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UNCONVENTIONAL NUCLEOTIDE ANALOGUES[1]

REACTION OF CARBENES WITH URACIL AND URIDINE DERIVATIVES

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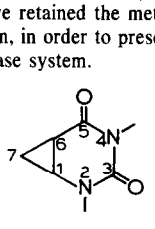
Abstract—Carbenes **2a–d** (:CCl_2, :CBr_2, :CFCl, :$CHCOOC_2H_5$) add to the 5,6-double bond of uracil derivatives **1a–e** to give adducts in modest to good yields. The unsymmetrically substituted carbenes :CFCl **2c** and :$CHCOOC_2H_5$ **2d** lead, as expected, to the formation of mixtures of *endo* and *exo*-isomers **3c–n** which were separated and identified *via* their ^{1}H NMR spectra. Reaction of **2d** with pyrimidine derivatives **5a,b** resulted in products which can be rationalized in terms of addition at either the 5,6- or the 3,4-double bond. Addition of carbenes **2a–c** to uridine derivatives gave diastereomeric adducts **12–16** which were isolated and identified. The two diastereomeric series, referred to as A and B, have been correlated and assigned the configurations 5*S*, 6*S* and 5*R*, 6*R*, respectively, on the basis of X-ray structure analysis of **12B**. The adducts of **2a,c** and the uridine derivatives **11a,b** have been deprotected to give 7,7-dihalocyclothymidines.

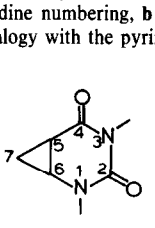
In preceding papers[3] we have described the synthesis and properties of a variety of nucleoside analogues in which the sugar moiety of the nucleoside was replaced by either amino acids or pyrrolidine derivatives. The results of the biological tests of such analogues suggested that the deletion of the carbohydrate was presumably too drastic a structural change to allow interactions which were critically associated with the binding of the nucleoside to the relevant enzyme(s) in the nucleic acids biosynthetic pathway. In the light of the aforementioned we have recently directed our attention to nucleoside analogues in which the ribose component is retained and a suitable modification is introduced in the nucleo-base system. In this connection it may be recalled that several naturally occurring and synthetic base-modified nucleosides show valuable biological properties.[4] A potentially versatile type of reaction which can lead to interesting variations in the base-component of pyrimidine nucleosides is that of carbenes with the 5,6-double bond of the pyrimidine system.[1,5] The nature of the specific carbene employed would bring about, amongst others, structural changes associated with the steric and conformational properties of the resulting analogue. That the addition of a methylene bridge across the 5,6-positions of uridine can lead to active substrates, was demonstrated by Torrence and Witkop,[6] who found that 5,6-methyleneuridine diphosphate (cyclothymidine diphosphate) underwent a polynucleotide phosphorylase catalyzed copolymerization with natural nucleoside diphosphates. Our interest in the carbene addition reaction derived further stimulation from the fact that the carbene adducts of uracil and uridine could, by ring-enlargement, be converted into the corresponding diazepine systems, which in themselves would constitute a novel class of potential antimetabolites. This communication presents the study of the reaction of halo- and carbethoxy-carbenes with pyrimidine derivatives and the synthesis of 2,4-diazabicyclo[4,1,0]heptane systems derived from carbene addition to uracil and uridine substrates.

Calculations indicate that the 5,6-double bond of uracil has a distinct enamine character.[7] However, its nucleophilic properties are considerably suppressed, in comparison with those of simple enamines, due to the presence of both the electron-withdrawing carbonyl group adjacent to the "enamine"-nitrogen and a second carbonyl group in conjugation with the double bond. Thus, Kunieda and Witkop[8] found no adduct upon the reaction of 1,3-dimethyluracil with the methylene carbenoid reagent iodomethylzinc iodide. In line with these results, none of the desired addition product could be obtained by us in orientation studies involving the attempted addition of dichlorocarbene—generated by either thermal decomposition of sodium trichloroacetate or the base-catalyzed α-dehydrohalogenation of chloroform[10]—to 1,3-dimethyluracil **1a**. However, when dichlorocarbene was generated by decomposition of phenyl(dichlorobromomethyl)merury[11] in a benzene solution of 1,3-dibenzyluracil **1b**, the crystalline adduct **3a** was produced in high yield (80%) (Table 1). The structure of **3a** followed from its spectroanalytical data (vide Experimental). Particularly significant in the ^{1}H NMR spectrum was the AB pattern of the bridgehead protons in **3a** (δ 2.69, H_5†; 3.22, H_6†; $J_{5,6}$ = 10 Hz). In an analogous reaction, heating a mixture of **1b** and phenyl(tribromomethyl)mercury (:CBr_2 precursor) yielded the crystalline adduct **3b**. The reaction of unsymmetrical carbenes **2c** and **2d** with substituted uracils led, as expected, to the formation of mixtures of isomeric adducts. The adducts were separated by chromatography and their structural assignment made on the basis of the ^{1}H NMR spectra. Thus, the addition products of **2c**-generated from phenyl(dichlorofluoromethyl) mercury

†While the formal IUPAC nomenclature for the adducts would number the bicyclic ring system as 2,4-diazabicyclo[4,1,0]heptane **a** we have retained the methanopyrimidine numbering, **b** in the discussion, in order to preserve the analogy with the pyrimidine nucleo base system.



a



b

Table 1. Adducts of carbenes with 1,3-disubstituted uracils

	yield	m.p.°C	H-5	H-6	H-7	$J_{5,6}$	$J_{6,7}$	$J_{5,7}$
3a	70	95–98	2.69	3.22		10		
3b	26	114–117	2.84	3.25		10		
3c	'12	84–86	2.84	3.33		'10.5	7.5†	17†
3d	10	140 142	2.65	3.14		10	0†	3.5†
3e	23	70.5–71.5	2.61	3.45	2.20	8.5	6	10
3f	33	82–83.5	2.70	3.45	2.01	8.5	3	5
3g	14	oil	2.40	3.19	1.95	8.5	6	10
3h	27	oil	2.67	3.27	1.63	8.5	3	5
3i	7	72–92	2.53	3.51	2.16	8.5	6.5	10
3j	7	49–53	2.51	3.43	1.82	8.5	3	4.5
3k	40	66–68	2.50	3.27	2.08	8.5	6	10
3l	23	oil	2.52	3.18	1.82	8.5	3	5
3m	2.5	oil	2.49	3.44	2.13	8	6.5	10
3n	4	oil	2.70	3.56	1.85	9	3	5

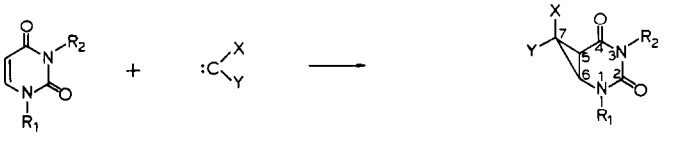
†H,F-coupling.

and 1,3-dibenzyluracil **1b**, were found to exhibit significantly different sets of H–F couplings. The isomer **3c** showed $J_{H,F}$ values of 17 Hz and 7.5 Hz while in **3d** only a single coupling of 3.5 Hz was observed. Since in cyclopropane derivatives *trans*-$J_{H,F}$ is smaller than *cis*-$J_{H,F}$,[12] the NMR-spectra provide the argument for the *endo*-chloro and *exo*-chloro assignment to **3c** and **3d**, respectively.

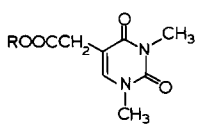
Ethoxycarbonylcarbene **2d**, generated by copper-catalyzed decomposition of ethyl diazoacetate,[13] reacted with 1,3-dialkyl substituted pyrimidines **1a–e**, in dimethoxyethane (DME), to give mixtures of the corresponding adducts **3e–3n** (Scheme 1) in which the *endo*-/*exo*-isomer ratio varied with the nature of the substituents. The isomer could be identified by the coupling of the proton α- to the ester function. The isomer with the larger coupling constants between C_7–H and the vicinal protons of the cyclopropane ring was, in each case, assigned the *endo*-ethoxycarbonyl configuration. The reaction of **2d** with **1a** yielded, in addition to the adducts **3e** and **3f**, a third product which was identified as **4a**. The structure of **4a** followed from its spectral data; IR(1730, 1700, 1670, 1640 cm^{-1}) NMR (δ 3.31, s, 5H, N_1–CH_3, $=C_5$–CH_2; 3.38, s, N_3–CH_3; 7.24, s, H_6). The formation of ester **4a** can be rationalized in terms of a thermal ring-opening of the adducts resulting in the observed skeletal rearrangement. That this reaction could be acid catalyzed was attested by the conversion of both **3e** and **3f** into **4a** upon heating in DME, in the presence of *p*-toluenesulfonic acid. Heating of **3e** and **3f** in 10% hydrochloric acid resulted in their conversion to **4b**, quantitatively.

In view of the fact that in the N_3-unsubstituted derivatives of uracil the biologically significant hydrogen is retained, it was decided, to examine the reaction of the carbenes with pyrimidine ethers. Reaction of 1 methyl - 2 - oxo - 4 - methoxy - 1,2 - dihydropyrimidine **5a**[14] with dichlorocarbene resulted in a mixture from which a small quantity of a crystalline (m.p. 221–223°), as yet unidentified product has been isolated. In case of carbene **2d**, 2,4-dimethoxypyrimidine reacted to yield 1-ethoxycarbonylmethylene - 4 - methoxy - 2 - oxo - 1,2 - dihydropyrimidine **5c**. (Scheme 2). Comment on the possible mechanism of formation of **5c** follows in the sequel. When the monoether **5a** was employed as the substrate, reaction with excess of **2d** led to the formation of three products, namely, the bicyclic adducts **6** and **7**, which were isolated as a mixture, and the disubstituted uracil derivative **9a**. It is noteworthy that no *endo*-ethoxycarbonyl adduct could be identified in the reaction mixture. While the formation of **7** is presumably the result of hydrolysis of **6** during isolation, that of **9a** deserves comment. It should be borne in mind that the pyrimidine system **5a** possesses, in addition to the 5,6-double bond, a second electron rich site in the form of the N_3=C_4 linkage. Addition to the latter double bond, leading to **8**, and a subsequent hydrolytic three-ring opening would account satisfactorily for the formation of **9a**. A similar sequence of events, starting with the addition of **1d** to the C_2=N_1 site of 2,4-dimethoxypyrimidine, explains the above mentioned formation of **5c**. Interestingly, the reaction of **5b** with **2d** yielded the uracil derivative **9b** as the sole product. A possible rationalization of this result may be made in terms of the steric hindrance, due to the bulky N_1-substituent in **5c**, which the carbenoid reagent encounters in its approach to the 5,6-double bond of the substrate. The electronegative effect of the ether oxygen in **5b** may also contribute to a preferred addition at N_3=C_4, by suppression of reaction at the C_5=C_6 double bond.

The aforementioned results prompted us to apply the



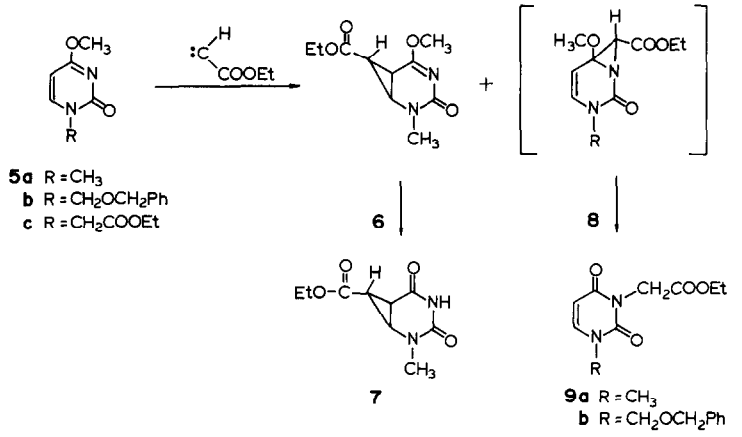
R_1	R_2		X	Y
1a CH_3	CH_3	2a	Cl	Cl
1b $PhCH_2$	$PhCH_2$	2b	Br	Br
1c $PhCH_2OCH_2$	CH_3	2c	Cl	F
1d $PhCH_2OCH_2$	$PhCH_2$	2d	H	COOEt
1e $PhCH_2CH_2CH_2$	CH_3			



4a R = Et
4b R = H

	X	Y	R_1	R_2
3a	Cl	Cl	$PhCH_2$	$PhCH_2$
3b	Br	Br	$PhCH_2$	$PhCH_2$
3c	Cl	F	$PhCH_2$	$PhCH_2$
3d	F	Cl	$PhCH_2$	$PhCH_2$
3e	COOEt	H	CH_3	CH_3
3f	H	COOEt	CH_3	CH_3
3g	COOEt	H	$PhCH_2$	$PhCH_2$
3h	H	COOEt	$PhCH_2$	$PhCH_2$
3i	COOEt	H	$PhCH_2OCH_2$	CH_3
3j	H	COOEt	$PhCH_2OCH_2$	CH_3
3k	COOEt	H	$PhCH_2CH_2CH_2$	CH_3
3l	H	COOEt	$PhCH_2CH_2CH_2$	CH_3
3m	COOEt	H	$PhCH_2OCH_2$	$PhCH_2$
3n	H	COOEt	$PhCH_2OCH_2$	$PhCH_2$

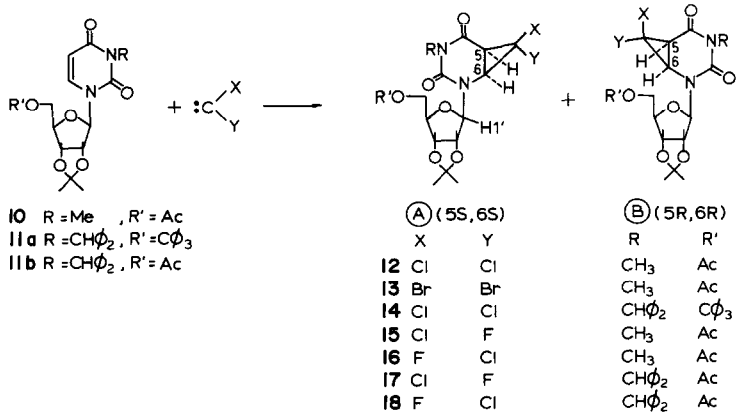
Scheme 1.



Scheme 2.

reaction of carbenes with pyrimidines to suitable uridine derivatives. The choice of the protected nucleosides **10** and **11** (Scheme 3), for the latter study, was determined by the need to avoid complications arising from the potential reactivity of carbenes with ionizable hydrogens. Addition of carbenes of the type $:CX_2$ to the 5,6-double bond of the uridine system should, in view of the asymmetric sugar moiety, lead to the formation of diastereomeric adducts (5*R*, 6*R* and 5*S*, 6*S*) in each case. In accordance with this expectation, **10** reacted with excess of the precursors ($PhHgCX_2Y$) of dichlorocarbene **2a** and dibromocarbene **2b** to give mixtures of isomeric adducts **12A,B** and **13A,B** respectively (Table 2). Similarly **11a** gave, upon reaction with **2a**, the corresponding adducts **14A** and **14B**. Consistent with these observations was the fact that the unsymmetrical carbene :CFCl **2c** added to **10** to result in the formation of a pair of *endo*-chloro **15A,B** and a pair of *exo*-chloro **16A,B** isomers. The individual isomers described in Scheme 3 were isolated, in pure state, from the mixtures by chromatography and their gross structures were attested by their spectroanalytical data (see Experimental). Distinction between the diastereomeric series **A** and **B** was based upon the differences in the chemical shifts of the $C_{1'}$-protons. In the **A**-series, the latter proton was found to show, uniformly, a chemical shift (δ 5.58–5.64) at a higher field than in the corresponding **B**-series (δ 6.03–6.16). Furthermore, the CD spectra of the **A**-isomers exhibited a negative maximum in the range 248–262 nm, while the corresponding **B**-isomers showed a positive maximum in the same range. Typical relevant portions of the ^1H NMR and CD spectra of diastereomers **12A** and **12B** are presented in Figs. 1 and 2. Difference in the chemical shifts of the $H_{1'}$-protons, in each of the isomer-pairs, can be explained by considering the conformational properties of the nucleosides. The relative positioning of the base and sugar moieties of the nucleoside, involving rotation about the glycosidic ($C_{1'}$–N_1) bond, significantly influences the chemical shift of the $H_{1'}$ proton. In the *anti*-conformation this proton lies in the deshielding region of the C_2 carbonyl[15] From the foregoing observations it can be concluded that the **A** and **B** series may be associated with (a) opposite configurations about the C_5,C_6-carbons (CD-spectra) and (b) conformational differences, implying a *syn*-conformation for the **A**-series and an *anti*-conformation for the **B**-series (^1H NMR spectra). The conformational assignments are supported by NOE measurements for the diastereomers **12A** and **12B**. Upon irradiation of $H_{1'}$ in case of **12A** a Nuclear Overhauser Effect of 10% was observed for H_6; while no effect whatsoever could be detected for **12B**. Although the magnitude of the NOE in **12A** is small, it may be regarded as significant in the light of its comparison with the NOE of **12B** and in conjunction with the difference in chemical shifts of the $H_{1'}$ protons between the two isomers.

The conformational preference of the diastereomeric series **A** and **B** suggest that, in the adducts, there are



	X	Y	R	R'
12	Cl	Cl	CH_3	Ac
13	Br	Br	CH_3	Ac
14	Cl	Cl	$CH\Phi_2$	$C\Phi_3$
15	Cl	F	CH_3	Ac
16	F	Cl	CH_3	Ac
17	Cl	F	$CH\Phi_2$	Ac
18	F	Cl	$CH\Phi_2$	Ac

Scheme 3.

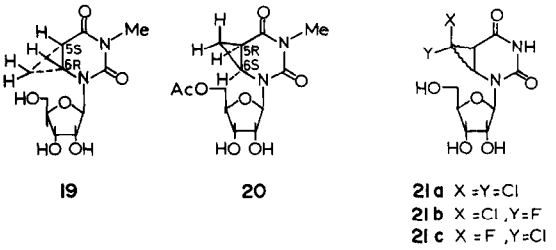
Table 2. Chemical shifts (δ)[a] of significant protons and CD[b](ORD) data of compounds **1–10**

Compound	C(5)H	C(6)H	NMe	C(1')H	C(2')H[d]	C(3')H[d]	Ac		$\lambda_{max}[\theta]$
10	5.82	7.33	3.32	5.70	5.05	4.88	2.09		
12A	3.00	3.63	3.15	5.60	5.02	4.81	2.07	255	−26000
12B	3.04	3.81	3.17	6.10	4.80	4.71	2.08	255	+22000
13A	3.07	3.76	3.16	5.62	4.84	4.72	2.08	262	−9600
13B	3.10	3.80	3.21	6.16	4.6–4.9(m)		2.11	262	+9900
15A	3.08dd	3.70dd	3.16	5.58	5.02	4.81	2.09	248	−29000
15B	3.08dd	3.90dd	3.16	6.03	4.6–4.9(m)		2.03	249	+27500
16A	2.84dd	3.55	3.16	5.64	4.93	4.78	2.07	248	−24000
16B	2.87dd	3.66	3.18	6.04	4.6–4.8(m)		2.06	249	+22000
19	2.26	3.37	3.14	5.99				230	+27200
								258	−7500
20	2.19	3.32	3.12	5.95			2.07	244	+26000
									$\lambda_{max}[\phi]$[c]

Spectra taken in: [a]$CDCl_3$; [b]ethanol. [c]The NMR and ORD spectra of compound 19 were taken in D_2O and H_2O, respectively, for comparison with the reported data. *d*-centres of multiplets.

appreciable steric interactions between the geminal halogens and the ribose framework and, furthermore, that in one of the two possible diastereomers such interactions are sufficiently severe so as to alter the normal *anti*-conformation of uridine, to a *syn*-conformation in the adduct. This suggestion is given substance by the fact that the ^1H NMR spectra of the diastereomers of **19**,[6] (Scheme 4) in which the halogens are replaced by hydrogens, do not show a difference in the chemical shifts of the $H_{1'}$ protons.

In order to correlate the configuration of the adducts obtained in this work with that of N_3-methylcyclothymidine, reported by Kunieda and Witkop,[8] **13A** and **13B** were hydrolysed and the resulting products reduced by $(n\text{-}C_4H_9)_3SnH$ to isomerically pure **19** and **20**, respectively. These chemical transformations would not be expected to affect the configuration of the cyclopropane ring. Product **19** has been reported by Kunieda and Witkop and the diastereomer with a positive Cotton effect (ORD) at 260 nm has been assigned the 5*R*, 6*S* configuration.[8] This assignment involves the assumption that the cyclopropane ring in **19** exhibits an *anti*-octant behaviour and contributes in a sense opposite to the Cotton effect of the 5(*S*)-methyl group of 5(*S*)-5-methyl-



Scheme 4.

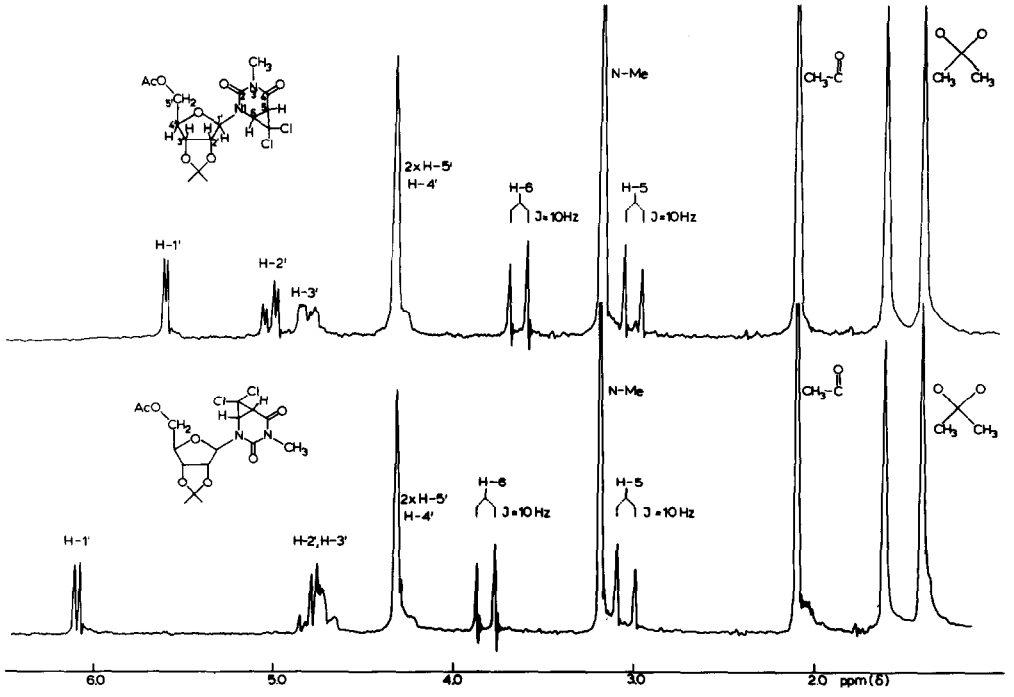


Fig. 1. NMR spectra of diastereomers **12A** and **12B**.

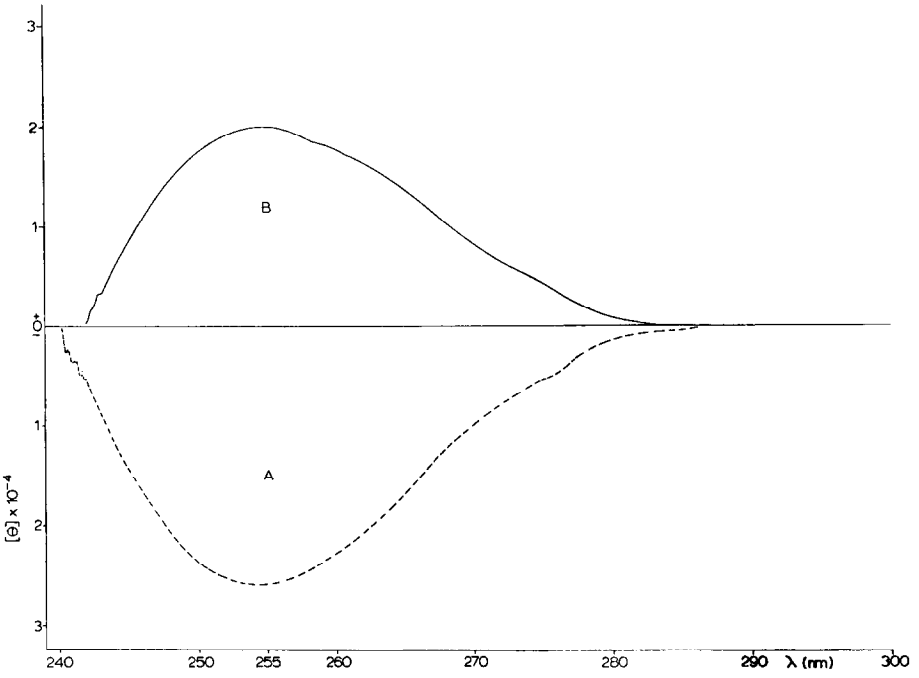


Fig. 2. CD curves of 3-methyl-5'-acetoxy-2'3'-(isopropylidine)uridine-dichlorocarbene adducts.

5,6-dihydrouridine. The product of reduction of **13A** (compound **19** in our work) exhibited a negative Cotton effect at 258 nm, implying, on the basis of the result of Kunieda and Witkop, a 5*S*, 6*R* configuration. The reduction product **20**, with a positive Cotton effect may therefore be assigned the 5*R*, 6*S* configuration. This configurational correlation implies a 5*S*, 6*S* and 5*R*, 6*R* configurations for the carbene adducts of the **A** and **B** series, respectively. An X-ray analysis† of the diasteromer **12B** confirmed both the 5*R*, 6*R* confirmation and the *anti*-conformation in the crystal phase.

Reaction of uridine derivatives **11a,b** (which contain a potentially removable group at N_3) with $:CCl_2$ and :CFCl precursors yielded the isomeric adducts **14A,B**, **17A,B** and **18A,B**. The latter were separated and classified as belonging to the **A** or **B** type on the basis of the chemical shifts of the $H_{1'}$-protons. Treatment of the adducts **14A,B** with Dowex 50W (H^+-form) in aqueous methanol and **17A,B** and **18A,B** with aqueous HCl/EtOH, removed the protecting groups on the ribose moiety. Catalytic hydrogenolysis resulted in the smooth deprotection of N_3 to yield the corresponding 7,7-dihalocyclothymidines **21a–c**. The halocyclothymidine derivatives undergo a facile ring-expansion reaction to yield novel nucleosides. These transformations will be described in a separate communication.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Unicam SP200 spectrometer and NMR spectra were run on Varian Associates Model A-60D and HA-100 instruments, using TMS as an internal standard. UV spectra were recorded on a Cary-14 spectrophotometer. Mass spectra were obtained with a Varian Mat-711 spectrometer. ORD/CD were recorded on a Cary-60, equipped with a Cary 6002 CD-attachment. Unless stated otherwise IR and NMR spectra are taken in $CHCl_3$ and $CDCl_3$, respectively. All carbene-reactions were carried out in a nitrogen atmosphere. Analyses were carried out by Mr. H. Pieters of the microanalytical Department of this laboratory.

Addition of dichlorocarbene **2a** *to* 1,3-*dibenzyluracil* **1b**. 1,3-Dibenzyluracil **2b**[6] (1.00 g) and 2.4 g $PhHgCBrCl_2$ were dissolved in 7 ml benzene and the solution was refluxed for 2 h. After filtering and evaporation of solvent the residue was purified by column chromatography (silica; ethylacetate/cyclohexane 1:5). Besides 0.14 g of the starting material, 0.89 g of adduct **3a** was isolated (81%, corrected for starting material), m.p. 95–98°C. IR (1700, 1660 cm^{-1}). NMR δ 2.69 (1H, d, J = 10, H-5), 3.22 (1H, d, J = 10, H-6), 4.71 (2H, AB pattern, J = 15, CH_2-N-1), 4.89 (2H, s, CH_2-N-3), 7.3 (10h, m, arom.). (Found: C, 60.9; H, 4.3; N, 18.8 Calc. for $C_{19}H_{16}Cl_2N_2O_2$: C, 60.81; H, 4.31; N, 18.89%).

Addition of dibromocarbene **2b** *to* 1,3-dibenzyluracil **1b**. A solution of 1,3-dibenzyluracil (1.00 g) and $PhHgCBr_3$ (1.81 g) in 10 ml benzene was refluxed for 40 h. After filtering and evaporation of the solvent, the residue was purified by column chromatography (silica, ethyl acetate/cyclohexane 1:4). Besides 322 g of the starting material, 411 mg of the adduct **3b** (38%; corrected for starting material) was isolated, m.p. 114–117°C. IR(1710, 1670 cm^{-1}). NMR δ 2.84 (1H, d, J = 10, H-5), 3.25 (1H, d, J = 10, H-6), 4.72 (2H, AB-pattern, J = 14.5, CH_2-N-1), 4.93 (2H, s, CH_2-N-3), 7.3 (10H, m, arom.).

Addition of fluorochlorocarbene **2c** *to* 1,3-*dibenzyluracil* **1b**. A solution of dibenzyluracil **1b** (1.00 g) and phenyl (dichlorofluoromethyl)mercury (2.60 g) in 5 ml benzene was refluxed for 2 h. The reaction mixture was filtered, the filtrate concentrated and the residue purified by column chromatography (silica; ethylacetate/cyclohexane 1:7). Besides 0.64 g of the starting material, 0.19 g **3c** (12%) and 0.16 g **3d** (10%) was isolated. **3c**: m.p. 84–86°C. IR: 1700, 1670 cm^{-1} (2 carbonyls); NMR δ 2.84 (1H, d × d, $J_{5,6}$ = 10.5, J_{HF} = 17, H-5), 3.33, 4.71 (2H, AB-pattern, J = 15, CH_2-N-1). 4.96 (2H, s, CH_2-N-3). 7.3 (10H, m. arom.). (Found: C, 63.7; H, 4.7; Cl, 9.8; F, 5.3; N, 7.7. Calc. for $C_{19}H_{16}FClN_2O_2$: C, 63.60; H, 4.50; Cl, 9.88; F, 5.30; N, 7.81%). **3d** m.p. 140–142°C. IR: 1700, 1670 cm^{-1} (2 carbonyls); NMR δ 2.65 (1H, d × d, $J_{5,6}$ = 10, J_{HF} = 3.5, H5), 3.14 (1H, d, $J_{5,6}$ = 10, J_{HF} = 0, H-6), 4.72 (2H, s), 4.98 (2H, s). 7.3 (10H, m). (Found: C, 63.5; H, 4.6. Calc. for $C_{19}H_{16}FClN_2O_2$: C, 63.60, H, 4.50%).

†We are indebted to Dr. H. Schenk, Laboratorium voor Kristallografie, University of Amsterdam, for determining the crystal structure of **12B**. Details of the structure will be published elsewhere.

1 - *Benzyloxymethylene* - 4 - *methoxy* - 2 - *oxo* - 1,2 - *dihydropyrimidine* **6b**. To a solution of 9.68 g 2,4-dimethoxypyrimidine **5** in 30 ml of ether was added 10.8 g phenyloxymethylene chloride. After a spontaneous reaction the solvent was evaporated and the residue recrystallized from alcohol/petroleum ether. Yield 47%. M.p. 71–72°C. IR: 1675, 1645, 1320 cm^{-1}. NMR δ: 3.91 (3H, s, OMe), 4.60 (2H, s, Ph–CH_2–O–), 5.30 (2H, s, N–CH_2–O), 5.86 (1H, d, J = 7, H-5), 7.26 (5H, m, arom.), 7.54 (1H, d, J = 7, H-6).

1-*Benzyloxymethylene*-3-*methyluracil* **1c**. A solution of 2.00 g **6b** in 10 ml of methyliodide was refluxed for 65 h. After evaporating excess of the reagent, the reaction mixture was purified by column chromatography (silica, ethylacetate/hexane). Besides 0.13 g starting material 1.09 g **2c** (55%) was isolated. M.p. 89–91°C. IR: 1710, 1670, 1640 cm^{-1}; NMR δ 3.29 (3H, s, CH_3), 4.62 (2H, s, benzylmethylene), 5.23 (2H, s, N–CH_2–O), 5.75 (1H, d, J = 8, H-5), 7.3 (6H, m, aromatic protons +H-6).

1-*Benzyloxymethylene*-3-*benzyluracil* **1d**. A mixture of 1.00 g **6b** and 1.00 g benzylbromide was heated to 90°C for 6 h. Chromatography (silica; ethylacetate/cyclohexane 1:2) afforded 0.74 g **2d** (56%). M.p.: 66–68°C. IR 1710, 1665 cm^{-1}; NMR δ 4.61 (2H, s, O–CH_2–Ph), 5.13 (2H, s, N–CH_2–Ph), 5.24 (2H, s, O–CH_2–N), 5.78 (1H, d, J = 8, H-5), 7.3 (11H, m, aromatic protons +H-6).

1-*Phenylallyl*-3-*methyluracil*. A mixture of 2.80 g 2,4-dimethoxypyrimidine and 3.94 cinnamylbromide (1 eqv.) was heated at 130°C for 3 days. Chromatography (silica, ethylacetate/cyclohexane 3:1) afforded besides 16% 1,3 bis(cinnamyl)uracil 2.12 g (44%) of the title product, m.p. 113–115°C. IR: 1700, 1655; NMR δ: 3.35 (3H, s, CH_3), 4.50 (2H, d, CH_2-N-1), 5.75 (1H, d, J = 8, H-5), 6.0–6.8 (AB- part of ABX pattern). 7.20 (1H, d, J = 8, H-6), 7.34 (5H, m, arom.).

1-(3'-*Phenylpropyl*)-3-*methyluracil* **1e**. The aforementioned compound (2.00 g) was dissolved in 60 ml ethanol and after addition of 100 mg 10% Pd-carbon hydrogenated at atmospheric pressure. Filtration and evaporation afforded 1.93 g (96%) of **1e**. M.p.: 57–59°C. ($CHCl_3$/petroleum ether). IR 1700, 1660, 1635 cm^{-1}. NMR: δ 2.08 (2H, m, CH_2–CH_2–CH_2), 2.68 (2H, t, CH_2–Ph) 3.30 (3H, s, N–CH_3), 3.75 (2H, t, N–CH_2), 5.67 (1H, d, J = 8, H-5), 7.11 (1H, d, J = 8, H-6), 7.2 (m, arom.).

Addition of carbethoxycarbene **2d** *to* 1,3-*dialkyluracil derivatives*. *General procedure*. Copper-powder was activated by successive washing with 5% hydrochloric acid (×2), water (×2), alcohol and ether, followed by drying for 1 h under reduced pressure (15 mm Hg). The activated copper-powder (200 mg) was added to a solution of 3 mmol of 1,3-dialkyluracil **1a–e** in 5 ml DME. The mixture was stirred thoroughly and was heated to reflux. A solution of ethyldiazoacetate (1.00 g) in 10 ml DME was added over a period of 1 h. After the addition was complete, the reaction-mixture was refluxed for another 2 h, filtered and evaporated (1 h at 50° and 0.1 mm Hg). The residue was purified by column chromatography (silica, eluent: ethylacetate/cyclohexane).

Adduct **3e**. M.p. 70.5–71.5, yield 23%. IR: 1720, 1700, 1665 cm^{-1}. NMR δ: 1.22 (3H, t, C_2H_5), 2.20 (1H, d × d, $J_{5,7}$ = 10, $J_{6,7}$ = 6, H-7), 2.61 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 10, H-5), 3.07(3H, s, NCH_3), 3.45 (1H, d × d, $J_{5,6}$ = 8.5, $J_{6,7}$ = 6, H-6), 4.13 (2H, q, C_2H_5). (Found: C, 53.2; H, 6.4; N, 12.4. Calc. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38%).

Adduct **3f**. M.p. 82–83.5°, yield 33%, IR: 1710, 1670, NMR δ: 1.28 (3H, t, C_2H_5), 2.01 (1H, d × d, $J_{5,7}$ = 5, $J_{6,7}$ = 3, H-7), 2.70 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 5, H-5), 3.12 (3H, s, NCH_3), 3.17 (3H, s, NCH_3), 3.45 (1H, d × d, $J_{6,5}$ = 8.5, $J_{6,7}$ = 3, H-6), 4.21 (2H, q, C_2H_5). (Found: C, 53.1; H, 6.3; N, 12.5. Calc. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38%).

Adduct **3g**. Yield 14%; IR: 1730, 1710, 1670 cm^{-1}; NMR δ: 1.12 (3H, t, C_2H_5), 1.95 (1H, d × d, $J_{5,7}$ = 10, $J_{6,7}$ = 6, H-7), 2.40 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 10, H-5), 3.19 (1H, d × d, $J_{5,6}$ = 8.5, $H_{6,7}$ = 6, H-6), 3.78 (2H, AB-part of ABX_3-pattern, C_2H_5), 4.64 (2H, s, CH_2-N-1), 5.05 (2H, s, CH_2-N-3), 7.3 (10H, m, arom.).

Adduct **3h**. Yield 27%; IR: 1700, 1660 cm^{-1}; NMR δ: 1.18 (3H, t, C_2H_5), 1.63 (1H, d × d, $J_{5,7}$ = 5, $J_{6,7}$ = 3, H-7), 2.67 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 5, H-5), 3.27 (1H, d × d, $J_{5,6}$ = 8.5, $J_{6,7}$ = 3, H-6), 4.07 (2H, q, C_2H_5), 4.72 (2H, AB-pattern, J = 15, CH_2-N-1), 4.98 (2H, s, CH_2-N-3), 7.3 (10H, m, arom.).

Adduct **3i**. M.p. 72–92°, yield 7%; IR: 1720, 1665 cm^{-1}; NMR δ: 1.10 (3H, t, C_2H_5); 2.16 (1H, d × d, $J_{5,7}$ = 10, $J_{6,7}$ = 6.5, H-7), 2.53 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 10, H-5), 3.23 (3H, s, NMe), 3.51 (1H, d × d, $J_{5,6}$ = 8.5, $J_{6,7}$ = 6.5, H-6), 3.98 (2H, AB-part of ABX_3 pattern, C_2H_5), 4.59 (2H, s, OCH_2Ph), 5.07 (2H, s, CH_2-N-1), 7.31 (5H, m, arom.). (Found: C, 61.4; H, 5.9; N, 8.4. Calc. for $C_{17}H_{20}N_2O_5$: C, 61.41; H, 6.07; N, 8.43%).

Adduct **3j**. M.p. 49–53°, yield 7%; IR: 1705, 1670 cm^{-1}; NMR (CCl_4), δ: 1.22 (3H, t, C_2H_5), 1.82 (1H, d × d, $J_{5,7}$ = 4.5, $J_{6,7}$ = 3, H-7), 2.51 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 4.5, H-5), 3.03 (3H, s, NCH_3), 3.43 (1H, d × d, $J_{6,5}$ = 8.5, $J_{6,7}$ = 3, H-6), 4.10 (2H, q, C_2H_5), 4.51 (2H, s, Ph–CH_2–O), 5.05 (AB-pattern, J = 11, –CH_2–N-1). (Found: C, 61.5; H, 6.2; N, 8.6. Calc. for $C_{17}H_{20}N_2O_5$: C, 61.43: H, 6.07; N, 8.43%).

Adduct **3k**. M.p. 66–68°, yield 40%; IR: 1710, 1690, 1650 cm^{-1}; NMR δ: 1.10 (3H, t, Et), 2.08 (1H, d × d, $J_{5,7}$ = 10, $J_{6,7}$ = 6, H-7), 2.50 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 10, H-5), 2.65 (2H, t, CH_2-Ph), 3.20 (3H, s, NCH_3), 3.27 (1H, d × d, $J_{5,6}$ = 8.5, $J_{6,7}$ = 6, H-6), 4.02 (2H, q, C_2H_5), 7.2 (5H, m, arom.). (Found: C, 65.3; H, 6.6; N, 8.3. Calc. for $C_{18}H_{20}N_2O_4$: C, 65.44; H, 6.71; N, 8.48%).

Adduct **3l**: Yield 23%, IR: 1715, 1695, 1660 cm^{-1}; NMR (CCl_4) δ: 1.24 (3H, t, C_2H_5), 1.82 (1H, d × d, $J_{5,7}$ = 5, $J_{6,7}$ = 3, H-7), 2.52 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 5, H-5), 2.64 (2H, t, CH_2Ph), 3.02 (3H, s, NCH_3), 3.18 (1H, d × d, $J_{5,6}$ = 8.5, $J_{6,7}$ = 3, H-6), 3.25–3.85 (2H, AB-part of ABX_2-system, CH_2-N-1), 4.11 (2H, q, C_2H_5).

Adduct **3m**. Yield 2.5%; IR: 1720, 1670 cm^{-1}; NMR: δ 2.13 (1H, d × d, $J_{5,7}$ = 10, $J_{6,7}$ = 6.5, H-7), 2.49 (1H, d × d, $J_{5,7}$ = 10, $J_{5,6}$ = 8, H-5), 3.44 (1H, d × d, $J_{5,6}$ = 8, $J_{6,7}$ = 6.5, H-6), 4.55 (2H, s, O–CH_2–Ph), 4.98 (2H, AB-pattern, J = 15, CH_2-N-1), 5.01 (2H, s, CH_2-N-3).

Adduct **3n**. Yield 4%; IR: 1730, 1665 cm^{-1}; NMR: δ 1.85 (1H, d × d, $J_{5,7}$ = 5, $J_{6,7}$ = 3, H-7), 2.70 (1H, d × d, $J_{5,7}$ = 5, $J_{5,6}$ = 9, H-5), 3.56 (1H, d × d, $J_{5,6}$ = 9, $J_{6,7}$ = 3, H-6), 4.58 (2H, s, O–CH_2–Ph), 4.96 (2H, s, CH_2-N-3), 5.15 (2H, AB-pattern, J = 11, CH_2-N-1).

Product **4a**. M.p. 70.5–72.5°; IR: 1730, 1700, 1670, 1640 cm^{-1}; UV (ethanol) 270 nm (ϵ = 8850); NMR δ: 1.24 (3H, t, C_2H_5), 3.31 (5H, s, CH_3-N-1 + CH_2-COOEt), 3.38 (3H, s, CH_3-N-3), 4.17 (2H, q, C_2H_5), 7.24 (1H, s, H-6).

Reaction of carbethoxycarbene **2d** *with* 2,4-*dimethoxypyrimidine*. Activated copper-powder (0.30 g) was added to 2,4-dimethoxypyrimidine (2.20 g) and the mixture was heated to 90° with vigorous stirring. A solution of ethyl diazoacetate (5.0 g, 2.3 eq.) in 15 ml DME was added over a period of 2 h. The mixture was refluxed for another 2 h, filtered and evaporated at reduced pressure (15 mm Hg). The residue was purified by column chromatography (silica, ethyl acetate/cyclohexane 3:1). **5c** Was isolated in 29% yield. IR: 1740, 1665, 1640 cm^{-1}; NMR δ: 1.24 (3H, t, C_2H_5), 3.92 (3H, s, OCH_3), 4.20 (2H, q, C_2H_5), 4.56 (2H, s, CH_2-N-1), 5.88 (1H, d, J = 7, H-5), 7.45 (1H, d, J = 7, H-6).

Reaction of carbethoxycarbene **2d** *with* **5a**. Activated copper-powder (0.50 g) was added to a solution of **5a** (1.00 g, 7.1 mmol) in 30 ml DME and the mixture was heated to reflux. A solution of ethyl diazoacetate (2.20 g) in 20 ml DME was added over a period of 1 h. The mixture was refluxed for another 2 h, filtered and evaporated at reduced pressure (0.1 mm Hg). The residue was purified by column chromatography. Besides starting material (540 mg), a mixture of **6** and **7** (477 mg, 30%) and **9a** (85 mg, 5%) were collected, IR: 1740–1720, 1670 cm^{-1}, NMR δ: 1.29 (3H, t, C_2H_5), 3.40 (3H, s, NCH_3), 4.22 (2H, q, C_2H_5), 4.68 (2H, s, CH_2-N-3), 5.75 (1H, d, J = 8, H-5), 7.25 (1H, d, J = 8, H-6), UV (ethanol): 267 nm (ϵ = 8500). **7b** Could be obtained in a pure form by recrystallization from chloroform/cyclohexane, m.p. 164–166°, IR, 3450, 3300, 1710, NMR δ: 1.27 (3H, t, C_2H_5), 2.08 (1H, d × d, $J_{5,7}$ = 5, $J_{6,7}$ = 3, H-7), 2.62 (1H, d × d, $J_{5,6}$ = 8.5, $J_{5,7}$ = 5, H-5), 3.14 (3H, s, NCH_3), 3.43 (1H, d × d, $J_{5,6}$ = 8.5, $J_{6,7}$ = 3, H-6), 4.21 (2H, q, C_2H_5). (Found: C, 50.9; H, 5.7; N, 13.3. Calc. for $C_9H_{12}N_2O_4$, C, 50.92; H, 5.70: N, 13.20%).

Reaction of carbethoxycarbene **2d** *with* **5b**. The reaction was carried out with 6.7 equivalents of ethyl diazoacetate following the aforementioned procedure. After column chromatography, uracil derivative **9b** was isolated in 14% yield, besides 57% of the starting material. IR: 1740, 1720, 1675; NMR δ: 1.25 (3H, t, C_2H_5), 4.20 (2H, q, C_2H_5), 4.60 (2H, s, OCH_2Ph), 4.65 (2H, s, CH_2-N-3), 5.23 (2H, s, CH_2-N-1), 5.79 (1H, d, J = 8, H-5), 7.3 (6H, m, H-6, arom.).

Reaction of dichlorocarbene **2a** *with* **10**. A solution of 3-methyl-2',3'-isopropylidene-5'-acetyl uridine **10** (340 mg, 1.00 mmol) and $PhHgCCl_2Br$ (3.56 g, 8.08 mmol) in 8 ml benzene was refluxed for 4 h. The reaction-mixture was cooled, filtrated and evaporated to dryness. The residue was purified by column chromatography (silica, ethylacetate/cyclohexane 1:3–1:2). Besides starting material (51 mg, 15%), adduct **12A** (122 mg, 29%) and **12B** (137 mg, 32%) have been isolated. **12A**: M.p. 106–108°; IR: 1720, 1680 cm^{-1}, NMR (see Table 2). (Found: C, 45.4; H, 4.7; N, 6.5. Calc. for $C_{16}H_{20}Cl_2N_2O_7$: C, 45.40; H, 4.76; N, 6.62%). **12B**: M.p. 90–92°; IR: 1720, 1680 cm^{-1} NMR (see Table 2). (Found: C, 45.4; H, 4.7; N, 6.5; Cl, 16.8. Calc. for $C_{16}H_{20}Cl_2N_2O_7$: C, 45.40; H, 4.76; N, 6.62; Cl, 16.75%).

Reaction of dibromocarbene **2b** with **10**. A solution of 3-methyl-2',3'-isopropylidene-5'-acetyl uridine **10**, (635 mg, 1.87 mmol) and $PhHgCBr_3$ (2.00 g; 3.78 mmol), in 10 ml benzene was refluxed for 2 h. After cooling, the mixture was filtered and evaporated to dryness. The residue was purified by column chromatography (silica, ethylacetate/cyclohexane 1:3–1:1). Besides starting material (407 mg, 64%), adducts **13A** (145 mg, 15%) and **13B** (154 mg, 16%) were isolated. **13A**: IR: 1720, 1670 cm^{-1}; NMR, CD (see Table 2). **13B**: IR: 1720, 1670 cm^{-1}; NMR, CD (see Table 2).

Reaction of chlorofluorocarbene **2c** *with* **10**. A solution of 3-methyl-2',3'-isopropylidene-5'-acetyl uridine **10** (1.70 g) and $PhHgCCl_2F$ (12.65 g) in 25 ml benzene was refluxed for 10 h. After cooling, the mixture was filtered and evaporated to dryness. The residue was purified by column chromatography (silica, ethylacetate/cyclohexane). The adducts **15B** and **16B** were collected as a mixture and were separated by recrystallization from chloroform/ether/petroleum ether, b.p. 40–60°. The adducts **15A** and **16A** were isolated as spectroscopically pure compounds. **15B**: yield 16%; IR: 1740, 1720, 1680 cm^{-1}; NMR + CD (see Table 2). **15B**: yield 17%; m.p. 150–156° (dec.); IR: 1740, 1720, 1680 cm^{-1}; NMR + CD (see Table 2). (Found: C, 47.2; H, 5.1; N, 7.0. Calc. for $C_{16}H_{20}ClFN_2O_7$: C, 47.24; H, 4.96; N, 6.89%). **16A**: yield 10% IR: 1740, 1720, 1680; NMR + CD (see Table 2). **16B**: yield 12%; IR: 1740, 1720, 1680; NMR + CD (see Table 2).

3-Methylcyclothymidine **19A**. In a typical experiment, dibromocarbene adduct **13A** was hydrolysed during column chromatography. The product, 3-methyl-7,7-dibromocyclothymidine (m.p. 160–170°, dec., from ethanol. (Found: C, 30.7; H, 3.3; N, 6.5. Calc. for $C_{11}H_{14}Br_2N_2O_6$: C, 30.88; H, 3.15; N, 6.45%), (36 mg) was dissolved in 1.0 ml dry dioxane. (n-$C_4H_9)_3SnH$ (0.10 ml) was added and the mixture was kept at room temperature for 4 days. After evaporation of the solvent, the residue was purified by TLC (silica, ethylacetate/ethanol 4:1). The product **19A** was isolated in 88% yield (20 mg). Spectra (NMR + ORD) were in agreement with those described in the literature[8] (see Table 2).

3-Methylcyclothymidine **19B**. Analogously, dibromocarbene adduct **13B** was converted to **19B**. Spectral data (NMR, CE, see Table 2) were in agreement with those described in the literature.

7,7-Dichlorocyclothymidine **21a**. A solution of 3-benzhydril-2',3'-isopropylidene-5'-trityluridine **11a** (536 mg, 0.77 mmol) and $PhHgCCl_2Br$ (2.74 g, 6.2 mmol) in 10 ml benzene was refluxed for 2 h. After cooling the solution was filtered, evaporated to dryness and the residue was purified by column chromatography (silica, ethylacetate/cyclohexane). Besides starting material (260 mg, 49%), adducts **14A** (134 mg, 23%) and **14B** (93 mg, 15%) were isolated. **14A**: IR: 1710, 1670 cm^{-1}; NMR δ: 1.34, 1.54 (6H, 2 × s, $C(CH_3)_2$), 2.65 (1H, d, J = 10, H-5); 3.40 (2H, m, H-5'); 3.70 (1H, d, J = 10, H-6), 3.45 (1H, m, H-4'), 4.7–5.1 (2H, m, H-2', H-3'); 5.69 (1H, d, J = 2, H-1'), 7.3 (26H, m, arom.). **14B**: IR: 1710, 1670 cm^{-1}; NMR δ: 1.36, 1.54 (6H, 2 × s, $C(CH_3)_2$), 2.79 (1H, d, J = 10, H-5), 3.48 (2H, m, H-5'), 3.85 (1H, d, J = 10, H-6), 4.17 (1H, m, H-4'), 4.80 (2H, m, H-2', H-3'), 6.23 (1H, m, H-1'), 7.35 (26H, m, arom.).

Isomer **14A** (230 mg) was dissolved in ethanol (40 ml), and successively 1.5 ml H_2O and 2.0 ml Dowex 50 × 4(H^+) were added. The mixture was stirred 4 days at room temperature. The solution was filtered and evaporated to dryness and the residue was purified by column chromatography (silica, ethyl acetate). Yield 59 mg 3-benzhydril-7,7-dichlorocyclothymidine (40%). To a solution of the latter compound (40 mg) in 15 ml of methanol, 10 mg 10% Pd/C was added, and the mixture was hydrogenated at atmospheric pressure for 6 h. The solution was filtered and evaporated and the residue was purified by column chromatography (silica, ethylacetate/ethanol 10:1). The 7,7-dichlorocyclothymidine **21aA** (16 mg, 61%) was collected as white crystals (dec. 170°). **21aA**: IR(KBr) 3600–3200, 1700, 1680 cm^{-1}; NMR (CD_3OD), δ 3.06 (1H, d, J = 10, H-5), 3.80 (2H, m, H-5'), 4.0 (1H, m, H-4'), 4.1–4.3 (2H, m, H-2', H-3'), 4.37 (1H, d, J = 10, H-6), 6.07 (1H, d, J = 4, H-1'). **21aB**: IR(KBr): 3600, 3200, 1700, 1680 cm^{-1}; NMR(CD_3OD): δ 3.00 (1H, d, J = 10, H-5), 3.7–3.8 (2H, m, H-5'), 3.9–4.1 (1H, m, H-4'), 4.10 (1H, d, J = 10, H-6), 4.15 (1H, m, H-3', 4.35 (1H, m, H-2'), 5.92 (1H, d, J = 5, H-1').

7-Chloro-7-fluorocyclothymidines **21b,c**. A solution of 3-benzhydril-2',3'-isopropylidene-5'-aceto-uridine **11b** (1.05 g, 2.07 mmol) and $PhHgCCl_2F$ (4.00 g, 10.5 mmol) in 15 ml benzene was refluxed for 12 h. The mixture was cooled, filtered and evaporated to dryness. The residue was purified by column chromatography (silica, ethylacetate/cyclohexane 1:3–1:2. Besides starting material (346 mg, 33%) the adducts **17B** and **18B** were isolated as a mixture (342 mg, 29%) and adducts **17A** **18B** were isolated as a mixture (342 mg, 29%) and adducts **17A** (164 mg, 14%) and **18A** (108 mg, 9%) as the pure compounds. **17A**: IR: 1720, 1675; NMR δ 1.34, 1.54 (6H, 2 × s, $C(CH_3)_2$), 2.04 (3H, s, Ac), 2.99 (1H, d × d, $J_{5,6}$ = 10.5, J_{HF} = 17, H-5), 3.65 (1H, 2 × d, $J_{5,6}$ = 10.5, J_{HF} = 7, H-6), 4.21 (3H, m, H-4', H-5'), 4.83 (1H, m, H-3'), 4.94 (1H, m, H-2'), 5.54 (1H, d, J = 2, H-1'), 7.3 (11H, m, $CHPh_2$). **18A**: IR: 1715, 1670 cm^{-1}; NMR δ: 1.34, 1.55 (6H, 2 × s, $C(CH_3)_2$), 2.05 (3H, S, Ac), 2.82 (1H, d × d, $J_{5,6}$ = 10, J_{HF} = 4, H-5), 3.45 (1H, d, $J_{5,6}$ = 10, J_{HF} = 0, H-6), 4.23 (3H, m, H-4', H-5'), 4.72 (1H, m, H-3'), 4.90 (1H, m, H-2'), 5.64 (1H, d, J = 2, H-1'), 7.3 (11H, m, $CHPh_2$). A mixture of **17B** and **18B** (351 mg) in 10 ml dioxane and 0.70 g 10% Pd/C was hydrogenated at 50PSI. After 3 h the reduction was complete and the mixture was filtered and evaporated. The residue was purified by column chromatography (silica, ethylacetate/cyclohexane 1:1). The product (182 mg, 74%) could be separated in two isomers by fractional recrystallization, 7-exo-fluoro-7-endochloro-2,3'-isopropylidene-5'-acetylcyclothymidine (104 mg, 42%) and 7-exo-chloro-7-endofluoro-2',3'-isopropylidene-5'-acetylcyclothymidine (63 mg, 26%). The former (93 mg) was dissolved in a mixture of 0.6 ml 10% hydrochloric acid and 2.4 ml of ethanol and the solution was heated to 50° for 3 h. Thereafter, it was evaporated, dissolved in ethanol/benzene, evaporated once more and the residue recrystallized from ethanol. 7-exofluoro-7-endochlorocyclothymidine **21bB** was isolated as white crystals (47 mg, 64%). **21bB**: IR(KBr): 3500, 3300, 1710, 1690; NMR(CD_3OD), δ: 3.15 (1H, d × d, $J_{5,6}$ = 11, J_{HF} = 17, H-5), 3.7–4.3 (5H, m, H-2', H-3', H-4', H-5'), 4.44 (1H, d × d, $J_{5,6}$ = 11, J_{HF} = 8, H-6), 6.03 (1H, d, J = 4, H-1'). (Found: C, 38.7; H, 3.9; N, 9.0; F, 6.1. Calc. for $C_{10}H_{12}N_2O_6ClF$: C, 38.77; H, 4.00: N, 9.14; F, 6.20%). The same procedure as above afforded the isomers **21bA**, **21cA** and **21cB**. The yield of the reduction step was 71–87%, and that of the hydrolysis 64–73%. **21bA**: IR(KBr): 3400, 1710, 1690 cm^{-1}; NMR(CD_3OD), δ: 3.05 (1H, d × d, $J_{5,6}$ = 11, J_{HF} = 17, H-5), 3.67 (2H, m, H-5'), 3.9–4.4 (3H, m, H-2', H-3', H-4'), 4.16 (1H, d × d, $J_{5,6}$ = 11, J_{HF} = 8, H-6), 5.87 (1H, d, J = 5, H-1'). **21cA**: IR(KBr): 3400, 3200, 1740, 1660; NMR(CD_3OD), δ: 2.90 (1H, d × d, $J_{5,6}$ = 10, J_{HF} = 0, H-6), 3.9–4.4 (3H, m, H-2', H-3', H-4'), 5.96 (1H, d, J = 5, H-1'). **21cB**: IR(KBr): 3400, 1710, 1680; NMR(CD_3OD), δ: 2.94 (1H, d × d, $J_{5,6}$ = 10, J_{HF} = 4, H-5), 3.5–4.2 (5H, m, H-2', H-3', H-4', H-5'), 4.14 (1H, d, $J_{5,6}$ = 10, J_{HF} = 0, H-6), 6.06 (1H, d, J = 3, H-1').

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