O-HETARYL SUBSTITUTED CARBOHYDRATES AND THEIR NEUROTROPIC ACTIVITY

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N- and C-substituted monosaccharides, incluing their hetaryl derivatives, have found rather extensive application in clinical practice as inhibitors of nucleic acid metabolism with anticancer, antivirus, and immunodepressant activity [16]. C-Hetaryl-substituted carbohydrates [5], among which derivatives with anticoagulant [6], antimicrobial [8], and neurotropic activity [8] have been discovered, are of particular interest as a consequence of their fundamental nonhydrolyzability with respect to the C–C bond both in vito and in vitro [6]; this probably also facilitates the manifestation of interesting pharmacological properties by them.

From the point of view of their bological activity, relatively little study has been devoted to O-hetaryl derivatives of carbohydrates, and thus far individual examples have been presented [23, 26]. At the same time, like C-substituted monosaccharides [18], they are resistant to hydrolysis; however, they are obtained incomparably more easily than the latter [9]. For example, we recently demonstrated the exceptional ease of the formation of O-hetaryl derivatives of sugars in the Williamson synthesis under conditions of interphase catalysis (IPC) from acetylated monosaccharides and chloromethylated heterocycles [11]. In a continuation of these studies we obtained a number of O-hetaryl-substituted carbohydrates, the physicochemical and neurotropic properties of which are discussed in the present paper.

As substrates we used the readily accessible mono- (Ia), di- (IIa, IIIa), and trihydroxy (IVa) derivatives of cyclohexylidenated monosaccharides with different steric environments of the hydroxy groups. Halomethyl derivatives of pyridine, quinoline, benzimidazole, and imidazo[1,2-a]benzimidazole served as the reagents.

The reaction of the indicated substrates and reagents proceeded efficiently and without complications in the Makosza two-phase system [2] [a benzene solution of the components, 50% aqueous sodium hydroxide solution, and tributylbenzyl-ammonium chloride (TBBA) as the catalyst]. According to modern concepts [2], the following scheme is realized in this case (Q^+Cl^- is the catalyst, subscripts "a" and "o" denote the aqueous and organic phases, respectively, and Gl is an acetylated sugar residue):

$$(Na^+OH^-)_a + QCl^- \rightleftarrows (Na^+Cl^-)_a + (Q^+OH^-)_o,$$
$$(Q^+OH^-)_o + (GlOH)_o \rightleftarrows (Q^+OGl^-)_o + H_2O,$$
$$(Q^+GlO^-)_o + (xR)_o \longrightarrow (GlOR)_o + (Q^+x^-)_o.$$

As a result, we obtained the corresponding O-hetaryl derivatives (Ib-e, II-IV-b,c) of monosaccharides. Data on the synthesized compounds are presented in Table 1. The synthesis of VIb,d and VIIb,d was described in [11], but their pharmacological properites are discussed along with those of products Ib-e and II-IVb,c in the present paper.

The primary formation of per-O-substituted derivatives II,IVb,c, which occurs most efficiently in the case of IV when benzene is replaced by dioxane and aqueous alkli is replaced by solid alkali, was unexpected.

To ascertain the dependence of the pharmacological properties on the presence of hydro-

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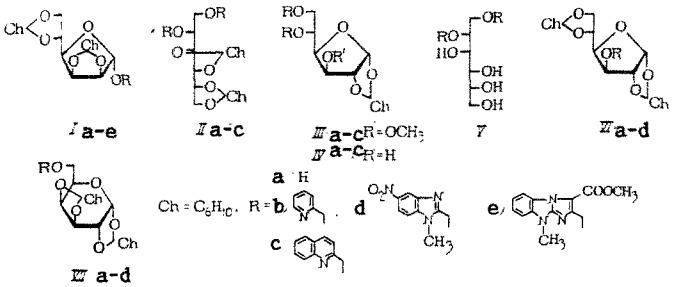


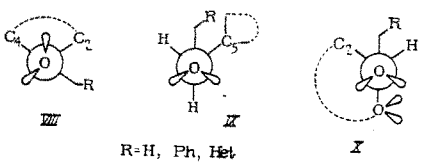
phobic cyclohexylidene fragments we subjected IIb to mid hydrolysis in trifluoroacetic acid; this is the most effective method for unblocking acetylated sugars [20]. The corresponding polyol was obtained in good yield (70%) in this case.

The structures proposed for O-hetaryl derivatives I-IV were confirmed by UV (hetaryl absorption bands at 250-350 nm, which are characteristic for the starting hetaryl systems [14, 17, 25]), IR (heteroarmatic absorption at 1500-1700 cm^{-1} and the absence of absorption of hydroxy groups), and PMR spectroscopy (the expected ratio of the intensities of the signals of the heteroaromatic protons at δ 7.0-9.0 ppm and of the protons of the cyclohexylidene protective groups at δ 1.5 ppm).

A study of the polarimetric properties of the mono-, di-, and trisubstituted derivatives gives information regarding the stereochemistry of the introduced heterocyclic groupings of compounds of the VI-VII type (Table 2).

The rotational contributions of the hetaryl groupings of compounds of the VI-VII type prove to be closer than one should have expected starting from the significant polarities of the heterocyclic fragments, which usually determine the magnitude of the contribution [1]. The rotational contribution of the introduced fragments in VI-VII is evidently determined primarily by their methylene groups, while in compounds of the I type these values are determined by the purely anomeric effects of restricted rotation of the heterocyclic fragment, resembling the syn and anti isomerization of N-glycosides [13].

According to the generally accepted concepts [1] the negative contributions of the methylene groups in compounds of the VI-VII type correspond to hindered rotamers VIII and IX, respectively, whereas the positive contribution in compounds of the VI type corresponds to rotamer X. This information will possibly prove to be useful in elucidating the mechanisms of the pharmacological activity of the indicated compounds.



The virtual absence of Cotton effects in the region of hetaryl absorption in the circular dichroism (CD) spectra is due primarily to the marked remoteness of the chromophores from the chiral centers, the strong absorption of the chromophores in the UV spectra, and , at least in some cases, their free rotation.

It is known that many medicinal preparations, including psychotropic, antispasmodic, and local-anesthetic preparations, give a membranotropic effect [4]; the interrelationship between this effect and certain forms of activity has been distinctly traced. For example, in [21] it was shown that the ability of phenothiazines to protect erythrocytes from hemolysis correlates with their neurotropic activity.

O-Hetaryl derivatives I-VII combine hydrophobic and hydrophilic fragments in their structures; this makes it possible to assume the existence for them of a membranotropic effect and, consequently, neurotropic activity. To study it we used a method based on the ability of psychotropic preparations to protect the neuroglial elements of the brain from the harmful activity of anticerebral antibodies in the blood serum of patients afflicted with schizophrenia [3]. The activity of the investigated compounds was judged from their ability to inhibit proceses involving peroxide oxidation of lipids (POL) of the brain to malonic dialdehyde (MDA), the percentage of which in test samples was determined by the thiobarbituric method.

TABLE 1. O-Hetaryl-Substituted Monosaccharides

Compound	Yield, %	Found, %			Empirical formula	Calc., %			$[\alpha]_D$, °C methanol	Reaction time, h
		C	H	N		C	H	N		
Ib	80	64,1	7,7	3,3	$C_{24}H_{33}NO_6H_2O$	64,1	7,8	3,1	+30	10
Ic	82	70,2	7,4	3,2	$C_{28}H_{35}NO_6$	69,9	7,3	2,9	+19,2	8
Id	98	60,9	6,4	7,6	$C_{27}H_{35}N_3O_8$	61,2	6,6	7,9	+15	10
Ie	80	64,3	6,7	7,2	$C_{31}H_{39}N_3O_8$	64,0	6,7	7,2	+37	18
IIb	84	68,6	7,2	5,3	$C_{30}H_{38}N_2O_6$	68,9	7,3	5,4	+6,7	7
IIc	80	73,8	7,1	4,5	$C_{38}H_{44}N_2O_6$	73,7	7,1	4,5	—1,1	10
IIIb	80	65,5	7,0	6,2	$C_{25}H_{32}N_2O_6$	65,7	7,0	6,1	—12	10
IIIc	80	69,9	6,3	5,3	$C_{33}H_{36}N_2O_6$	71,2	6,5	5,3	—16,7	13
IVb	70	67,8	6,3	7,9	$C_{30}H_{35}N_3O_6$	67,5	6,6	7,9	—28,5	30
IVc	68	73,5	5,9	5,7	$C_{42}H_{41}N_3O_6$	73,8	6,2	6,0	—35	13
V	75	59,1	6,8	7,5	$C_{18}H_{24}N_2O_6$	59,3	6,6	7,7	—4	48

EXPERIMENTAL CHEMICAL

The IR spectra of suspensions of the compounds in mineral oil or solutions in CCl_4 were recorded with an IR-71 spectrometer (East Germany). The UV spectra of solutions in methanol were obtained with a Specord UV-VIS spectrophotometer (East Germany). The PMR spectra of solutions in CCl_4 (0.3-0.4 m) were recorded with a Tesla BS-467 spectrometer (80 MHz) (Czechoslovakia) with hexamethyldisiloxane (HMDS) as the internal standard. The individuality of the substances and the course of the reactions were monitored by thin-layer chromatography (TLC) on alumimum oxide.

Compounds Ia and IIIa were obtained by a somewhat modified method [15], which is presented below. Dicyclohexylidenemannitol (IIa) was synthesized by the method in [19]. The 2-chloromethyl-substituted pyridines and quinolines were obtained by the method in [25], and 1-methyl-2-chloro-methyl-5-nitrobenziimidazole was obtained by the method in [14]. 2-Bromomethyl-3-methoxycarbonyl-9-methylimidazao[1,2-a]benzimidazole was obtained by bromination of the corresponding 2-methyl derivative of imidazo[1,2-a]benzimidazole [17] with bromosuccinimide in CCl_4.

2,3;5,6-Di-O-Cyclohexylidene-α-D-mannofuranose (Ia). A three-necked flask equipped with a reflux condenser and a dropping funnel was charged with 65 g (360 mmole) of D-mannose, 76.6 g (770 mmole, 80 ml) of cyclohexanone, and 50 ml of dioxane, after which 20 ml of concentrated sulfuric acid was added dropwise with stirring at 0°C in the course of 15 min. The thickened mixture was allowed to stand for 0.5 h, after which 0.6 liter of water was added, the aqueous mixture was stirred until disintegration of the lumps was complete, and 15% sodium hydroxide solution was added until the mixture was neutral. The mixture was filtered, and the precipitate was washed twice with 100-ml portions of hexane and air dried to give 106.3 g (86%) of Ia with mp 114-117°C (from benzene).

1,2-O-Cyclohexylidene-α-D-glucofuranose (IIIa). A 71-g (200 mmole) sample of 1,2;5,6-di-O-cyclohexylidene-3-O-methyl-α-D-glucofuranose [7] was dissolved in a mixture of 450 ml of glacial acetic acid and 150 ml of water at 70°C, after which 1 g of potassium hydroxide was added, and the mixture was allowed to stand for 0.5 h with monitoring of the course of the reaction by TLC. At the end of the reaction, 20 g of potassium hydroxide was added to the mixture, and ~ 300 ml of the solvent was removed by vacuum distillation; the residue was dissolved in 400 ml of water, and the resulting solution was washed with petroleum ether (three 100-ml portions) and extracted with chloroform (four 80-ml portions). The chloroform extract was dried over anhydrous sodium sulfate and evaporated; the residue was recrystallized from 200 ml of toluene, 50 ml of petroleum ether was added, and the mixture was stirred thoroughly and filtered. The precipitate on the filter was washed with 100 ml of benzene-petroleum ether (5:2) to give 30 g (55%) of IIIa.

O-Hetaryl-Substituted Carbohydrates Ib-e, IIb,c, and IIIb, c. Benzene solutions of starting carbohydrates Ia, IIa, or IIIa (~ 1 g) and the corresponding chloromethylated heterocyclic systems (based on 1 mole of the halomethyl derivative for each free hydroxy group of the monosaccharide) in the presence of 30 ml of 50% sodium hydroxide solution and 20 mg of TBBA were shaken until the reaction was complete. The benzene layer was then separated washed with water, and dried with anhydrous sodium sulfate. The solvent was removed by

TABLE 2. Rotational Properties of O-Hetaryl-Substituted Monosaccharides

Compound	$[M]_D^0$	$[M]_{500}^0$	$\Delta [M]_D^{0*}$	$\Delta [M]_{500}^{0*}$	Solvent	Lt. cited
Ia	+150	—	0	0	$CHCl_3$	[22]
Ia***	+127	+160	−23	—	CCl_4	—
Ib	+130	+212	−20	—	CH_3OH	—
Ic	+92	+273	−58	—	CH_3OH	—
Id	+79	+130	−71	—	CH_3OH	—
Ie	+215	+260	+65	—	CH_3OH	—
IIa	+38	—	0	0	$CHCl_3$	[24]
IIb	+43	+87	+5	—	CH_3OH	—
IIc	−5	−15	−43	—	CH_3OH	—
IIIa	−17	−34	0	0	CCl_4	—
IIIa***	−66	−93	−49	−59	CCl_4	[7]
IIIb	−55	−60	−140	−76	CH_3OH	—
IIIc	−93	−140	−76	−116	CH_3OH	—
IVa	+26	—	0	0	$(CH_3)_2CO$	—
IVb	−152	−180	−178	—	CH_3OH	—
IVc	−236	−450	−262	—	CH_3OH	—
VIa	+15	+5	0	0	CH_3OH	—
VIa***	−47	−72	−62	−77	CH_3OH	—
VIa***	−69	−109	−54	−104	$CHCl_3$	[7]
VIb	−65	−89	−80	−94	CH_3OH	[10]
VIc	−63	−94	−78	−99	CH_3OH	[10]
			−70**	−86**		
VIIa	−278	−415	0	0	CCl_4	[7]
VIIa***	−161	−222	+117	+193	CCl_4	[7]
VIIb	−175	−240	+103	+205	CH_3OH	[11]
VIIc	−165	−214	+113	+175	CH_3OH	[11]
			+117**	+201**		

Note. One asterisk pertains to $\Delta[M] = [M]_{sub} - [M]_{un}$, two asterisks pertain to the average $\Delta[M]$ value, and three asterisks pertain to R-CH_3.

evaporation, and the residue was chromatographed with a column packed with aluminum oxide by successive elution with petroleum ether, benzene, and chloroform. The fraction with R_f 0.5 was collected from the chloroform eluate, and the chloroform was evaporated to give chromatographically homogeneous products.

O-Hetaryl-Substituted Carbohydrates IVb, c. A mixture of 1 g (3 mmole) of 1,2-O-(1-cyclohexylidene) glucofuranose (IVa) [15] and the corresponding chloromethyl derivative [0.38 g (3 mmole) for 2-chloromethylpyridine and 0.42 g (3 mmole) for 2-chloromethylquinoline] in 50 ml of dioxane was shaken with 5 g of finely ground sodium hydroxide and 20 mg of TBBA at 20°C until the reaction was complete, after which the mixture was filtered. The dioxane was diluted with water, and the aqueous mixture was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated. Subsequent purification was carried out as described above for Ib, e.

1,2-Di-O-(Pyridylmethylenemannitol) (V). A solution of 1 g (2 mmole) of IIb in 20 ml of trifluoroacetic acid was maintained at 20°C until the reaction was complete (2 days), after which the solvent was evaporated under the vaccum of a water aspirator with heating. The residue was dissolved in chloroform, and product V was extracted with distilled water. Evaporation of the water gave 0.38 g of V in the form of a colorless syrup.

EXPERIMENTAL PHARMACOLOGICAL

The experiments were carried out on a homogenate of the brains of white mongrel rats of both sexes, which was prepared on the basis of 1 g of brain tissue per 30 ml of Tris·HCl buffer with pH 7.4. The test compound in the amount of 0.1 ml of a solution in dimethyl sulfoxide (DMSO) with a concentration of 100 μg/ml was introduced into a test sample containing 0.5 ml of the brain homogenate and 0.2 ml of the blood serum of patients afflicted with schizophreina. In control experiments, instead of the blood of patients, we introduced the blood serum of a healthy donor, which completely inhibited processes involving peroxide oxidation of lipids (POL) in the case of aerobic incubation at 37°C. In the latter case the reaction was stopped by the addition of 0.1 ml of fused trichloroacetic acid. A 2-ml sample of a 30% solution of this acid and 0.1 ml of a 0.75 M solution of thiobarbituric acid were then added to the test sample, after which the mixture was heated on a water bath for 15 min and centrifuged, and the optical density of the colored complex of malonic dialdehyde (MDA) was

determined with an SF-24 spectrophotometer at 535 nm. The percent of the decrease in the amount of MDA in the test sample with respect to the control was determined by taking into account the level of MDA in the control, in an experiment involving spontaneous POL under the influence of the blood serum of patients afflicted with schizophrenia, and in the presence of the investigated substance. The experimental data obtained on the inhibition of POL by the investigated substances were compared with the same effect of the known preparation Aminazine. The compounds and their POL inhibition (in percent) were as follows: Ib, 80; Ic, 90; Id, 20; Ie, 20; IIb, 70; IIc, 60; IIIb, 90; IIIc, 80; IVb, 60; V, 20; VIb, 70; VIc, 10; VId, 80; VIIb, 80; Aminazine, 90.

DISCUSSION OF RESULTS

As demonstrated in the experimental section, Ic and IIIb have neurotropic activity that is close to that of Aminazine. Somewhat lower activity is characteristic for derivatives Ib, IIb,c, IIIc, VIb,d, and VIIb. The remaining O-hetaryl derivatives of carbohydrates discussed in this paper do not have appreciable neurotropic activity.

In conclusion, let us note that the investigated compounds belong to the rare class of O-hetaryl derivatives of sugars. In view of the simplicity and universality of their production under conditions of interphase catalysis by the method proposed in the research one can count on the extensive study of these new biologically active substances with neurotropic activity. Let us also note that Ib-e are a new type of O-glycosides with a heterocyclic aglycone, the synthetic precursors for which can be obtained via a universal method [12].

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF STEREOISOMERIC DERIVATIVES OF trans-DECAHYDROQUINOLINE

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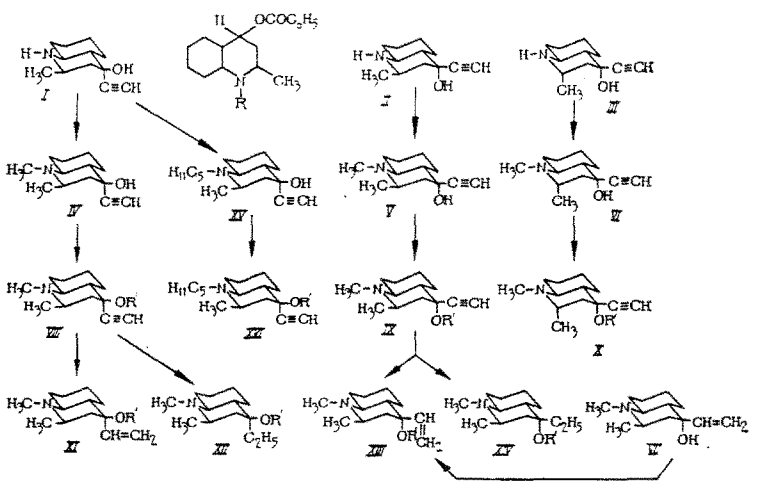
Compounds with high anesthetizing activity have been detected among oxygen derivatives of decahydroquinoline [8]. A number of stereoisomeric benzoic acid esters of 1-R-2-methyl-decahydroquinoline-4-ol (R = C_1-C_5 alkyl, allyl, etc.) have clearly expressed local-anesthetic activity [10]. However, they, like the anesthetics being used in practice, do not fully meet the modern requirements of practical medicine, chiefly because of their toxicity and irritating properties. The problem of the search for and creation of new effective local anesthetics therefore continues to remain an extremely urgent matter.

The simple and practicable methods that we have developed for obtaining three geometrical isomers of 2-methyl- (I-III) and 1,2-dimethyl-4-ethynyl-trans-decahydroqunolin-4-ol (IV-VI) [6,9] have created favorable possibilities for the synthesis of anesthetics of the decahydroquinoline series with ethynyl, vinyl, and ethyl groups attached to $C_{(4)}$, which have not been studied in a pharmacological respect. These studies make it possible to trace the dependence of the pharmacological properties of the compounds on the spatial orientation and nature of the substituents attached to $C_{(2)}$ and $C_{(4)}$.

In this connection, in the present research we obtained previously undescribed decahydroquinoline derivatives and studied their pharmacological properties.

Stereoisomeric acetylenic alcohols IV-VI [6, 9], which were obtained by N-methylation of noramino alcohols I-III, served as the starting substances.



R = alkyl C_1 - C_5 , allyl et al.; R'=COC_6H_5.

*Deceased.

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