EXPERIMENTAL CHEMICAL SECTION

IR spectra were recorded on a UR-20 (GDR) in CCl_4, UV spectra on a "Specord UV-VIS" (GDR) in ethanol, and mass-spectra on an MX-1303 spectrometer.

8-Chloro-6-phenyl-1-methyl-1,2,3,4-tetrahydro-1,5-benzdiazocin-2-one (Ia). To a solution of 9.8 g (0.04 mole) of 5-chloro-2-methylaminobenzophenone in 100 ml of dry chloroform is added 8.6 g (0.06 mole) of the hydrochloride of β-alanine acid chloride. The mixture is refluxed for 1.5 h, cooled to room temperature, neutralized with a solution of ammonia, and washed with water. The organic layer is evaporated in vacuum, 200 ml toluene added to the residue and the toluene–water azeotrope, and then the toluene distilled. The residue is crystallized from ethanol, to give 10.1 g (85%) of compound Ia with mp 169-170°. The other compounds I are prepared in the same way.

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SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF SOME QUINOGLYCOSIDES

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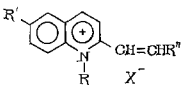
Continuing our work on the synthesis and study of the properties of quinoglycosides — potentially physiologically active substances — we have prepared a new series of compounds based on the N-arylates of quinaldine and acetylated mono- and disaccharides; the physicochemical and antimicrobial properties of these compounds have been examined.

The quinoglycosides are readily obtained by condensation of the active methyl group of quaternary salts of quinaldine with the active functional groups of the α-form of sugars; the reaction is carried out in pyridine or alcohol containing piperidine at 60-70°. The compounds obtained are dimethyl dyes of general formula:



where R is an aryl group; R', alkyl or benzo(f) substituent; =CHR", a completely acetylated residue of α-D-glucose (I, V, IX, and XIII), α-D-galactose (II, VI, X, and XIV), α-D-Maltose (III, VII, XI, and XV) and α-D-lactose (IV, VIII, XII, and XVI); X^- = Hal^- or ClO_4^-.

Structures of the compounds were confirmed by IR, UV, and visible absorption spectra.

Compounds I-IV show two absorption maxima in the UV, one at 236-238 nm, and the second at 315-318 nm. The benzo(f) derivatives V-XVI exhibit, in addition to these two bands, three bands at 368-371 nm which are characteristic for quinoline salts [1].

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TABLE 1. Physicochemical Properties of the Quinoglycosides

Compound	R	R'	X⁻	Yield, %	Decomp. temp., °C	Found, %		Empirical formula	Calc., %		λmax, nm	lg ε
						Hal	N		Hal	N		
I	$C_6H_4OCH_3$-p	OCH_3	ClO_4	73	133—5	4,52	1,72	$C_{34}H_{38}ClNO_{16}$	4,71	1,86	580	2,81
II	$C_6H_4OCH_3$-p	OCH_3	ClO_4	69	146—8	4,61	1,86	$C_{34}H_{38}ClNO_{16}$	4,71	1,86	582	2,90
III	$C_6H_4OCH_3$-p	OCH_3	ClO_4	76	122—4	3,32	1,28	$C_{46}H_{54}ClNO_{22}$	3,46	1,36	580	2,93
IV	$C_6H_4OCH_3$-p	OCH_3	ClO_4	62	167—9	3,38	1,22	$C_{46}H_{54}ClNO_{22}$	3,46	1,36	580	3,15
V	C_6H_5	Benzo(*f*)	I	65	138—9	16,23	1,67	$C_{36}H_{36}INO_{10}$	16,49	1,82	586; 638	3,30; 3,36
VI	C_6H_5	Benzo(*f*)	I	71	133—6	16,42	1,73	$C_{36}H_{36}INO_{10}$	16,49	1,82	584; 640	3,09; 3,11
VII	C_6H_5	Benzo(*f*)	I	67	126—8	11,78	1,23	$C_{48}H_{53}INO_{18}$	11,99	1,32	585; 640	3,89; 3,85
VIII	C_6H_5	Benzo(*f*)	I	63	152—5	11,81	1,28	$C_{48}H_{53}INO_{18}$	11,99	1,32	592; 636	3,64; 3,68
IX	$C_6H_4CH_3$-p	Benzo(*f*)	I	72	191—3	16,11	1,63	$C_{37}H_{37}INO_{10}$	16,21	1,78	592; 641	3,39; 3,63
X	$C_6H_4CH_3$-p	Benzo(*f*)	I	61	135—8	16,03	1,69	$C_{37}H_{37}INO_{10}$	16,21	1,78	595; 640	3,38; 3,66
XI	$C_6H_4CH_3$-p	Benzo(*f*)	I	59	193—7	11,63	1,19	$C_{49}H_{53}INO_{18}$	11,85	1,30	585; 645	4,08; 4,20
XII	$C_6H_4CH_3$-p	Benzo(*f*)	I	79	181—3	11,71	1,15	$C_{49}H_{53}INO_{18}$	11,85	1,30	600; 645	4,42; 4,26
XIII	$C_6H_4OCH_3$-p	Benzo(*f*)	ClO_4	81	127—9	4,38	1,63	$C_{37}H_{38}ClNO_{15}$	4,59	1,81	586; 640	3,18; 3,08
XIV	$C_6H_5OCH_3$-p	Benzo(*f*)	ClO_4	71	145—8	4,42	1,58	$C_{37}H_{38}ClNO_{15}$	4,59	1,81	586; 640	3,20; 3,08
XV	$C_6H_5OCH_3$-p	Benzo(*f*)	ClO_4	66	175—8	3,30	1,17	$C_{49}H_{53}ClNO_{23}$	3,34	1,32	586; 634	2,93; 2,84
XVI	$C_6H_5OCH_3$-p	Benzo(*f*)	ClO_4	73	121—4	3,19	1,22	$C_{49}H_{53}ClNO_{23}$	3,34	1,32	584; 632	3,16; 3,14

Note. For structure of carbohydrate residues —CHR^4, see subscripts to structural formulas.

TABLE 2. The Effect of the Nature of the Glycoside on the Second-Order Rate Constant in the Formation of Quinoglycosides

Glycoside residue	Effective rate constant $K \cdot 10^3$, liter/mole·min			E, kcal/mole	T
	40°C	50°C	60°C		
Pentaacetyl-D(+)glucosyl-	0,04	0,11	0,17	11,1	1,61
Pentaacetyl-D(+)maltosyl-	0,08	0,16	0,22	9,1	2,33

TABLE 3. Antimicrobial Activity of the Quinoglycosides

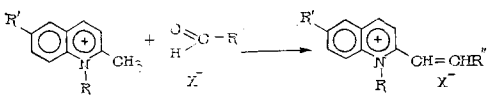
Compound	Test microorganism												
	Staph. aureus 209	E. coli 355	S. tuphy 495	S. gallinarum 395	Sh. Sonnei 10 041	B. subtilis 177	B. anthracoides 297	Kl. rhinoscleromatis	B. proteus vulgaris 409	Ps. aeruginosa 128	C. albicans 688	C. tropicalis 98	C. Krusei 97
	minimum concn. of the compound which supports growth of bacteria and fungi, μg/ml												
I	3,9	62,5	62,5	31,2	31,2	62,5	31,2	62,5	62,5	62,5	15,6	15,6	15,6
II	2,0	31,2	62,5	125,0	62,5	31,2	31,2	125,0	62,5	62,5	31,2	31,2	15,6
III	3,9	31,2	15,6	15,6	31,2	31,2	31,2	62,5	62,5	62,5	31,2	15,6	15,6
IV	3,9	31,2	31,2	31,2	62,5	62,5	62,5	125,0	125,0	125,0	31,2	15,6	15,6
V	3,9	125,0	125,0	125,0	125,0	62,5	62,5	250,0	250,0	250,0	31,2	15,6	15,6
VI	1,0	62,5	62,5	62,5	31,2	62,5	62,5	125,0	125,0	62,5	15,6	7,8	15,6
VII	3,9	250,0	250,0	250,0	62,5	62,5	31,2	250,0	500,0	500,0	7,8	7,8	15,6
VIII	1,0	125,0	250,0	125,0	62,5	125,0	125,0	250,0	500,0	500,0	15,6	15,6	15,6
IX	2,0	250,0	—	62,5	125,0	62,5	31,2	62,5	125,0	250,0	3,9	7,8	7,8
X	1,0	125,0	—	62,5	62,5	62,5	31,2	62,5	62,0	250,0	3,9	7,8	7,8
XI	2,0	62,5	125,0	62,5	62,5	62,5	15,6	62,5	125,0	125,0	15,6	15,6	15,6
XII	1,0	31,2	62,5	31,2	31,2	62,5	15,6	—	250,0	250,0	3,9	7,8	3,9
XIII	3,9	125,0	125,0	125,0	500,0	31,2	62,5	62,5	125,0	125,0	31,2	31,2	31,2
XIV	2,0	500,0	500,0	500,0	500,0	62,5	62,5	500,0	500,0	500,0	31,2	31,2	31,2
XV	15,6	250,0	125,0	250,0	250,0	125,0	31,2	125,2	250,0	250,0	31,2	15,6	—
XVI	31,2	500,0	500,0	250,0	250,0	250,0	62,5	500,0	1000,0	1000,0	31,2	31,2	—

In the visible region, alcoholic solutions of quinoglycosides show one absorption band with a maximum at 580-600 nm (for compounds I-IV). For compounds V-XVI, there are two maxima, one at 584-600 nm and the other at 630-645 nm, with considerably different intensities (Table 1).

In the IR, absorption at 1603-1340 cm^{-1} is due to the stretching vibrations of the C=C and C=N bonds of the quinoline nucleus, and absorption at 1230-1078 cm^{-1} to the deformation vibrations of the C–H of the quinoline ring. Absorption bands at 573 cm^{-1} are characteristic of the D(+)-glucose skeleton, and the band at 1740-1750 cm^{-1} is characteristic of the C=O of the acetyl group [2, 3].

The quinoglycosides are readily deacetylated in absolute methanol in the presence of $HClO_4$. The structure of the deacetylated products was confirmed by elemental analysis, bromometric titration, and periodate oxidation in which 4 moles of periodate are consumed and 3 moles of formic acid are formed.

The relative reactivities of the mono and disaccharide compounds were determined; no work on this has been reported in the literature. The reaction of the appropriate sugar with the quinoline salt to give a dimethine dye was studied. Such a reaction is analogous to the styryl condensation, the kinetics of which have been studied [4, 5]. The reaction proceeds in the following manner:



The progress of the reaction is followed by measuring the formation of the dye spectrophotometrically. The absorption of the dimethines, at concentrations of $0.3 \cdot 10^{-4}$ mole/liter, obeys the Beer–Lambert law. The reaction appears to follow the kinetic equation:

$$W = k\,[c_1]^{n_1}\,[c_2]^{n_2},$$

where n_1 and n_2 are partial reaction orders for the corresponding components and k is the effective rate constant of the reaction. In our case, the order for the salt and for the glycoside is approximately 1 and the total order is therefore 2.

To compare the relative reactivities of the sugars, the effective second-order rate constant was determined for identical initial concentrations of the quinoline salt and glycoside:

$$k = \frac{1}{t}\left(\frac{1}{c^1} - \frac{1}{c_0}\right),$$

where c_0 is the initial concentration of the salt; $c^1 = c_0 - c$; c, concentration of the dye at time t; t, time (in minutes). Data for the kinetic studies are given in Table 2. Comparison of the effective second-order rate constants shows that the acetates of the disaccharides are somewhat more reactive than the acetates of the monosaccharides in the condensation reaction with quinoline salts. This confirms a comparison of the energy of activation and temperature coefficients.

EXPERIMENTAL BIOLOGICAL SECTION

The activity of the quinoglycosides against 13 types of bacteria and fungi was determined using the method of serial dilution in liquid nutrient medium [6] (Table 3). Most of the compounds exhibited significant antistaphylococcus activity (minimum concentration, inhibiting growth of microbes is 1.0-31.2 μg/ml). The level of activity against staphylococcus depends markedly on the nature of the acetate group of the carbohydrate R". It can be seen from Table 3 that the most significant effect is caused by compounds containing a galactose acetate group (compounds II, VI, X, and XIV).

In this series, the benzo(f)quinoline part of the molecule (in compounds V-XVI), and in particular the substituent R, has a significant antimicrobial effect on staphylococcus; the p-tolyl group (compounds XI-XIV) has the greatest effect.

The quinoglycosides show less effect on test microbes of the intestinal group and on spore cultures (minimum inhibiting concentration of the compounds varies from 15.6-1000.0 μg/ml).

Antifungal activity is exhibited by the compounds at doses of 3.9-31.2 μg/ml; the most active were compounds IX, X, and XII, benzo(f)derivatives with a p-tolyl substituent on the heteroatom.

EXPERIMENTAL CHEMICAL SECTION

The UV spectra of the quinoglycosides were taken on an SF-4 spectrophotometer, in $1 \cdot 10^{-4}$ M solutions in alcohol. IR spectra were taken on a UR-10 (GDR) in pellets of KBr, NaCl, and LiCl. Visible spectra were taken on an SF-10 spectrophotometer in $1 \cdot 10^{-3}$ M solutions in alcohol.

Dimethine Perchlorate (I). A mixture of 0.76 g (0.002 mole) of 1-p-methoxyphenyl-6-methoxyquinaldine, 0.78 g (0.002 mole) of pentaacetylglucose and 10 ml of pyridine is heated on the steam bath for 1 hour. After cooling, the mixture is treated with dilute hydrochloric acid, filtered, and the precipitate washed on the filter with water and then ether and recrystallized from hexanol.

The other compounds in the series are prepared by the same method. The quinoglycosides are violet powders, readily soluble in ethanol, acetone, pyridine, and nitromethane, and slightly soluble in water on heating.

Deacetylation of Dimethine Perchlorate (I). A mixture of 0.70 g (0.001 mole) of I, 30 ml of methanol, and 2 ml of concentrated $HClO_4$ is stirred and heated for 40-50 min. After 2-3 days at room temperature, crimson crystals separate and are recrystallized from methanol to give 0.55 g (79%). Found, %: N 2.60, $C_{24}H_{28}ClNO_{11}$. Calculated, %: N 2.72.

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