in the case of the ρ series of compounds that contain substituents in the phenyl ring [4]. This should be explained by the fact that in series 1 and 2 the substituents are located directly in the pyridochromene system throughout which the positive charge is concentrated and interact more actively with it. In series 3 the substituents evidently have approximately the same effect on the stabilities of both ions II and IV, and in this case the ρ value is lower by a factor of two than in series 1 and 2.

EXPERIMENTAL

The previously found optical densities at the corresponding acidities of the medium [1, 2] were used to calculate the logarithms of the indicator ratios [log([IV]/[II])]. Verification of the observance of a linear dependence of log([IV]/[II]) on the acidity of the medium expressed in terms of acidity function $H_R - H_0$ was carried out by the method of least squares. The pK values of the quasi-tautomeric equilibrium were calculated from the equation $pK = (H_R - H_0) + \log([IV]/[II])$ [4] from seven points at a predesignated reliability of 0.98.

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THREE-DIMENSIONAL STRUCTURE OF 2-DIMETHYLAMINO-1,3-DIOXACYCLANES

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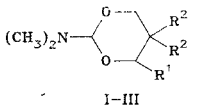
UDC 541.63:547.841:543.422.25

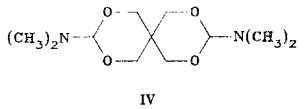
It was established by ^1H NMR spectroscopy that a chair conformation with an equatorial orientation of the dimethylamino group is the preferred conformation for methyl and 5,5-spiro derivatives of 2-dimethylamino-1,3-dioxanes.

It is known [1-5] that most substituted 1,3-dioxanes are chair conformers. Alkyl groups in the α position relative to the heteroatom ensure the preferableness of a conformation with an equatorial orientation of the substituents, whereas alkoxy groups ensure the preferableness of a conformation with an axial orientation of the substituents. At the same time, the literature does not contain information regarding the three-dimensional structure of nitrogen analogs of 2-alkoxy-1,3-dioxanes.

We have synthesized a number of 2-dimethylamino-1,3-dioxanes (I-IV):



I-III



IV

I $R^1=R^2=H$; II $R^1=CH_3$, $R^2=H$; III $R^1=H$, $R^2=CH_3$

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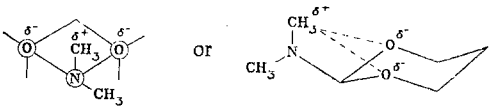
The configurations and primary conformations of I-IV were determined on the basis of an analysis of the character of the multiplet splitting and the chemical shifts of the resonance lines of the protons in the ^1H NMR spectra of 10% solutions of these compounds in carbon tetrachloride and deuteroacetone.

The protons of the methylene groups of the hydrocarbon part of the ring give complex multiplets in the spectrum of 2-dimethylamino-1,3-dioxane (Table 1 and Fig. 1a) as a consequence of a shift in the conformational equilibrium to favor a certain preferred conformation. The spin–spin coupling constants (SSCC) of these protons were 2.2 Hz for $^3J_{Ee}$, 5.0 Hz for $^3J_{Ea}$, 2.8 Hz for $^3J_{Ae}$, 11.2 Hz for $^3J_{Aa}$, −12.0 Hz for $^2J_{AE}$, and −13.4 Hz for $^2J_{ae}$. The observed difference in the vicinal and geminal SSCC, as well as the difference in the H_A, H_E, H_a, and H_e chemical shifts, is due to the effect of the electronegativities and orientational contributions of the O and C atoms. The SSCC and magnetic nonequivalence of the axial and equatorial protons attached to $C_{(4)}$ and $C_{(6)}$ ($\Delta\delta_{AE}$ = 0.32 ppm) and $C_{(5)}$ ($\Delta\delta_{ae}$ = 0.63 ppm) are characteristic for 1,3-dioxanes in the chair conformation [1, 6]. It should be noted that, in contrast to 2-alkoxy-1,3-dioxanes [7-9], the order of deshielding of the protons attached to $C_{(4)}$, $C_{(6)}$, and $C_{(5)}$ for the compound under consideration ($\sigma_E < \sigma_A << \sigma_a < \sigma_e$) is the same as in 2-alkyl-1,3-dioxanes [1]. This makes it possible to assume that in this case, as in the case of 2-alkyl-1,3-dioxanes, the substituent attached to $C_{(2)}$ is equatorially oriented. The proton attached to $C_{(2)}$ is consequently axially oriented, and its resonance is realized at δ 4.57 ppm, which is characteristic for axially oriented acetal protons [1, 10]. The absence of broadening of this signal, which constitutes evidence for the small value of the long-range SSCC, also makes it possible to ascribe an axial orientation to it [4]. In the case of 2-ethoxy-1,3-dioxane the $^5J_{HH}$ value for coupling between the equatorially oriented protons attached to $C_{(2)}$ and $C_{(5)}$ was 1 Hz [8]. Thus 2-dimethylamino-1,3-dioxane exists primarily in a chair conformation with an equatorially oriented dimethylamino group attached to $C_{(2)}$.

The reasons for the preferableness of an equatorial orientation of the polar $N(CH_3)_2$ group in the α position relative to the ring heteroatom — "the inverse anomeric effect" — have been discussed in a number of papers [11-13]. However, in connection with the small amount of study devoted to this problem, there is no unified opinion regarding the nature of this phenomenon. It has been shown for a number of 1,4-dioxanes that in the case of bulky 2-alkoxy substituents (tert-butoxy [14], phenanthryloxy [15], and trimethylsiloxy [16]) the steric effect predominates over the polar effect, and the conformational equilibrium is shifted to favor the formation of the equatorial conformer. The steric factor evidently also plays a substantial role in the case of the bulky dimethylamino group. Additional stabilization of the equatorial conformer occurs owing to induction of positive charge on the carbon atoms of the methyl group by the electron-withdrawing nitrogen atom.



A different orientation of the 4-CH_3 group is possible in the case of 2-dimethylamino-4-methyl-1,3-dioxane [9]. However, the spectrum of II (Table 1) is the spectrum of an individual isomer in the preferred chair conformation with an equatorial orientation of the $N(CH_3)_2$ group. The orientation of the 4-CH_3 group can be determined starting from the SSCC of the 4-H proton. The 6.2 Hz splitting is due to spin–spin coupling with the protons of the methyl group. The $^3J_{4H5a}$ value of 11.4 Hz and the $^3J_{4H5e}$ value of 3.2 Hz are characteristic for axial–axial and axial–equatorial coupling of the protons, respectively. In addition, the constant of 3.2 Hz gives angle θ ~ 55° on the Karplus curve [4]. This θ value constitutes evidence for a trans orientation of the 5-H_e and oxygen atoms of the heteroring [2]. These results confirm the correctness of the selection of the orientation of the substituents and the conformation of the ring. Thus the 4-CH_3 group is equatorially oriented, and II is the 4e-CH_3-2e-$N(CH_3)_2$ or cis isomer.

In the spectrum of 5,5-dimethyl-substituted 2-dimethylamino-1,3-dioxane the protons of the methylene groups attached to $C_{(4)}$ and $C_{(6)}$ resonate in the form of a typical AB quartet with a geminal constant of 10.8 Hz. The protons of the gem-dimethyl grouping attached to $C_{(5)}$ give two singlets. The magnetic nonequivalence of the H_A and H_E protons ($\Delta\delta_{AE}$ = 0.18

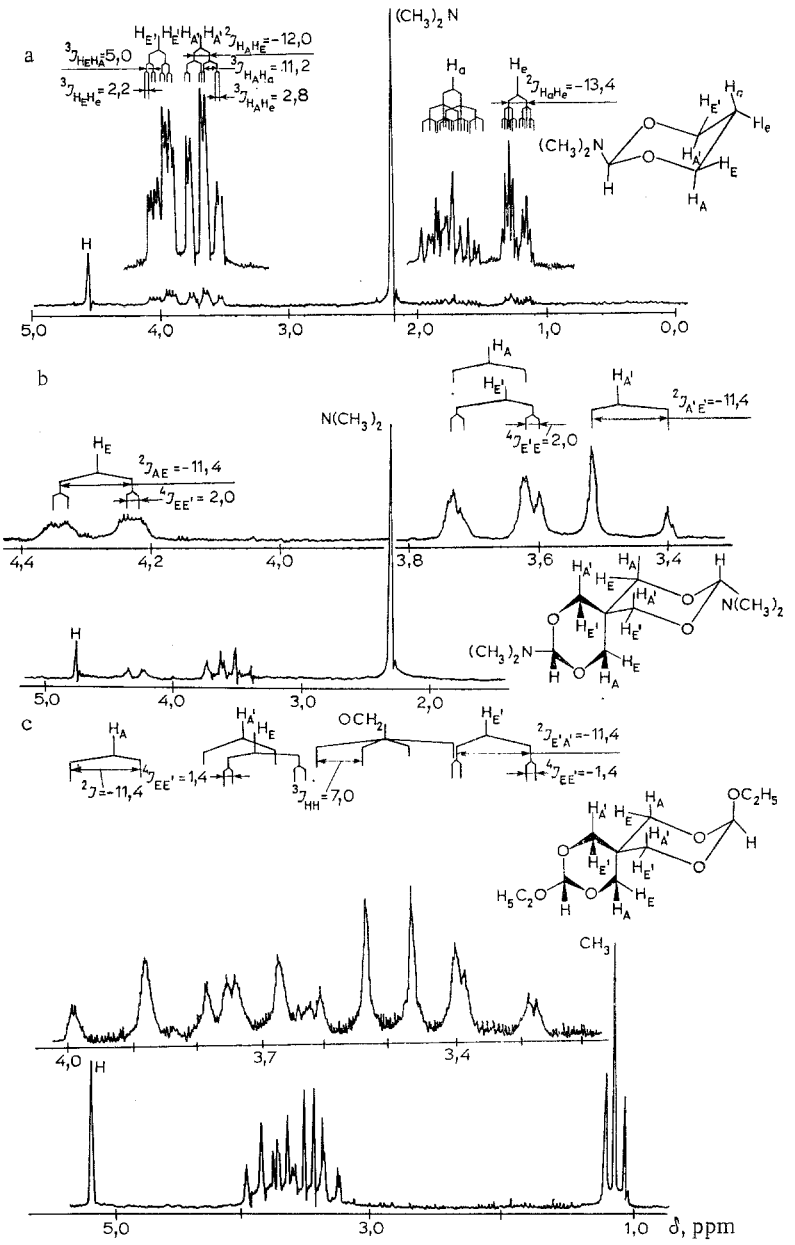


Fig. 1. ^{1}H NMR spectra of 2-dimethylamino-1,3-dioxacyclanes: a) 2-dimethylamino-1,3-dioxane (solution in CCl_4); b) 2,9-bis(dimethylamino)-1,3,8,10-tetraoxaspiro[4,4]undecane (solution in dimethyl sulfoxide); c) 2,9-diethoxy-1,3,8,10-tetraoxaspiro[4,4]undecane (solution in hexamethyldisiloxane).

ppm) and the CH_3a and CH_3e groups ($\Delta\delta_{ae}$ = 0.38 ppm) is the same as in the case of chair-form 5,5-dimethyl-2-alkyl-1,3-dioxanes [8] (for example, $\Delta\delta_{AE}$ = 0.20 ppm and $\Delta\delta_{ae}$ = 0.46 ppm for 2,5,5-trimethyl-1,3-dioxane). The small $\Delta\delta_{AE}$ value is explained by the orientational contribution of the axially oriented methyl group attached to $C_{(5)}$ [17]. The resonance of the substituents attached to $C_{(2)}$ is similar to the resonance of the substituents attached to $C_{(2)}$ in I and II. Thus, III, like I and II, is a chair isomer with an equatorially oriented 2° dimethylamino group. The correctness of the selection of the conformation in III is confirmed by the magnitude of the two long-range SSCC $^4J_{EE}$ = 1.2 Hz and $^4J_{(H_A,CH_3a)}$ = 1.0 Hz. The effect of the orientation on the coupling of protons through four or five σ bonds has been previously noted [4, 18]. When these bonds are arranged in a planar zigzag conformation, which is realized in the case of a chair, the long-range SSCC reach 1-3 Hz.

TABLE 1. Chemical Shifts and Spin—Spin Coupling Constants (SSCC) of the Protons of Some 2-Dimethylamino-1,3-dioxacyclanes

Compound	Solvent	δ, ppm								SSCC, Hz							
		2e (9e)	2a (9a)	4E¹ (11E¹)	4A¹ (11A¹)	5e	5a	6E (7E)	6A (7A)	$^2J_{EA}$	$^3J_{Ee}$	$^3J_{Ea}$	$^3J_{Ae}$	$^3J_{Aa}$	$^2J_{ae}$	$^4J_{EE^1}$	$^4J_{Aa}$
I	CCl_4	2,20	4,55	3,97	3,65	1,16	1,79	3,97	3,65	−12,0	2,2	5,0	2,8	11,2	−13,4	—	—
	$(CD_3)_2CO$	2,20	4,62	3,95	3,68	1,23	1,73	4,62	3,95	−12,2	2,2	5,0	2,8	11,2	−13,2	—	—
II	CCl_4	2,22	4,57	1,12	3,67	1,24	1,41	3,94	3,61	−11,4	1,6	5,0	3,2	11,4	−13,0	—	—
	$(CD_3)_2CO$	2,22	4,65	1,08													
III	CCl_4	2,22	4,47	3,48	3,30	0,69	1,07	3,48	3,30	−10,8	—	—	—	—	—	+1,2	1,0
	$(CD_3)_2CO$	2,23	4,60	3,49	3,39	0,66	1,05	3,49	3,39	−10,4	—	—	—	—	—	+1,2	0,6
IV	$(CD_3)_2SO$	2,32	4,76	3,65	3,48	—	—	4,28	3,68	−11,4	—	—	—	—	—	+2,0	—
	$(CD_3)_2CO$	2,21	4,67	3,57	3,42	—	—	4,28	3,59	—	—	—	—	—	—	+2,0	—
V	HMDS	5,15	1,07, 3,50	3,70	3,92	—	—	3,34	3,72	−11,0	—	—	—	—	—	+1,4	—
	$(CD_3)_2CO$	5,24	1,13, 3,56	3,62	3,92	—	—	3,57	3,87	−11,2	—	—	—	—	—	+1,2	—
	CCl_4	5,17	1,17, 3,52	3,62	3,89	—	—	3,41	3,74	−11,4	—	—	—	—	—	+1,2	—

In the spectrum of 2,9-bis(dimethylamino)-1,3,8,10-tetraoxaspiro[4,4]undecane* the chemical shifts of the substituents attached to $C_{(2)}$ and $C_{(9)}$ coincide (Fig. 1b and Table 1) and are similar to the shifts observed in the case of I-III. The configurations of the substituents attached to the acetal carbon atom of the two rings are consequently identical and are the same as in I-III. The protons of the methylene groups of the hydrocarbon part of the spiro system give two nonequivalent AB quartets with an identical geminal SSCC ($^2J_{HH}$ = −11.4 Hz) but with different chemical shifts. The latter is explained by the fact that in a molecule with a fixed spatial orientation of the bonds and atoms of both rings the $C_{(4)}$ and $C_{(6)}$ positions [like the $C_{(7)}$ and $C_{(11)}$ positions] are magnetically nonequivalent. It is apparent from an examination of a three-dimensional model that, as a consequence of the symmetry of the molecule, the environments of $C_{(6)}$ and $C_{(7)}$ are identical and are more susceptible to the effect of the magnetic fields of the oxygen atoms of the adjacent ring than the environments of the identical (to one another) $C_{(4)}$ and $C_{(11)}$ atoms. The nonequivalence of the geminal protons attached to $C_{(6)}$ and $C_{(7)}$ ($\Delta\delta_{AE}$ = 0.60 ppm) is consequently considerably greater than in the case of the protons attached to $C_{(4)}$ and $C_{(11)}$ ($\Delta\delta_{AE}$ = 0.17 ppm), the environments of which, as expected, are most similar to the environments of the corresponding protons attached to $C_{(4)}$ and $C_{(6)}$ in I-III. Each of the lines of the equatorial protons (the low-field components of the AB quartets) is split into a clearly expressed doublet with $^4J_{HH}$ = 2.0 Hz. The long-range coupling of the axial protons attached to $C_{(6)}$ and $C_{(7)}$, which are located at the ends of the planar zigzag $H_A-C_{(6)}-C_{(5)}-C_{(7)}-H_A$ fragment, could not be determined because of overlapping of the signals. Thus both six-membered rings exist in the preferred chair conformation with a diequatorial orientation of the dimethylamino groups attached to the acetal carbon atoms.

It seemed of interest to compare the stereochemical structure of IV and 2,9-diethoxy-1,3,8,10-tetraoxaspiro[4,4]undecane (V). Just as in the case of IV, the methylene protons of the hydrocarbon part of the ring of the latter give two AB quartets (Fig. 1c). However, in contrast to IV, the equatorial protons of each of the AB spin systems resonate at stronger field than the corresponding axial protons, as one can judge on the basis of the doublet structure of the high-field lines of the AB quartets. The inversion of the shielding constants of the protons under consideration can be understood if it is assumed that both rings exist in the preferred chair conformation, whereas the ethoxy substituents are axially oriented.

As a consequence of the exo configuration, the magnetic-anisotropic effect of the unshared pair of the oxygen atom of the ethoxy group is responsible for the preferred deshielding of the axial protons of the methylene groups of the hydrocarbon part of the spiro system and is insignificant for the corresponding equatorial protons. The resonance of the acetal protons is realized at 5.10-5.17 ppm, and this also constitutes evidence in favor of their equatorial orientation. Thus an anomeric effect is realized in the case of V.

EXPERIMENTAL

Compounds I-III were obtained by the reaction of equimolar amounts of dimethoxydimethylaminomethane with the corresponding polydiols by refluxing with simultaneous removal of the resulting methanol by distillation by the method in [19]. Compound V was obtained from ethyl orthoformate and pentaerythritol.

The ^1H NMR spectra of solutions of the investigated compounds were recorded with a Tesla BS-497 spectrometer (100 MHz) at room temperature with hexamethyldisiloxane as the internal standard.

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*For convenience in comparing the experimental data the numbering does not correspond with the IUPAC rules.

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SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES.

34.* SYNTHESIS OF 4-SUBSTITUTED 2-(3-INDOLYL)THIAZOLES

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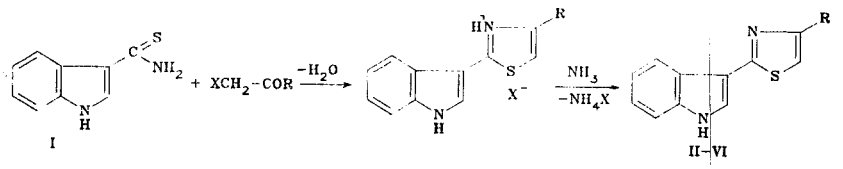
UDC 547.752'789:542.953.2:543.51'422.4

4-Substituted 2-(3-indolyl)thiazoles were synthesized by condensation of indole-3-thiocarboxamide with halomethyl ketones. Reactions involving the nucleophilic substitution of the chlorine atom in 4-chloromethyl-2-(3-indolyl)thiazole were examined.

There has recently been increased interest in noncondensed bisheterocyclic systems that contain indole and thiazole fragments simultaneously. The special interest in heterocycles of this type is due to the fact that substances with a broad spectrum of biological activity have been found among them [2-4]. It has also been noted that some indolyl-containing thiazoles display radioprotective properties [5].

In order to search for new potential biologically active substances we synthesized some previously undescribed indolylthiazoles and studied their properties. In the present research for the synthesis of heterocycles of the indicated type we used the reaction of the accessible indole-3-thiocarboxamide (I) with α-halo-substituted carbonyl compounds. There has thus far been only one report of the synthesis of indolylthiazoles from thiocarboxamides of the indole series [6].

The condensation of thiocarboxamide I with α-halomethyl ketones was carried out by refluxing mixtures of equimolar amounts of the reagents in alcohol for several hours. The resulting 4-substituted 2-(3-indolyl)thiazole hydrohalides were converted to free bases II-VI by treatment with ammonium hydroxide.



I II-VI

X=Cl, Br; II R=CH_3, III R=C_6H_5, IV R=4-$CH_3OC_6H_4$, V R=2- thienyl, VI R=CH_2Cl

*See [1] for communication 33.

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