SYNTHESIS AND INVESTIGATION OF DIMETHINE COMPOUNDS BASED ON DERIVATIVES OF QUINALDINE AND ACETYLATED SUGARS

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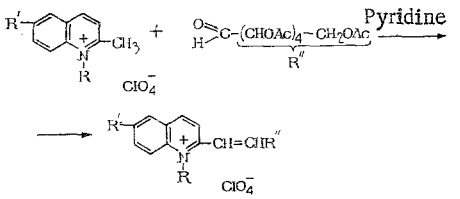
The synthesis of carbohydrates carbon substituted with heterocyclic radicals was achieved not very long ago, but information is already widespread in the literature on their use in the analytical chemistry of sugars for the identification of aldoses, and of aldonic, uronic and saccharic acids. The analogous compounds with a tetrazole ring are used as biological indicators [1]. Authors have reported the biological activity of the indicated carbohydrates and also the antimicrobial action of some derivatives with a thiadiazolinium ring in relation to Mycobacterium tuberculosis and also the antitumor effect of compounds of the benzimidazole series.

Since carbohydrates play a basic role in the life activity of the animal world, and quinolinum salts [2] are used as bactericidal and fungicidal agents and possess antitumor activity towards lymphoma 8 and certain forms of sarcoma, it seemed of interest to carry out the purpose-directed synthesis of compounds of the quinoglycoside type as potentially physiologically active substances. The promising nature of such a synthesis of carbon-substituted carbohydrates is also underlined by the stability towards hydrolysis of the carbohydrate–aglycone bond [3].

In study [4] the marked reactivity of the aldose form of sugars was reported which permits the latter, in addition to the inherent chemical interactions of monosaccharides, to enter into condensation reactions. We have carried out condensation of the aldehyde forms of mono- and disaccharides with quaternary N-alkyl(aryl)quinolinium salts at the methyl group and dimethine dyes, the quinoglycosides, were obtained. The influence of the carbohydrate residue on the color of compounds has been studied and their antimicrobial activity investigated.

The condensation reaction was carried out according to the scheme:



R and R' are alkyl and aryl substituents, R'' are the fully acetylated derivatives of glucose, galactose, maltose, and lactose (Table 1).

The synthesis was carried out in alcohol with addition of piperidine or in pyridine; the reaction occurred more effectively in the latter case. The final reaction products were isolated by repeated precipitation with ether and were purified by crystallization from a water–alcohol (3:1) mixture. The quinoglycosides were fine crystalline powders of a raspberry or violet color mostly with high melting points (with decomposition).

The structure of the synthesized compounds was confirmed by data of elemental analysis, by quantitative addition of bromine to the double bond, and by the determination of the number of acetyl groups in the molecule by hydrolysis. The visible, UV, and IR spectra were

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TABLE 1. Properties of the Synthesized Quinoglycosides

Compound	R	R′	Yield, %	Decomposition temp. °C	Found, %		Empirical formula	Calculated, %		λ_{max} nm	log ε
					Hal	N		Hal	N		
I	CH_3	H	38	102—8	5,50	2,03	$C_{27}H_{32}ClNO_{14}$	5,63	2,22	560	2,25
II	CH_3	H	41	116—8	5,47	2,07	$C_{27}H_{32}ClNO_{14}$	5,63	2,22	586	2,47
III	CH_3	H	40	116—7	3,55	1,48	$C_{39}H_{48}ClNO_{22}$	3,86	1,52	566	2,92
IV	CH_3	H	44	107—8	3,80	1,68	$C_{39}H_{48}ClNO_{22}$	3,86	1,52	570	2,70
V	C_2H_5	H	42	217—9	4,97	1,94	$C_{28}H_{34}ClNO_{14}$	5,13	2,02	562	2,63
										602	2,70
VI	C_2H_5	H	37	216—9	4,48	1,90	$C_{28}H_{34}ClNO_{14}$	5,13	2,02	562	2,18
										604	2,30
VII	C_2H_5	H	39	212—5	3,69	1,49	$C_{40}H_{50}ClNO_{22}$	3,80	1,50	562	2,27
										606	2,34
VIII	C_2H_5	H	37	225—7	3,71	1,24	$C_{40}H_{50}ClNO_{22}$	3,80	1,50	562	2,29
										606	2,29
IX	C_6H_5	H	40	152—4	4,84	1,91	$C_{32}H_{34}ClNO_{14}$	5,10	2,02	524	2,42
										563	2,60
X	C_6H_5	H	53	140—2	4,79	2,19	$C_{32}H_{34}ClNO_{14}$	5,10	2,02	517	2,11
										563	2,29
XI	C_6H_5	H	63	147—9	3,89	1,42	$C_{44}H_{50}ClNO_{22}$	3,61	1,43	518	2,14
										564	2,31
XII	C_6H_5	H	82	142—4	3,81	1,34	$C_{44}H_{50}ClNO_{22}$	3,61	1,43	514	2,08
										559	2,20
XIII	n-$CH_3C_6H_4$	CH_3	43	180—2	4,90	1,87	$C_{34}H_{38}ClNO_{14}$	4,93	1,94	569	2,77
XIV	n-$CH_3C_6H_4$	CH_3	69	110—5	4,86	1,90	$C_{34}H_{38}ClNO_{14}$	4,93	1,94	577	2,64
XV	n-$CH_3C_6H_4$	CH_3	78	140—8	3,91	1,16	$C_{46}H_{54}ClNO_{22}$	3,51	1,39	580	3,00
XVI	n-$CH_3C_6H_4$	CH_3	81	130—6	3,62	1,12	$C_{46}H_{54}ClNO_{22}$	3,51	1,39	578	3,17
XVII	n-BrC_6H_4	Br	67	215—7	22,92	1,58	$C_{32}H_{33}BrClNO_{14}$	23,01	1,64	583	2,79
XVIII	n-BrC_6H_4	Br	72	135—9	22,97	1,60	$C_{32}H_{33}BrClNO_{14}$	23,01	1,64	580	2,93
XIX	n-BrC_6H_4	Br	74	62—9	17,07	1,01	$C_{44}H_{48}Br_2ClNO_{22}$	17,16	1,23	577	2,52
XX	n-BrC_6H_4	Br	82	90—9	17,09	1,17	$C_{44}H_{48}Br_2ClNO_{22}$	17,16	1,23	582	2,64
XXI	$C_{10}H_7$	H	37	162—5	4,69	1,71	$C_{36}H_{36}ClNO_{14}$	4,79	1,89	563	2,81
										600	3,04
XXII	$C_{10}H_7$	H	47	198—9	4,75	1,80	$C_{36}H_{36}ClNO_{14}$	4,79	1,89	574	3,02
										604	3,21
XXIII	$C_{10}H_7$	H	64	125—9	3,85	1,01	$C_{48}H_{52}ClNO_{22}$	3,44	1,35	526	2,90
										568	3,09
XXIV	$C_{10}H_7$	H	61	136—9	3,29	1,26	$C_{48}H_{52}ClHO_{22}$	3,44	1,35	526	2,80
										570	2,98

Note. R″ for (I, V, IX, XIII, XVII, XXI) was the aldehyde form of glucose pentaacetate $C_{16}H_{22}O_{10}$; for (II, VI, X, XIV, XVIII, XXII) it was the aldehyde form of galactose pentaacetate $C_{16}H_{22}O_{10}$; for (III, VII, XI, XV, XIX, XXIII) it was the aldehyde form of fully acetylated maltose $C_{28}H_{38}O_{18}$; and for (IV, VIII, XII, XVI, XX, XXIV) it was the aidehyde form of fully acetylated lactose $C_{28}H_{38}O_{18}$.

TABLE 2. Antimicrobial Activity of Quinoglycosides

Compound	Staph. aureus 209	E. coli 355	S. typhi 495	S. gallinarum 395	Sh. sonnei 10041	B. Subtilis 177	B. anthracoides 297	Kl. rhinoscleromatis	B. proteus vulgaris 709	B. aeruginosa 128	C. albicans 688	C. tropicalis 98	C. Krusei 97
	minimal concentrations of preparations retarding growth of bacteria and molds, μg/ml												
I	31,2	250	250	62,5	62,5	125,0	31,2	250	250	500	62,5	31,2	62,5
II	31,2	500	500	125	62,5	62,5	31,2	125	500	500	62,5	62,5	62,5
III	3,9	500	500	125	125	125	250	500	500	500	15,6	31,2	15,6
IV	31,2	500	1000	500	250	500	31,2	500	500	500	31,2	31,2	31,2
V	15,6	1000	500	250	125	125	125	500	1000	1000	62,5	31,2	62,5
VI	500	1000	1000	1000	1000	125	250	500	1000	1000	500	125	125
VII	1000	1000	1000	1000	1000	500	125	500	1000	1000	125	125	125
VIII	125	1000	1000	1000	1000	500	500	1000	1000	2000	125	125	125
IX	3,9	62,5	31,2	31,2	31,2	31,2	62,5	62,5	62,5	125	15,6	15,6	31,2
X	15,6	1000	500	125	500	500	31,2	500	500	500	15,6	15,6	31,2
XI	3,9	31,2	15,6	15,6	31,2	31,2	31,2	62,5	125	125	15,6	31,2	15,6
XII	125	—	—	—	—	—	250	500	500	500	125	125	62,5
XIII	7,8	31,2	31,2	62,5	62,5	31,2	62,5	125	125	125	31,2	31,2	31,2
XIV	3,9	500	125	125	—	—	31,2	—	500	500	32,2	31,2	31,2
XV	1,0	125	125	125	125	125	62,5	62,5	125	125	15,6	31,2	31,2
XVI	3,9	62,5	125	125	62,5	62,5	15,6	62,5	125	125	31,2	31,2	31,2
XVII	62,5	62,5	125	125	125	62,5	31,2	125	125	125	62,5	62,5	62,5
XVIII	7,8	125	125	125	250	—	—	62,5	—	—	31,2	31,2	31,2
XIX	31,2	125	125	250	125	62,5	62,5	125	250	250	31,2	31,2	62,5
XX	31,2	125	250	250	31,2	31,2	31,2	125	125	250	15,6	15,6	15,6
XXI	7,8	62,5	125	125	62,5	31,2	31,2	62,5	62,5	62,5	15,6	15,6	15,6
XXII	2,0	125	125	125	62,5	15,6	15,6	62,5	62,5	62,5	31,2	15,6	15,6
XXIII	2,0	31,2	250	125	31,2	31,2	31,2	125	125	250	31,2	15,6	15,6
XXIV	3,9	62,5	125	125	62,5	62,5	31,2	125	250	250	31,2	31,2	31,2

taken and studied which also confirmed the structure of the studied compounds. Experimental data characterizing the physicochemical properties of the quinoglycosides are given in Table 1.

While analyzing the spectral data the unexpressed influence of the nature of the carbohydrate residue on the absorption maximum in the visible portion of the spectrum was noted. Thus compounds (I-IV, XIII-XX) had one main absorption maximum in the 560-586 nm region, and the character of their curves was also the same. Compounds (V-XII, XXI-XXIV) were characterized by two maxima, a short wave in the 514-526 and 562-574 nm region and a long wave in the 559-570 and 602-606 nm region. The short wave and long wave absorption maxima differed insignificantly in intensity. A more appreciable influence on the absorption maximum of the quinoglycosides was expressed by the nature of the substituent at the nitrogen heteroatom. The UV spectra of the studied substances contained two absorption bands, a short wave less intense band in the 237-245 nm region and a long wave more marked band in the 316-321 nm region which was peculiar to the quinolinium salt [5].

On analysis of spectrograms in the IR region it was established that absorption bands at 575 cm^{-1} characterized skeletal vibrations of the D(+)-glucose residue while absorption bands in the 1740-1750 cm^{-1} region were characteristic for C–O group vibrations of acetates. Absorption bands at 1603-1340 cm^{-1} were assigned to stretching vibrations of C=C and C=N ring bonds of the quinoline nucleus. The 1230-1078 cm^{-1} region describes planar deformation vibrations of C-H bonds in the quinoline nucleus. The band of high intensity with a maximum at 1085-1040 cm^{-1} was assigned to vibrations of the ClO_4^- ion [6, 7].

The activity of the synthesized substances in relation to 13 test cultures of bacteria and molds was determined by the method of serial dilutions in liquid nutrient medium [8]. As follows from Table 2 the antimicrobial activity of the quinoglycosides varied within wide limits. Certain relationships were recorded between the extent of the influence on microorganisms and structure of the chemical compounds of this series. The anticoccal activity clearly increased on introducing an α-naphthyl radical as a substituent at the nitrogen heteroatom (compare preparations (XXI, XXII, XXIII, and XXIV) on the one hand and the remaining substances on the other). A marked influence on staphylococci was shown by compounds (XV, XIV, and XVI) containing p-tolyl groups on the nitrogen atom of the quinoline nucleus and also a methyl group at various positions of the condensed nucleus. In addition no appreciable influence was recorded on the degree of antimicrobial activity by the character of the glycoside in the sterile portion of the quinoglycoside molecule.

Action was displayed by the studied substances at doses of 15.6-1000.0 μg/ml in relation to gram negative bacteria of the enteric group but certain pseudomonas were sensitive to these compounds at a concentration of 2000.0 μg/ml.

The yeast-like molds of the Candida family proved to be sensitive to quinoglycosides at doses of 15.6-500.0 μg/ml but no appreciable differences in sensitivity were established for *C. albicans*, *C. tropicalis*, and *C. Kruzei* towards the indicated substances.

It is perfectly evident that a bromine atom and a CH_3 group at position 6 of the quinoline nucleus and in the p-position of the phenyl radical on the nitrogen heteroatom proved not to influence the biological activity of the quinoglycosides.

EXPERIMENTAL

Visible spectra of quinoglycosides were taken on an SF-10 spectrophotometer (concentration of alcohol solutions was 10^{-3} mole/liter), UV spectra on an SF-4 spectrophotometer (concentration of alcohol solutions was 10^{-4} mole/liter), and IR spectra on a UR-10 spectrophotometer (DDR) in KBr, NaCl, and LiF disks.

α-(1-Phenylquinolin-2)-β-[pentaacetate-D(+)-glucoso]-dimethine [9]. A mixture of 1-phenylquinaldinium perchlorate (0.62 g, 0.002 mole), fully acetylated glucose (0.78 g, 0.002 mole), and pyridine (10 ml) was heated on a boiling water bath for 1 h. On cooling the reaction mixture was treated with dilute hydrochloric acid. The solid was filtered off, washed with water, and many times with ether. Recrystallization was from hexyl alcohol or from a mixture of water–alcohol.

Compounds (I-XXIV). These compounds were obtained by a similar method. The quinoglycosides dissolved well in organic solvents (ethanol, acetone pyridine, nitromethane) and compounds (I-XIV) dissolved in water on heating. The alcohol solutions of preparations (X-XII) displayed an intense yellow coloration.

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