Tetrahedron. Vol. 29, pp. 2277 to 2283. Pergamon Press 1973. Printed in Great Britain

CONFORMATION OF SUBSTITUTED BENZYLIDENE AND ISOPROPYLIDENE NUCLEOSIDES

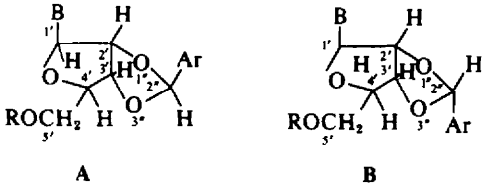
A. M. BELIKOVA, N. I. GRINEVA* and G. N. KABASHEA
Institute of Organic Chemistry of Siberian Division of the Academy of Sciences, Novosibirsk, 90, U.S.S.R.

(*Received in the UK* 2 *January* 1973; *Accepted for publication* 26 *February* 1973)

Abstract—PMR and CD spectroscopy has been used to show that the phenyl grouping at $C^{2''}$ of the dioxolane ring in each diastereomeric benzylidene nucleoside occupies the axial position, most probably due to electrostatic interaction with the heterocyclic base residue. The conformation of the ribose moiety of benzylidene nucleosides is somewhat different from that of isopropylidene analogues; the C_s-conformation of ribose is characteristic of *trans*-benzylidene uridines and of isopropylidene uridine and adenosine.

Recently the conformation of 2',3'-O-[4-(N-2-chloroethyl-N-methylamino)benzylidene]-nucleotides[1] and -oligonucleotides[2,3] has been studied in this laboratory in connection with the development of an approach to selective modification of nucleic acids, using these nucleotides as alkylating agents.[4,5]

Circular dichroism spectra[1] (CD) indicated that a strong electrostatic interaction takes place between the phenyl substituent and heterocyclic base in both *trans*- and *cis*-diastereomers of substituted benzylidene nucleosides and nucleotides A and B respectively).



A B

(B is adenine-9 or uracil-1;
Ar is phenyl or *p*—N(CH₃)CH₂CH₂Cl
R is hydrogen or phosphate)

Figure 1 shows CD spectra of 2',3'-O-[4-(N-2-chloroethyl-N-methylamino)benzylidene]-uridine-5'-methyl phosphate (A3) and -adenosine-5'-methyl phosphate (B1) in aqueous soln.[1] The double Cotton effect in the longer wavelength region (π–π^* transition) is believed to be due to the non-bonded intramolecular interaction between the aryl substitute and the base, rather than to the presence of the dioxolane ring, since a model compound (isopropylidene uridine, A2) exhibits a CD spectrum similar to that of uridine-5'-methyl phosphate (A1 on Fig. 1) over this wavelength range. The conclusion is supported by the loss of the double Cotton effect by uracil ring cleavage in benzylidene uridine.[1]

Studies of molecular models reveal that conformations with an aryl group in the normally favoured equatorial position do not bring together the aryl grouping and the base residue, in benzylidene nucleosides and nucleotides. Distances between the rings of 3–4 Å, typical of base stacking in nucleic acids,[6] are impossible even in conformations with axial aryl at $C^{2''}$, although separation is small enough (5–6 Å) to allow stabilising interaction of dipole moments. Optical activity is then due to perturbation of the symmetry of the benzene chromophore;[7] the intensity of the double Cotton effect decreases with increasing temperature until it practically disappears at 82° (Fig. 1C) suggesting that at higher temperatures conformations with equatorial aryl[1] are predominant. Conformations that provide the possibility of dipole–dipole interaction of aryl substituents with the base residues in *trans*- and *cis*-benzylidene nucleosides are shown in Fig. 2. Studies of models revealed that the minimum distance between the aryl group and the base residue can be achieved by minor change of the normally favoured conformations of the ribose moiety and of the dioxolane ring. The conformations of both the latter two moieties, and the aryl grouping have been studied in both diastereomers of 2',3'-O-[4-(N-2-chloroethyl-N-methylamino)benzylidene]-adenosin (**1**), 2',3'-O-[4-(N-2-chloroethyl-N-methylamino)benzylidene] uridine (**2**) and 2',3'-O-benzylidene uridine (**3**) in comparison with the conformation of isopropylidene adenosine (**4**), isopropylidene uridine (**5**) and that of uridine and adenosine themselves in dimethylformamide solution by PMR spectroscopy.

The PMR spectra of benzylidene nucleosides in dimethylformamide are shown in Figs. 3 and 4.

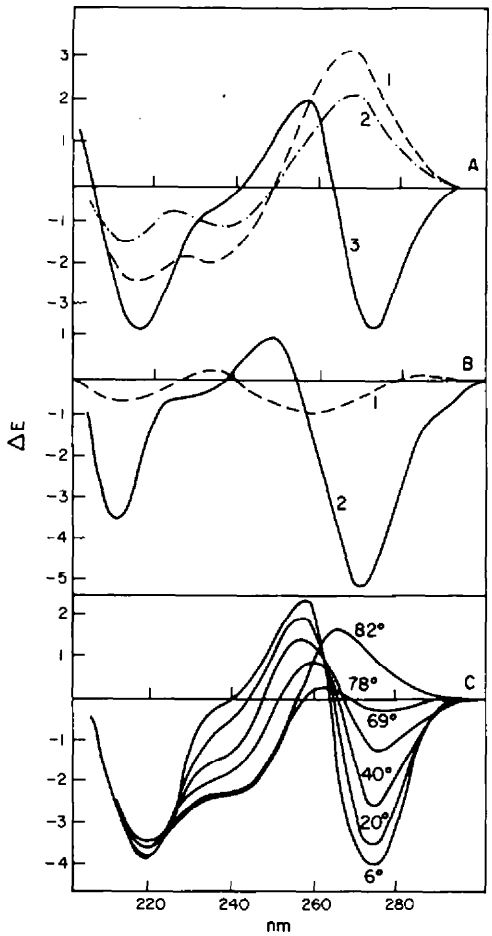


Fig 1. Circular dichroism spectra of nucleoside derivatives in aqueous solution.[1] 20°, 1 cm cuvette, "Roussel Jouan" dichrograph. A – Uridine-5'-methylphosphate (1); isopropylidene uridine (2); 2',3'-O-[4-(N-2-Chloroethyl-N-methylamino)benzilylidene]uridine-5'-methylphosphate (3). B – Adenosine-5'-methylphosphate (1); 2',3'-O-[4-(N-2-chloroethyl-N-methylamino)benzylidene adenosine-5'-methylphosphate (2). C – Temperature effect on CD spectra of 2',3'-O-[4(N-2-chloroethyl-N-methylamino)benzylidene]uridine-5'-methylphosphate.

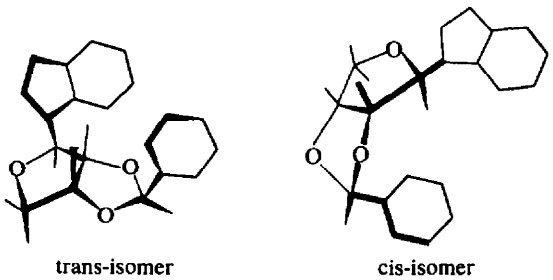


Fig 2. Conformation of *cis* and *trans* isomers of benzylidene nucleosides.

The chemical shifts and the coupling constants are given in the Table. The PMR signals were assigned on basis of the proton coupling patterns suggested by the form of multiplets and on the basis of integrated intensities (see Figs. 3 and 4, and Table). The doublet in spectrum of **2** at 4·31–4·40 ppm. (H^1, 60 Mc/s) is assigned to the H^5 proton of uracil rather than to $H^{2''}$ of the *cis*- and *trans*- isomers of benzylidene nucleosides as proposed by Baggett *et al*[8] because irradiation at frequency corresponding to $\tau = 2{\cdot}11$ ppm (resonance of H^6) leads to collapse of the doublet mentioned into a singlet.

The PMR spectra of **1**, **4** and **2**, **3** and **5** permitted assignment of the two signals specific for benzylidene nucleosides, **1** and **2**, ($\tau = 3{\cdot}8$–$4{\cdot}1$ ppm, integral intensity 1 proton) to their $H^{2''}$-proton. These signals overlap in the spectra of **2** and **3** with the $H^{1'}$-doublet, but are well resolved in the spectrum of **1**. The signals of aromatic protons are doubled (Figs. 3 and 4) and the ribose proton signals of **1**–**3** are complicated in comparison with that of **4** and **5**. This phenomenon, and the existence of two $H^{2''}$ signals, indicate that there are mixture of *cis* and *trans* diastereomers. According to other authors,[9–11] the upfield $H^{2''}$ signals are those corresponding to the *cis*-isomers while the downfield $H^{2''}$ signals belong to protons of the *trans*-isomers of benzylidene nucleosides. The *trans*:*cis* ratio was 1·7 in **1**, and 1 in **2** and **3**.

Figures 3 and 4 show that the $H^{2''}$-signals of **1** and **2** are shifted 0·3 ppm ($\Delta\tau_1$) downfield compared with the H^2-signal of 2-[4-(N-2-chloroethyl-N-methylamino)phenyl]-1,3-dioxalane (**6**) (H^2, $\tau =$ 4·41 ppm). This shift is not due to the presence of condensed tetrahydrofuran moiety since the $H^{2'}$-signals of 2,3-o-benzylidene-1,4-anhydroerythritol[12] were observed at $\tau = 4{\cdot}67$ (*cis*-) and at $\tau = 4{\cdot}36$ (*trans*-), whereas the chemical shift of H^2-signal of 2-phenyl-1,3-dioxalane was $\tau = 4{\cdot}66$. Observed $\Delta\tau = 0{\cdot}31$ ppm (for *cis* $H^{2''}$) is close to usual axial-equatorial shifting[9, 12, 13] and $\Delta\tau$ for *trans* $H^{2''}$ is 0·11–0·23 instead of 0·28–0·35 ppm, in good accordance with the above consideration. The heterocyclic base cannot cause the shift of $H^{2''}$ resonance, since the more anisotropic benzene ring does not deshield protons at a similar distance more than 0·1 ppm.[14] Thus we can conclude that $H^{2''}$ in benzylidene nucleosides **1**, **2** and **3** are equatorial due to dipole–dipole interaction between phenyl substituent at $C^{2''}$ and uracil and adenine bases.

It is seen in Fig. 3(c) that the $H^{4'}$, $H^{1'}$ and the aromatic proton signals of the *cis*- isomer of **1** are all shifted downfield between 0·05 and 0·13 ppm compared with the corresponding signals of the *trans*-isomer. On the contrary, the $H^{2'}$ and the $H^{3'}$ signals of the *cis*- isomer are shifted upfield compared with those of the *trans*- isomer. This chemical shift difference pattern strongly suggests again that in benzylidene nucleosides there is no fixation of the phenyl residue plane

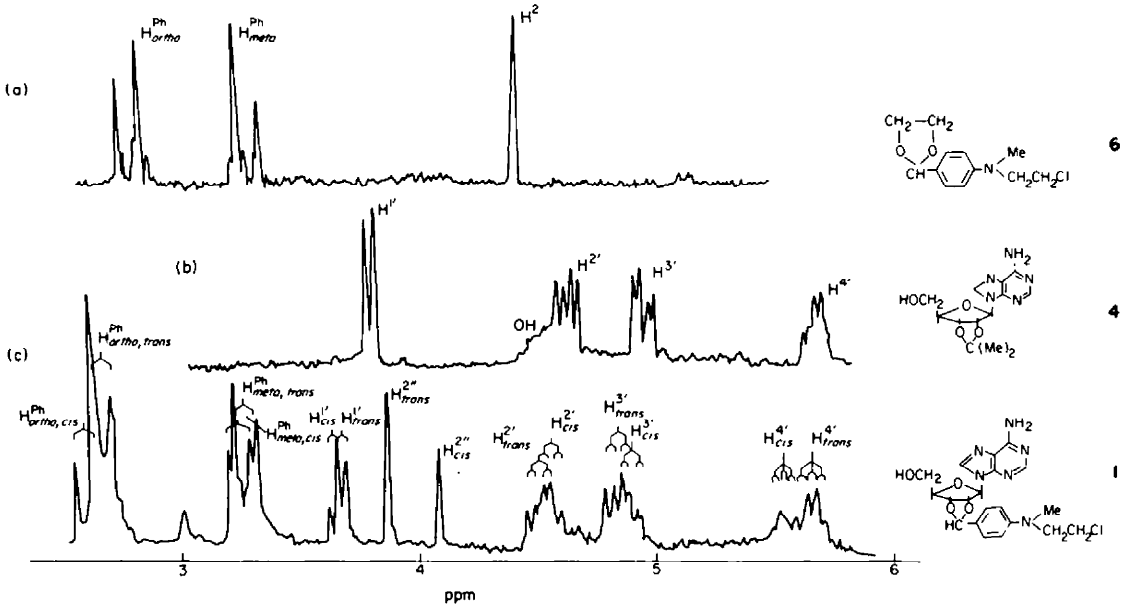


Fig 3. PMR spectra of 2-phenyl-1,3-dioxolane and adenosine derivatives in dimethylformamide. (a)—2-[4-(N-2-chloroethyl-N-methylamino)phenyl]dioxolane-1,3 (6) (b)—Isopropylidene adenosine (4). (c)—2′,3′,-O-[4-(N-2-chloroethyl-N-methylamino)benzylidene]adenosine (1).

similar to that characteristic of base stacking, where distance between base planes is 3–4 Å and prohibits rotation of base residues. If such fixation were the case, the chemical shift differences would be opposite because $H^{2'}$ and $H^{3'}$ would be exposed to the anisotropic field of the benzene ring. For this reason, there also ought to be an upfield shift of $H^{2'}$ signals of 1 compared with 4, but this is not observed. The above discussed dipole–dipole interaction does not prohibit free rotation of the phenyl residue around the $C^{2'}$-phenyl bond since the dipole moment of this grouping is oriented along this rota-

Table. Chemical shifts and coupling constants of adenosine and uridine derivatives in dimethylformamide.

Compound	Index in text	Configuration	Chemical shifts, ppm on τ-scale					Coupling constants, cps			The ribose conformation
			$H^{1'}$	$H^{2'}$	$H^{3'}$	$H^{4'}$	$H^{2''}$	$J_{1'2'}$	$J_{2'3'}$	$J_{3'4'}$	
Uridine			4·03	5·75	5·80	6·01	—	4·5	4·8	3·0	$C^{1'}$-exo,O-endo(weak) ($T^{0}_{1'}$)
2′,3′-O-Isopropylidene uridine	5	–	4·08	5·11	5·16	5·88	—	2·2	6·3	3·0	$C^{4'}$-exo (weak) ($V_{4'}$)
2′,3′-O-Benzylidene uridine	3	*cis*-	3·93	4·9	4·95	5·65	4·00	2·3		2·2	planar
		trans-	3·96			5·73	3·83	2·4		4·0	$C^{4'}$-exo ($V_{4'}$)
2′,3′-O-[4-(N-2-Chloroethyl-N-methylamino)benzylidene]-uridine	2	*cis*-	3·91	4·96	5·02	5·65	4·09	2·4		2·5	planar
		trans-	3·96			5·78	3·95	2·3		3·8	$C^{4'}$-exo ($V_{4'}$)
2′,3′-O-Isopropylidene adenosine	4	–	3·72	4·62	4·94	5·68	—	3·2	6·2	2·2	$C^{1'}$-exo ($V_{1'}$)
2′,3′-O-[4(N-2-Chloroethyl-N-methylamino)-benzylidene]adenosine	1	*cis*-	3·63	4·54	4·89	5·53	4·07	3·3	6·6	1·8	$C^{2'}$-endo ($V^{2'}$)
		trans-	3·67	4·51	4·83	5·66	3·85	3·1	6·6	3·9	$C^{4'}$-exo,O-endo(weak) ($T^{0}_{4'}$)

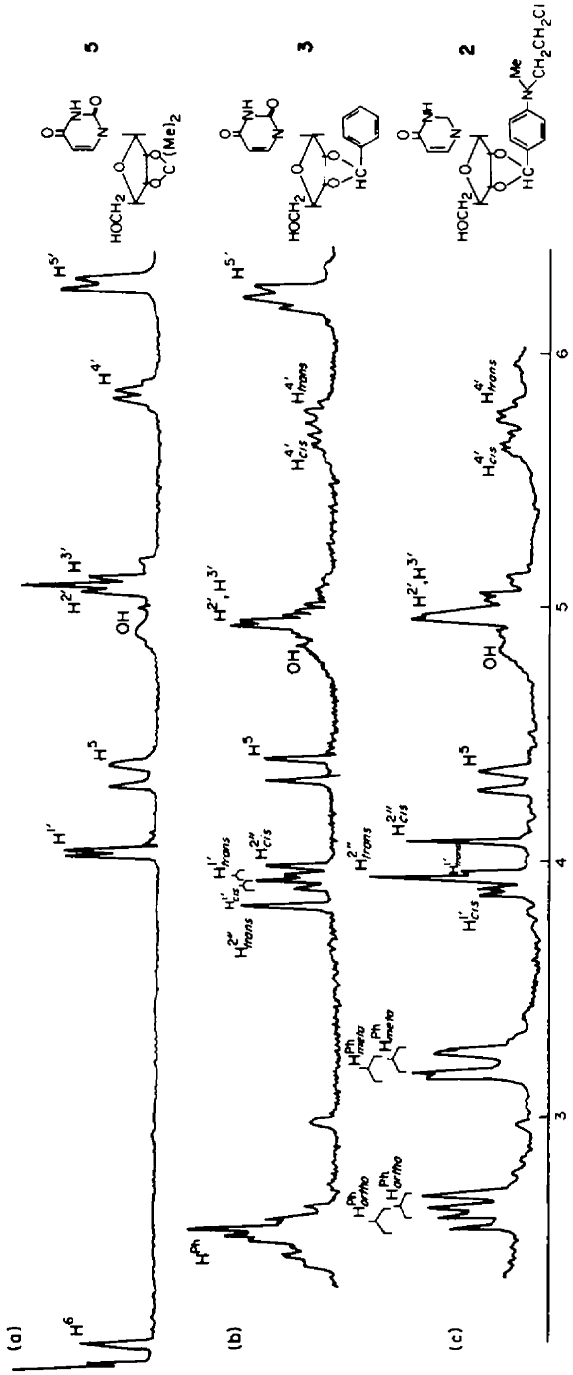


Fig 4. PMR spectra of uridine derivatives in dimethylformamide. (a)—Isopropylidene uridine (5). (b)—2′,3′-O-Benzylidene uridine (3). (c)—2′,3′-O-[4-(N-2-chloroethyl-N-methylamino)benzylidene]-uridine (2).

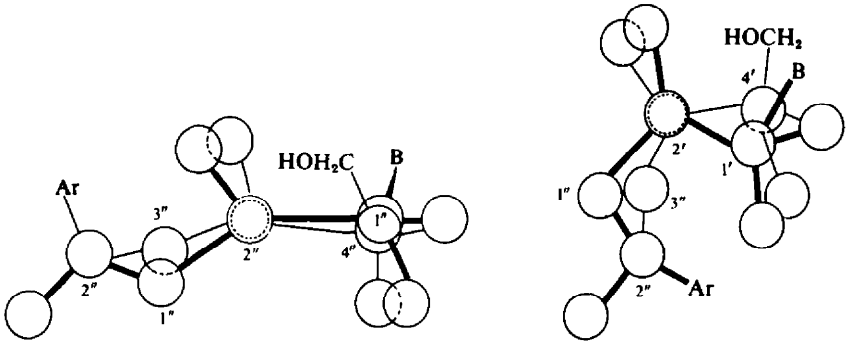


Fig 5. Conformation of dioxolane ring of benzylidene nucleosides.

tion axis. Hence, it seems that the free rotation averages out the anisotropic field of the phenyl residue.

The coupling of ribose protons in **4**, **5**, adenosine and uridine, were considered in relation to the conformations of the isopropylidene derivatives **4** and **5**. The cyclic ribose protons in uridine and its derivatives represent a system of interacting nuclei of the type A_2CLMX, where $A_2 = 2H^{5'}$, $C = H^{4'}$, $L = H^{3'}$, $M = H^{2'}$, $X = H^{1'}$, while the ribose protons of adenosine are a system of the type A_2CKMX, where $A = 2H^{5'}$, $C = H^{4'}$, $K = H^{3'}$, $M = H^{2'}$ and $X = H^{1'}$. Relative range of chemical shifts is $\tau_X < \tau_M \leqslant \tau_{L,K} < \tau_C < \tau_{A_2}$ (Figs 3, 4). The PMR spectra of uridine and **5** in DMF are simple, and all the coupling constants of ribose protons can be discerned. There is a significant difference between the coupling constants $J_{1'2'}$ of uridine (4·5 cps) and those of **5** (2·2 cps). The $H^{2'}$ and $H^{3'}$ signals of uridine (5·75 and 5·80 ppm) are two overlapping quartets having external lines slightly relaxed (system AB). The $H^{2'}$ and $H^{3'}$ signals of **5** are shifted downfield on average 0·65 ppm compared with uridine, the shift being largely due to formation of dioxalane ring. The coupling constants $J_{2'3'}$, $J_{1'2'}$, and $J_{3'4'}$ were found from the coupling patterns of the signals of $H^{1'}$, $H^{2'}$, $H^{3'}$ and $H^{4'}$. The $H^{4'}$ sextet is typical of coupling of 3 protons two of which are equivalent ($H^{5'}$-protons). The $J_{3'4'}$, value for uridine and **5** are equal to 3 cps.

The conformations of nucleosides and of isopropylidene nucleosides were finally deduced on basis of the coupling constant values of ribose protons and of the dihedral angles between adjacent C–H-bonds calculated from these $J_{i,j}$-constants.

It appeared that the ribose residue of uridine in dimethylformamide solution is in the $C^{1'}$-exo, O-endo (weak) conformation ($T^{(weak)}_{1'}$-conformation).

The value of the coupling constant $J_{1',2'}$ of **5** equal to 2·2 cps suggests that compared with uridine, the ribose moiety of **5** is more planar. The dihedral angle between $C^{1'}$-H and $C^{2'}$-H that follows from this value is equal to 120° suggesting that $H^{1'}$ and $H^{2'}$ in **3** are in the bisectral position. As for the $\phi_{3'4'}$, it appeared somewhat greater than 120°. Hence, it was concluded that the ribose moiety in **5** is in the $C^{4'}$-exo conformation ($V_{4'}$ weak). With adenosine and isopropylidene adenosine (**4**), formation of the dioxalane cycle involving $C^{2'}$–$C^{3'}$ results in flattening of the ribose moiety as indicated by decrease of $J_{1'2'}$ from 7·5 cps to 3·2 cps and by $J_{3'4'}$ of **4** equal to 2·2 cps. The conformation of ribose in **4** has $C^{1'}$-exo ($V_{1'}$-conformation).

The $J_{1'2'}$-constant values for the two isomers of **1** appeared very close (3·3 and 3·1 cps, respectively), whereas the $J_{3'4'}$ constants were different (1·8 cps for **1**-*cis* and 3·9 cps for **1**-*trans*). It follows that the conformation of ribose in the *trans*-benzylidene nucleoside **1** is C_2 ($C^{4'}$-exo, O-endo (weak), i.e., $T^{0}_{1'}$ (weak)), while in the *cis*-isomer of **1** it is C_s ($C^{2'}$-endo, i.e. $V^{2'}$). Unfortunately, it appeared impossible to measure directly the coupling constants of the benzylidene nucleoside **2**.

Considerable difficulties have been encountered in the interpretation of the PMR-spectrum of **2** (Fig. 4) since the $H^{1'}$-doublet of the *trans*-isomer partially overlaps the signals of $H^{2'}$. Moreover, the small difference of the chemical shifts of $H^{2'}$ and $H^{3'}$ signals of the *cis*- and *trans*- isomers results in an unresolved multiplet in the corresponding region of the spectrum. The coupling constants were estimated as follows: $J_{1'2'}$—from the coupling of $H^{1'}$; $J_{3'4'}$—from the width of the $H^{4'}$-sextet (12 and 10·5 cps) and from the $J_{4'5'}$-constant estimated in its turn from the coupling of $H^{5'}$. The $J_{4'5'}$-values of the two isomers appeared close (about 4 cps), and thus $J_{3'4'}$ (*trans*) $= 12 - 2 \times 4 = 4$ cps, and $J_{3'4'}$ (*cis*) $= 10{\cdot}5 - 2 \times 4 = 2{\cdot}5$ cps.

In *cis*-**2**, ribose is in an almost planar conformation ($J_{1'2'} \approx J_{3'4'}$, all ribose protons are bisectral). The $J_{1'2'}$ of *trans* **2** are the same as that of **5** and *cis* **2**, but $J_{3'4'}$ seems to be more than $J_{3'4'}$ of **5**, i.e. the $C^{4'}$ in *trans* **2** is out of the ribose plane. Thus, $\phi_{3'4'}$ and consequently $J_{3'4'}$ change because of displacing $C^{4'}$ in regard to other carbon atoms of ribose. Analogous changes in coupling constants and

dihedral angles are observed for diastereoisomers of **3**. The ribose moiety of *cis* isomers of **2** and **3** seems to be in the planar conformation while it is $C^{4'}$–exo, i.e. $V_{4'}$–conformation in *trans* **2** and **3**. Changing from *cis* **1** to *trans* **1**, as for *cis* and *trans* **2** and **3**, alters $\phi_{3'4'}$, but does not affect $\phi_{1'2'}$. In the case of **1** $C^{3'}$ moves, and $C^{4'}$ is brought out of the plane in **2** and **3**.

Thus, ribose conformation of benzylidene nucleosides is different for *cis*- and *trans*-configurations. The ribose conformational changes from isopropylidene to benzylidene nucleosides are small but oppositely directed for *cis*- and *trans*-configurations. Maximal change of dihedral angles is about 10°.

The ribose conformation of *cis* **1** and **2** is closer to that of **4** and **5** than that of *trans* **1** and **2**, as seen from similarity of $J_{3'4'}$ for *cis* isomers. Probably, the dipole–dipole interaction is more effective in the *cis* isomer of a benzylidene nucleoside.

The changes of conformation concern both ribose and dioxolane ring. Since the ribose conformation can change rather little, the interaction of phenyl ring and heterocyclic base seems mainly to cause a conformational change of dioxolane ring. Conformations[10] of the latter can vary from an envelope (C_s) or halfchair (C_2).[10] In the envelope conformation the dioxolane ring is puckered in the $O^{1''}$–$C^{2''}$–$O^{3''}$ region[15] and flattened in the $C^{2'}$–$C^{3'}$ region because $C^{2'}$–$C^{3'}$ is involved in a rigid condensed sing system. Dihedral angles $\phi_{2'3'}$ and equatoriality of $H^{2''}$, assist interpretation of the dioxalane conformation. The $\phi_{2'3'}$ angles of **1** and **2** are no more than 5–10°. The $C^{2''}$-exo-conformation is possible for the *trans*-configuration (with the $C^{2''}$ top of the envelope directed opposite the $C^{2'}$–$C^{1'}$ and $C^{3'}$–$C^{4'}$) and $C^{2''}$-endo-conformation for *cis*-configuration of **1** and **2**. These conformations of dioxolane ring are stabilised by interactions between the benzene ring and heterocyclic base. The halfchair conformation of dioxolane ring allows the same interaction (favoured for 1,3-dioxolane[10,15]) $C^{2''}$-exo, $O^{1''}$-endo- for *trans* ($T^{1''}_{2''}$) and $C^{2''}$-endo, $O^{1''}$-exo-conformations for *cis* **1** and **2** ($T^{2''}_{1''}$) where the angle $C^{2'}$–$O^{1''}$–$C^{2''}$ is less than one of $C^{3'}$–$O^{3''}$–$C^{2''}$. The contribution of $O^{1''}$-endo or $O^{1''}$-exo conformations is not too large since the conformation allotted to the ribose moiety restricts these possibilities, as do the requirements of the tetrahedral angles of $C^{2'}$ or $C^{3'}$ atoms. But nevertheless, proximity of the benzene ring and heterocyclic base is promoted, if $O^{1''}$ and $C^{2''}$ are pointed on the opposite sides of the $C^{2'}$, $C^{3'}$, $O^{3''}$ plane even slightly (Fig. 5).

EXPERIMENTAL

The compounds are prepared by cited methods **1**,[5] **2**,[16], **3**,[17] **4**,[19] **5**.[18] 2-[4-(N-2-Chloroethyl-N-methylamino)-phenyl]dioxolane-1,3 (**6**) was obtained by treatment of 4-(N-2-chloroethyl-N-methylamino)benzaldehyde with ethyleneglycol in the presence of ethyl orthoformate, ethanol and HCl. Separation of dioxolane is carried out by means of thin layer chromatography on Al_2O_3 after neutralization of the reaction mixture by triethylamine and vacuum evaporation of excess reagents. Yield 30%; $R_f = 0{\cdot}50$ [petroleum–diethyl ether (3:7)], λ_{max} 262 nm (dioxan). **6** is quantatively hydrolyzed to the initial aldehyde (λ_{max} 245 and 348 nm) in 0·02 N HCl. Some hydrolysis of **6** is observed at neutral pH, also.

Adenosine and uridine were obtained from "Reanal" and are recrystallized. DMF was refluxed over P_2O_5, distilled and dried over "Linde 4A" molecular sieves.

PMR spectra were measured at 37° using a "Varian H-100" spectrometer. (Hexamethyldisoloxane as internal reference.) The concentrations of the solutions were 15–20%. The accuracy of the $J_{i,j}$ values was about ±0·1 cps; dihedral angles are estimated by application of Karplus equation,[20]

$$J = J_0 \cos^2 \phi - 0{\cdot}28 \text{ cps},$$

where the constant $J_0 = 8{\cdot}5$ cps, if $0 \leqslant \phi \leqslant 90°$
or $J_0 = 9{\cdot}5$ cps, if $90° \leqslant \phi \leqslant 180°$.

These J_0 magnitudes are used for ribose protons.[21]

There is some discrepancy between the dihedral angles $\phi_{2'3'}$ in benzylidene and isopropylidene nucleosides, calculated from $J_{2'3'}$ by Karplus equation with these J_0, and the angles $\phi_{2'3'}$, obtained from models on the basis of the angles $\phi_{1'2'}$ and $\phi_{3'4'}$ obtained from $J_{1'2'}$ and $J_{3'4'}$. This may be accounted for by reducing J_0 values for $H^{2'}$ and $H^{3'}$ in Karplus equation, when $C^{2'}$ and $C^{3'}$ of ribose entered in condensed dioxolane ring. J_0 change for protons entering the rigid rings is shown[22] for 1,2-O-isopropylidene-α-D-xylofuranose derivatives. Therefore the $J_{2'3'}$ were not taken for consideration of the ribose conformation. $\phi_{2'3'}$ were estimated from models of compounds constructed on the basis of $\phi_{1'2'}$ and $\phi_{3'4'}$. If some J_0 change had occurred for $\phi_{1'2'}$ and $\phi_{3'4'}$ calculation also, it should not be important for conclusions obtained in this work because the conclusions were based on the comparison of changing coupling constants of protons for isopropylidene and benzylidene nucleosides, i.e. compounds with the same rigid condensed rings.

REFERENCES

[1] A. M. Belikova, N. I. Grineva, V. F. Zarytova, G. N. Kabasheva, D. G. Knorre, *Doklady Akad. Nauk USSR*, **95**, 1337 (1970).

[2] G. I. Baram, V. G. Budker, N. I. Grineva, D. G. Knorre, A. Ya. Kozorovitsky, G. G. Shamowsky, *Dokl. Akad. Nauk USSR* **201**, 95 (1971).

[3] N. I. Grineva, V. F. Zarytova, G. N. Kabasheva, D. G. Knorre, A. Y. Kozorovitsky, *Dokl. Akad. Nauk USSR* **198**, 282 (1971).

[4] V. V. Vlasov, N. I. Grineva, V. F. Zarytova, D. G. Knorre, *Mol. Biologiya USSR*, **4**, 201 (1970).

[5] A. M. Belikova, N. I. Grineva, *Izvestiya Sibirsk. Otdeleniya Acad. Nauk USSR, Seriya chim. Nauk*, 1971, issue 5, 119.

[6] M. M. Warshaw, J. Tinoco, *J. Mol. Biol.*, 1965, **13**, 54; P. O. P. Ts'o, *Molecular Associations in Biology*, p. 39. (Edited by B. Pullman) Acad. Press, 1968.

[7] P. Crabbé, *Topics in Stereochemistry*, Edited by N. L. Allinger and E. L. Eliel) Vol. 1, p. 2. Interscience, 2 (1967).

[8] N. Baggett, A. B. Foster, J. M. Webber, D. Lipkin, B. E. Phillips, *Chem. Ind.*, 136 (1965).

[9]N. Baggett, K. W. Buck, A. B. Foster, M. N. Randall, J. M. Webber, *J. Chem. Soc.*, 3394 (1965).
[10]W. E. Willy, G. Binsch, E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 5394 (1970).
[11]Y. Rommelaere, M. Anteunis, *Bull. Soc. Chim. Belg.*, **79**, 11 (1970).
[12]N. Baggett, K. W. Buck, A. B. Foster, J. M. Webber, *J. Chem. Soc.*, 3401 (1965).
[13]U. U. Samitov, R. M. Aminova, *J. Struct. Chemiyi USSR* **5**, 207 (1964).
[14]C. E. Johnson, F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
[15]E. L. Eliel, *Accs Chem. Res.*, **3**, 1 (1970).
[16]A. M. Belikova, V. F. Zarytova, N. I. Grineva, *Tetrahedron Letters*, 3557 (1967).
[17]D. Lipkin, B. E. Phillips, H. Hunter, *Tetrahedron Letters* N21, 18 (1959).
[18]A. Hampton, I. C. Frantantoni, P. M. Carrol, S. C. Wang, *J. Am. Chem. Soc.* **87**, 5481 (1965).
[19]F. Cramer, G. Weimann, *Chem. Ber.* **94**, 996 (1962).
[20]M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).
[21]C. D. Jardetzky, *J. Am. Chem. Soc.* **82**, 229 (1960).
[22]R. I. Abraham, L. D. Hall, L. Hough, K. M. Melanchman, *J. Chem. Soc.* 3699 (1962).