminoquinolines have high antimalarial activity,[11,12] it was of great interest to study their effect on other pathogenic protozoa. The *in vitro* action of the whole series of compounds was studied on *Trichomonas vaginalis* and *Entamoeba histolytica*. The experiments were carried out with the freshly prepared strain No. 33 of *Trichomonas* in glucose-serum medium, and with a laboratory strain of dysentery amœbae (strain 'A' of the Institute of Malarial and Medicinal Parasitology and Helminthology AMN USSR) grown on Pavlov medium.

Exploratory concentrations were carried out at the concentrations of 1 : 1,000; 1 : 10,000; and 1 : 100,000. Compounds which were active at a concentration of 1 : 10,000 or lower were studied more carefully in regard to dilutions at which parasitic growth was inhibited. The results of these experiments are given in Table VIII. The activities of the compounds are given in dilutions which inhibit the growth of the parasites *in vitro*. Activity was designated as zero if the compound did not inhibit growth at a dilution of 1 : 10,000.

Table VII. Fungistatic activity of derivatives of 4-(δ-diethylamino-α-methylbutylamino)-6-methoxy- and -7-chloroquinoline

No. of compound	Fungistatic Dilutions (1 : ×)				
	Microsporum lanosum	*Trichophyton gypseum*	*Achorion Schönleini*	*Candida albicans*	*Actinomyces sp.*
I	—	—	8,000	—	—
II	1,000	1,000	4,000	—	—
III	1,000	1,000	4,000	—	—
IV	1,000	1,000	8,000	—	—
V	1,000	1,000	1,000	—	—
VI	0	0	0	—	—
VII	0	0	2,000	—	—
VIII	1,000	1,000	4,000	—	—
IX	0	0	1,000	—	—
X	4,000	4,000	8,000	—	—
XI	2,000	2,000	16,000	—	—
XII	—	—	2,000	—	—
XIII	0	0	0	—	—
XIV	0	0	0	—	—
XV	1,000	1,000	4,000	—	—
XVI	—	—	16,000	—	2,000,000
XVII	1,000	1,000	1,000	—	2,000,000
XVIII	2,000	1,000	4,000	—	—
XIX	8,000	16,000	8,000	—	—
XX	2,000	1,000	2,000	—	—
XXI	2,000	2,000	2,000	—	—
XXII	2,000	2,000	16,000	—	—
XXIII	—	—	—	—	—
XXIV	4,000	2,000	8,000	—	—
XXV	4,000	8,000	30,000	—	—
XXVI	0	1,000	1,000	—	—
XXVII	—	—	—	—	—
XXVIII	—	—	—	—	—
XXIX	—	—	—	—	—
XXX	—	—	—	—	—
XXXI	0	0	0	—	—
XXXII	0	1,000	2,000	—	—
XXXIII	0	0	1,000	0	0
XXXIV	1,000	2,000	4,000	0	4,000
XXXV	1,000	0	4,000	0	2,000
XXXVI	30,000	30,000	60,000	8,000	120,000
XXXVII	0	0	0	0	0
XXXVIII	2,000	2,000	1,000	0	4,000
XXXIX	0	1,000	0	0	0
XL	0	0	0	0	0

Table VIII. Effect of derivatives of 4-(δ-diethylamino-α-methylbutylamino)-6-methoxy- and -7-chloroquinoline on certain pathogenic protozoa

No. of compound	Dilutions (1:×) which inhibited the growth of the protozoa		No. of compound	Dilutions (1:×) which inhibited the growth of the protozoa	
	Trichomonas vaginalis	*Entamoeba histolytica*		*Trichomonas vaginalis*	*Entamoeba histolytica*
I	1,000	0	XXI	1,000	64,000[a]
II	0	0	XXII	1,000	0
III	5,000	10,000	XXIII	—	—
IV	200,000	1,000[a]	XXIV	10,000	1,000
V	0	0	XXV	10,000	10,000
VI	1,000	0	XXVI	0	0
VII	1,000	—	XXVII	—	—
VIII	1,000	—	XXVIII	1,000	0
IX	1,000	32,000[a]	XXIX	—	—
X	10,000	10,000	XXX	10,000	—
XI	1,000	64,000	XXXI	0	0
XII	10,000	0	XXXII	0	—
XIII	0	0	XXXIII	0	1,000
XIV	0	1,000	XXXIV	1,000	1,000
XV	1,000	0	XXXV	1,000	1,000
XVI	5,000	0	XXXVI	200,000	1,000
XVII	0	1,000	XXXVII	1,000	1,000
XVIII	1,000	1,000	XXXVIII	1,000	1,000
XIX	100,000	0	XXXIX	0	1,000
XX	1,000	10,000	XL	1,000	1,000

[a] Inactive in experimental amœbiasis in young rats.

The data in Table VIII reveal that the derivatives of 2-styrylquinoline as a rule have little effect on *T. vaginalis* and *E. histolytica*, but 4-nitro substituted derivatives of 6-methoxy- or 7-chloro-4-diethylaminoalkylamino-2-styrylquinolines have considerable activity against *T. vaginalis*. This action is selective, the same compounds having barely any activity against *E. histolytica*. One of these substances, namely, 2-(*p*-nitrostyryl)-4-δ-diethylamino-α-methylbutylamino-6-methoxyquinoline (IV), subsequently named Trichomonacid,[13] was studied clinically in cases

of trichomoniasis and was shown to exhibit high therapeutic activity in local applications, and a well-established effect on internal administration.

Several compounds which were active against *E. histolytica in vitro* had no chemotherapeutic effect on experimental amœbiasis in young rats.

Some of these compounds were studied in mice infected with *Lamblia muris*.[14] High activity was discovered for 2-(2-chlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline (Aminochinol, XVII). In clinical trials, this drug showed high therapeutic effectiveness in various forms of lambliasis, surpassing considerably the medicinal effects of quinacrine.

Conclusions

This study of the antimicrobial properties of derivatives of styrylquinolines showed that these compounds possess a definite activity provided that they contain a diethylaminoalkylamino group in position 4. Other substituents in this position such as chloro, methoxy, ethoxy, phenoxy, benzyloxy and some others, tend to reduce or abolish activity in the respective compound.

4-Diethylaminoalkylamino derivatives of 7-chloro- or 6-methoxy-2-styrylquinoline suppress the growth and development of bacteria, actinomycetes, pathogenic fungi and protozoa. Among bacteria, Gram-negative organisms (*E. coli*, *B. typhi*, *S. paradysenteriae*, *Ps. aeruginosa*, *Pr. vulgaris*) are less sensitive than Gram-positive cocci, diphtheria and anthrax bacilli. Still more sensitive are mycobacteria and actinomycetes. Pathogenic fungi are relatively insensitive to the compounds studied, and so are, as a rule, the pathogenic protozoa, *T. vaginalis* and *E. histolytica*. However, some of the test compounds were found very effective against *T. vaginalis*, particularly some of the nitro derivatives. 2-(4-Nitrostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinoline triphosphate (Trichomonacid, IV) was found to be a highly effective drug for trichomoniasis.

In vivo tests revealed chemotherapeutic activity against experimental tuberculosis in white mice for a series of compounds. Clinical investigation of one of these substances, i.e. 2-(4-chlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline

(XVI) indicated that its activity is relatively insignificant in tuberculosis patients, but 2-(2-chlorostyryl)-4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline (Aminochinol, XVII) was used in patients suffering from actinomycosis with a therapeutic effect in a series of cases.

Aminochinol also showed high chemotherapeutic activity against experimental lambliasis of mice (*Lamblia muris*). Clinical investigations in several hospitals of the Soviet Union demonstrated that Aminochinol has good therapeutic properties in various forms of lambliasis.

Summary. A series of derivatives of 2-styrylquinoline has been synthesized. Those compounds which have a diethylaminoalkylamino group in the 4-position of the quinoline nucleus possess pronounced antimicrobial activity, suppressing the growth and development of bacteria, actinomycetes, pathogenic fungi and protozoa.

In experiments *in vivo* numerous compounds exhibited chemotherapeutic activity in experimental tuberculosis in white mice. High activity against *Trichomonas vaginalis* was displayed by 2-(4-nitrostyryl)-4-(δ-diethylamino-α-methylbutylamino)-6-methoxyquinoline triphosphate, and against *Lamblia muris* by 2-(2-chlorostyryl)-4-(δ-diethylamino-α-methylamino)-7-chloroquinoline triphosphate.

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