SYNTHESIS OF ANOMERIC 5-CYCLOPROPYL-2'-DEOXYURIDINES AND ^{1}H NMR SPECTROSCOPIC STUDY OF THEIR CONFORMATION

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The title compounds *Ia,b* were prepared by ammonolysis of the corresponding *p*-tolyl nucleosides *IIa,b* obtained by the silylation method in the yields of 26% and 53%, respectively. Conformation of the furanose ring in the free (*Ia, b*) as well as blocked (*IIa, b*) nucleosides was investigated by ^{1}H NMR spectroscopy.

The conjugation of cyclopropane ring[1] with unsaturated systems has been studied on many compounds of various structural types. Some time ago, within the framework of investigation of this interaction, we prepared several uracil derivatives containing a cyclopropane ring[2,3] and studied their electronic spectra and photochemical behaviour[4]. In this paper we describe the synthesis of anomeric 5-cyclopropyl-1-(D-*erythro*-pentofuranosyl)uracils (*Ia,b*) and study in detail their conformation using ^{1}H NMR spectroscopy. Compound *Ib* may be regarded as an analogue of highly potent virostatics derived from 5-vinyl-2'-deoxyuridine[5-7].

Reaction of silylated 5-cyclopropyluracil with 3,5-di-*p*-toluyl-D-*erythro*-pentofuranosyl chloride in acetonitrile afforded a mixture of anomeric 5-cyclopropyl-1-(3,5-di-*p*-toluyl-D-*erythro*-pentofuranosyl)uracils (*IIa, b*) in a 79% yield (the anomer ratio $\alpha : \beta = 1 : 2$). It is noteworthy that under comparable conditions the silylated 5-alkyluracils are known to react with the mentioned glycosyl chloride to give predominantly the α-anomers[8,9]. The free nucleosides *Ia,b* were prepared by ammonolysis of the corresponding *p*-toluyl derivatives *IIa,b*. The anomeric configuration of *Ia,b* and *IIa,b*, as determined by ^{1}H NMR spectroscopy, agreed with the results of CD spectral measurements on free nucleosides *Ia,b*.

^{1}H NMR *Spectroscopy*

The anomeric proton H-1' in the spectrum of compound *Ia* appears as a doublet of doublets ("quartet") and the difference between the chemical shifts of protons

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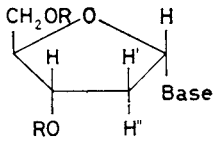
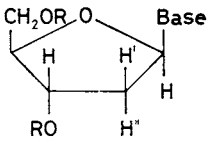
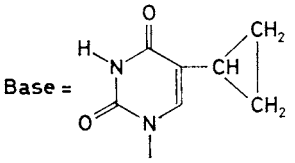
H-2′ and H-2″ is 0·58 ppm. In the spectrum of *Ib* the H-1′ proton signal is a triplet, and the difference between the H-2′ and H-2″ signals is only 0·03 ppm. These facts[10–12] clearly show that compound *Ia* is the α-anomer whereas compound *Ib* is the β-anomer. However, neither the triplet–quartet rule[10,11] nor the rule[12] based on the chemical shift differences between the protons at $C_{(2')}$ can be used for anomeric configuration assignment to the blocked nucleosides *IIa,b*. In the spectra of both these compounds the H-1′ proton appears as a doublet of doublets ("quartet") and also the difference between chemical shifts of the protons at $C_{(2')}$ is large (~0·45 ppm), as seen from Table I. In this case the anomeric configuration can be ascribed only indirectly from the configuration of the free nucleosides *Ia,b*.



Ia, R = H
IIa, R = *p*-CH_3Bz



Ib, R = H
IIb, R = *p*-CH_3Bz



A direct assignment of multiplets due to the individual protons H-2′ and H-2″ in *Ia,b* and *IIa,b* from their chemical shifts only is difficult. It can be, however, done indirectly using the magnitude of the vicinal coupling constant between the proton H-3′ and the protons H-2′ and H-2″ (*cis* and *trans*, respectively, relative to H-3′) in the probable conformations of the furanose ring. The pseudorotation analysis[13], currently used for conformational description of five-membered sugar rings, is based, *inter alia*, on the concept of a dynamic equilibrium between two conformational states. For β-2′-deoxyribosides[14], in the solid state as well as in solution, these states are characterized by the phase angle of pseudorotation, $P \sim 0-36°$ in the *N* region of the pseudorotation cycle and $P \sim 145-215°$ in the *S* region. For these two regions the value of $J_{2',3'}$ is about 5·5–7·0 Hz whereas $J_{2'',3'}$ is 10–12 Hz for the *N* and 0–1 Hz for the *S* region of the pseudorotation cycle. As seen from the spectra of compounds *Ia,b* and *IIa,b*, one of the vicinal coupling constants between the H-3′ proton and the protons at $C_{(2')}$ is larger than 6 Hz whereas the other is smaller than 5 Hz. The multiplet with the larger coupling constant was therefore ascribed to the H-2′ proton and the other to the H-2″ proton.

In the lowest field there are signals due to the H-6 proton of the base, the chemical shifts being invariably larger for the α-anomer than for the β-anomer in both the free and blocked series. On the other hand, the multiplets of the cyclopropane ring protons appear at the highest field (δ(CH) 1·47–1·61); (δ(CH_2) 0·30–0·87). Of the seven protons in the 2-deoxyribose moiety, a doublet of doublets, or a triplet, of the H-1′ (δ 6·22–6·41) is shifted most downfield, the chemical shift for the α--anomer being smaller than for the β-anomer both for the free and the blocked nucleosides. Other protons follow in the upfield direction (δ 5·62–3·61) in the order H-3′, H-4′, H-5′, and H-5″. Most upfield (δ 2·95–2·30) are signals of the protons at $C_{(2')}$, already discussed above. The signals of the geminal protons H-5′ and H-5″ were assigned as usual[15,16].

The allylic coupling constant between the H-6 proton of the base and the methine cyclopropane proton is approximately the same for all the measured compounds (~1·2 Hz). From the conformational point of view, however, only the vicinal coupling constants of the 2-deoxyribose protons are important (Table I). Of them, the constant $J_{1',2'}$ has the highest value. The $J_{1',2''}$ constants are substantially lower for the α- than for the β-anomers. Constants $J_{2',3'}$ for all the derivatives are in the narrow interval 6·1–6·7 Hz, being invariably higher than the $J_{2'',3'}$ constants. Similar relations between the vicinal constants have been found for the α- and β-anomers of 5-ethyl-2′-deoxyuridine[17].

Conformation

Conformational properties of the furanose ring and population of rotamers about the $C_{(5')}$—$C_{(4')}$ bond have been determined from the vicinal coupling constants of the 2-deoxyribose protons (Table I). Conformational parameters of compounds *Ia,b* and *IIa,b* have been calculated using the program of Guschlbauer[18]. The computation procedure is described in detail elsewhere[19] and the calculated values of pucker amplitude τ_m, phase angle P and populations of the individual conformers ${}^{N}X$, ${}^{S}X$ and rotamers g_+, t and g_- are given in Table II.

As shown by the ${}^{S}X$ values (Table II), conformational types of the *S* region of the pseudorotation cycle strongly predominate both in the α- and β-anomer of the free as well as blocked derivatives. The same results were obtained by Shugar and coworkers[17] for anomeric 5-ethyl-2′-deoxyuridines. Obviously, the conformational equilibrium of the 2-deoxyribose ring is not influenced by configuration of the anomeric center, being determined mainly by interactions within the ring. The anomers differ only in the predominant conformational type: whereas the β-anomers exist preponderantly in the ${}^{2}E$ type, the α-anomers prefer the ${}_{3}E$ or the ${}_{3}T^{2}$ type. The g_+ rotamer about the $C_{(5')}$—$C_{(4')}$ bond is more populated in the β- than in the α-anomer. In all compounds, the pucker amplitude τ_m is 38–40°.

As concerns the conformation about the nucleoside bond, the *anti*-conformation

TABLE I

^{1}H NMR parameters of nucleosides *Ia,b* and *IIa,b*

Compound	Solvent	Chemical shifts, ppm										
		H-1′	H-2′	H-2″	H-3′	H-4′	H-5′	H-5″	H-6	CH[a]	CH_2—CH_2[a]	
Ia	D_2O	6·22	2·71	2·13	4·44	4·39	3·68	3·61	7·67	1·59	0·38—0·54	0·73—0·85
Ib	D_2O	6·27	2·38	2·35	4·47	4·02	3·85	3·78	7·61	1·58	0·44—0·52	0·77—0·87
IIa	$CDCl_3$	6·33	2·95	2·50	5·59	4·87	4·56	4·52	7·24	1·61	0·32—0·46	0·62—0·83
IIb	$CDCl_3$	6·41	2·30	2·72	5·62	4·53	4·75	4·67	7·17	1·47	0·30—0·45	0·51—0·71

Compound	Solvent	Coupling constants, Hz									
		$J_{1'2'}$	$J_{1'2''}$	$J_{2'3'}$	$J_{2''3'}$	$J_{3'4'}$	$J_{4'5'}$	$J_{4'5''}$	$J_{6,CH}$	$J_{2'2''}$	$J_{5'5''}$
Ia	D_2O	7·5	2·6	6·1	2·6	1·5	4·0	5·1	1·2	−14·8	−12·4
Ib	D_2O	6·8	6·4	6·7	4·6	4·1	3·2	4·3	1·1	−14·5	−12·5
IIa	$CDCl_3$	7·2	1·9	6·5	1·0	1·3	4·2	4·3	1·2	−15·5	−12·2
IIb	$CDCl_3$	8·9	5·3	6·4	1·5	2·2	2·8	3·7	1·2	−14·2	−12·2

[a] Multiplets of cyclopropane protons.

in both anomers (at least for the free nucleosides *Ia,b*) is indicated by the following arguments. A different conformation about the glycosidic bond should lead to markedly different (>0·1 ppm) chemical shifts of the H-1′ proton for the anomers, which has not been observed. Further, it is known[20,21] that a proton *cis* relative to a hydroxyl group is more shielded than a *trans*-proton. Thus, the H-2″ proton should appear about 0·3 ppm more upfield than the H-2′ proton. At the same time, the base makes the H-2′ proton in the β-anomer to appear more upfield than the H-2″ proton. Simultaneous operation of both these effects (shielding by the hydroxyl and the base), leads then to the relation $\delta_{H-2'} \sim \delta_{H-2''}$ for the β-anomer and $\delta_{H-2'} - \delta_{H-2''} \sim 0{\cdot}6$ ppm for the α-anomer (Table I). Thus, conformation about the nucleoside bond in the free nucleosides *Ia,b* is the same, either *syn* or *anti*. In 1-(β-D-ribofuranosyl)cyanuric acid and orotidine the base has been found to be *syn*-oriented[22]. In the cited case, the carbonyl group shields the H-2′ proton shifting its signal about 0·3 ppm downfield as compared with the corresponding signal in uridine. In the free nucleosides *Ia,b* (Table I) the H-2′ proton in the β-anomer appears upfield showing that the conformation about the glycoside bond is *anti*. This is confirmed also by the fact that the H-4′ signal in the α-anomer is shifted 0·37 ppm downfield relatively to that of the β-anomer. If the base were *syn*-oriented, the reverse should be observed.

We tried to estimate the conformation of the cyclopropane ring in compounds *Ia,b* using theoretical calculation for 5-cyclopropyluracil. Rotation of the cyclopropane ring relatively to the uracil nucleus plane was studied by the PCILO method[23–26]. The suitability of this method for description of the interaction between the cyclopropane ring and the uracil π-system was tested using vinylcyclopropane as the model compound. The results obtained by the PCILO method were compared with the relative energy *versus* rotation angle curve, derived from

TABLE II

Calculated conformational parameters of nucleosides *Ia,b* and *IIa,b*

Compound	Conformational equilibrium	Pseudorotational parameters					$C_{(5')}$—$C_{(4')}$ rotamer population		
		τ_m	^NX	^NX	^SP	^SX	g_+	t	g_-
Ia	${}_2T^3 \rightleftharpoons {}_3T^2$	40	347	0·19	193	0·81	0·38	0·31	0·31
Ib	${}^3E \rightleftharpoons {}^2E$	38	18	0·41	162	0·59	0·55	0·28	0·17
IIa	${}_2E \rightleftharpoons {}_3E$	39	344	0·18	196	0·82	0·45	0·28	0·27
IIb	${}^3E \rightleftharpoons {}^2E$	40	18	0·20	162	0·80	0·65	0·22	0·13

Raman spectroscopy[27], and with theoretical data, obtained by *ab initio* calculations[28] in the STO-3G and 4-31G bases. Since the PCILO method leads to qualitatively the same conclusions, it is suitable for conformational studies on 5-cyclopropyluracil.

The dependence of 5-cyclopropyluracil energy on the dihedral angle H—C_α—$C_{(5)}$—$C_{(6)}$ is depicted in Fig. 1. (For $\varphi = 0$ the cyclopropane ring is *trans*-oriented to the double bond). As seen, the curve has two minima: for $\varphi = 0°$ (*trans*) and $\varphi = 120°$ (*gauche*). The probability of the cyclopropyl existing in various regions of the conformational cycle at a temperature T was estimated from the Boltzmann distribution and from the energy data calculated by the PCILO method. Fig. 2 shows probability densities for the rotamers (defined by the dihedral angle φ) at four temperatures. In a given interval of the angle φ, the relative number of molecules is defined by the area below the curve in this interval. The ratio of population of the *trans*-conformation ($-30° < \varphi < 30°$) to that of the *gauche* and *cis* conformations ($90° < \varphi < 270°$) at temperatures 223 K, 273 K, 298 K, and 323 K is 49·2 : 50·8, 42·2 : 57·8, 39·8 : 60·2, and 37·9 : 62·1, respectively. Thus, at room temperature, conformations with the cyclopropane ring oriented toward the $C_{(5)}$—$C_{(6)}$ bond slightly predominate although the absolute minimum of the rotation curve is at $\varphi = 0$. However, the minimum is sharp and its neighbourhood is therefore less populated.

EXPERIMENTAL

Analytical samples were dried at 25°C/7 Pa for 8 h. Melting points were determined on a Kofler block and are uncorrected. CD spectra were measured on a Roussel–Juan Dichrographe CD 185,

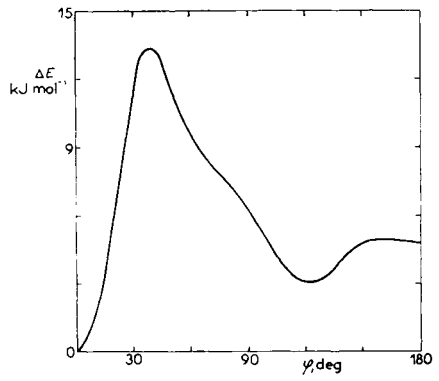


FIG. 1

Barrier to rotation in 5-cyclopropyluracil, calculated by PCILO method

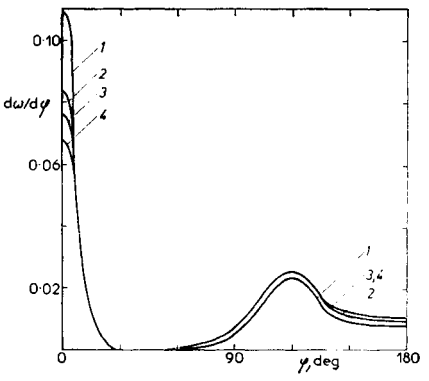


FIG. 2

Probability densities for conformer population in 5-cyclopropyluracil at various temperatures (in K). Curve *1* 223; *2* 273; *3* 298; *4* 323

Model II, in a 0·2 cm cell at room temperature. ^{1}H NMR spectra were taken on a Varian XL-200 (200 MHz) instrument at 25°C; 10 mg sample/0·5 ml solvent, in deuterium oxide (Aldrich, 99·8% ^{2}H) for *Ia, b* and deuteriochloroform (Aldrich, 99·8% ^{2}H) for *IIa,b*; internal standard sodium disilapentanesulfonate (DSS) and tetramethylsilane (TMS), respectively. Signals were ascribed to the individual protons on the basis of chemical shifts, multiplicities and decoupling experiments. The complete set of accurate chemical shifts and coupling constants for the sugar part was determined for each nucleoside by the simulation-iterative procedure (accord between the experimental and calculated spectra ±0·01 ppm for δ, and ±0·1 Hz for J).

5-Cyclopropyl-1-(3,5-di-O-*p*-toluyl-D-*erythro*-
-pentofuranosyl)uracils (α- and β-Anomer, *IIa,b*)

A solution of 5-cyclopropyl-2,4-bis(trimethylsilyloxy)pyrimidine[29] (0·8 g; 2·70 mmol) in acetonitrile (5 ml) was mixed with 3,5-di-O-*p*-toluyl-D-*erythro*-pentofuranosyl chloride[30,31] (1·03 g; 2·65 mmol). After stirring for 3 h at room temperature, the mixture was taken down *in vacuo* and the residue was chromatographed on a column (2 × 40 cm) of silica gel in toluene–ethyl acetate (2 : 1). Crystallization of the faster fraction from ethanol afforded 0·712 g (53%) of the β-anomer *IIb*, crystallization of the slower fraction from the same solvent gave the α-anomer *IIa* (0·315 g; 26%; the yields refer to the starting halogenose). α-Anomer: m.p. 164—166°C (ethanol). For $C_{28}H_{28}N_2O_7$ (504·5) calculated: 66·65% C, 5·59% H, 5·55% N; found: 66·45% C, 5·48% H, 5·45% N. β-Anomer: m.p. 178—179°C (ethanol). Found: 66·22% C, 5·48% H, 5·45% N.

5-Cyclopropyl-1-(α-D-*erythro*-pentofuranosyl)uracil (*Ia*)

Compound *IIa* (0·160 g) was added to 3·3 mol l^{-1} methanolic ammonia. After stirring for 3 h at room temperature, the compound dissolved and the solution was set aside for 3 days at room temperature. The solvent was evaporated *in vacuo* and the residue extracted three times with a mixture of acetone and ethyl acetate (1 : 1; à 25 ml). The insoluble portion was crystallized from 90% ethanol at +5°C overnight; yield 68·9 mg (81%), m.p. 213—214°C. CD spectrum (methanol, c 0·14 mg/ml, 0·2 cm cell): Θ_{277} −5 290, Θ_{220} +9 342. For $C_{12}H_{16}N_2O_5$ (268·3) calculated: 53·72% C, 6·01% H, 10·42% N; found: 54·07% C, 5·99% H, 10·52% N.

5-Cyclopropyl-1-(β-D-*erythro*-pentofuranosyl)uracil (*Ib*)

Compound *IIb* (0·480 g) was ammonolyzed as described for *IIa*. The extraction gave 0·248 g (97%) of the crude nucleoside which was crystallized from 90% ethanol at +5°C overnight; yield 0·160 mg (63%) of *Ib*, m.p. 211—212°C. CD spectrum (methanol, c 0·18 mg/ml, 0·2 cm cell): $\Theta_{276.5}$ +7 861, Θ_{225} −2 457. For $C_{12}H_{16}N_2O_5$ (268·5) calculated: 53·72% C, 6·01% H, 10·44% N; found: 53·47% C, 5·99% H, 10·38% N.

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