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5'-SUBSTITUTED 2,2'-ANHYDROURIDINES

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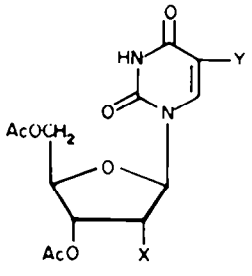
Abstract—3',5'-Di-O-acetyl-2'-halogenouridines (**1a**, **1c** and **1d**) can be partially deacetylated at C-5' by transesterification with methanol-HCl, providing the 3'-O-acetyl derivatives **2a–2c**. These can be converted into the 5'-O-mesyl derivatives **3a–3c**, and latter into the 5'-chloro compounds **3d–3f**. All 5'-substituted 2'-halogeno compounds give the corresponding 2,2'-anhydrouridine derivatives **4a–4c** on treatment with NaOMe. Structures were proved by IR and ^{1}H-NMR.

In our previous paper the conversion of 2,2'-anhydrouridine into 2',5-dibromouridine was described.[1] Investigating the reactivity of the two OH groups of the sugar moiety we could show, that, on deacetylation with methanolic HCl, the 5'-O-acetyl group of the corresponding 3',5'-di-O-acetyl derivative **1a** was cleaved much faster, yielding the 3'-O-acetyl compound **2a**.

Similar nucleoside derivatives with a free 5'-OH group can be obtained either by multi-step syntheses, using a blocking group at O-5' (i.e. trityl[2] or methoxyacetyl[3]) which can be removed selectively after acetylation, or by using the less readily available 2-acyloxyisobutyryl halides[4] as a reagent. For this reason the general applicability of the aforementioned partial deacetylation was investigated.

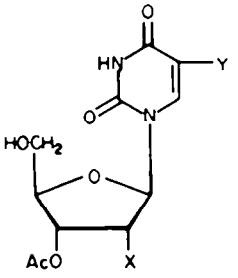
In the case of tri-O-acetyluridine **1b**, no significant difference in the reaction rates of the acetyl groups towards transesterification was observed, consequently the presence of the 2'-halogen atom in **1a** must be essential for any rate differences. This assumption was proved by investigating the corresponding 2'-chloro- and 2'bromo-uridine derivatives **1c** and **1d**, which, on similar



1a: X = Br, Y = Br
1b: X = AcO, Y = H
1c: X = Cl, Y = H
1d: X = Br, Y = H

treatment, provided the crystalline 3'-O-acetyl compounds **2b** and **2c**, respectively, in good yield. As 2'-halogeno-uridines can be obtained in excellent yields from 2,2'-anhydrouridine[5] using the method of Codington *et al.*,[6] the transesterification reaction is valuable in preparing selectively blocked pirimidine nucleosides containing a free 5'-OH group.

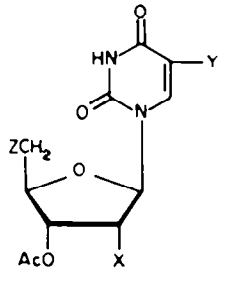
The transesterification reaction can also be applied to 3',5'-di-O-benzoyl-2'-halogeno-uridines, but the 3'-O-benzoyl derivatives obtained could not be crystallized, and had to be purified by column chromatography.



2a: X = Br, Y = Br
2b: X = Cl, Y = H
2c: X = Br, Y = H

The structure of the 2 type mono-esters was proved spectroscopically, and is discuseed in detail for the 2'-chloro compound **2b** (Table 1). The IR data [3180 (νNH), 1710, 1680, (νC=O) and 1630 cm^{-1} (νC=C)] as well as the NH signal at 11.6 ppm in the ^{1}H-NMR spectrum (which is coupled with H-5) are characteristic for the pirimidyldione ring. The H-3' signal of the carbohydrate moiety appears downfield at 5.3 ppm as a double doublet, due to the presence of the 3'-O-acetyl group and the coupling with both vicinal protons (H-2' and H-4').

The free 5'-OH group of **2a**, **2b** and **2c** was converted with mesyl chloride in pyridine into the 5'-O-mesyl esters **3a–3c**, respectively. The mesyloxy group of these compounds is easily substituted by nucleophiles, so that the 5'-chloro derivatives **3d–3f** were obtained as byproducts when the reaction mixture was kept at room temperature for 24 hr. The mesyloxy compounds can be converted



3a: X = Br, Y = Br, Z = MsO
3b: X = Cl, Y = H, Z = MsO
3c: X = Br, Y = H, Z = MsO
3d: X = Br, Y = Br, Z = Cl
3e: X = Cl, Y = H, Z = Cl
3f: X = Br, Y = H, Z = Cl

Table 1. ^{1}H-NMR data of compounds **2b**, **3b**, **4a**, **4b** and **4c** in ppm*

	H-1'	H-2'	H-3'	H-4'	H-5'	H-6	H-5	other
2b	6,10	4,80	5,30	4,20	3,7	7,85	5,75	AcO 2,15; NH 11,6
	d (7)	2xd(4,6)	2xd(3,4)	t(3,4)	broad	d (8)	2xd(8,2)	OH 3,4 broad
3b	6,10	4,95	4,40	4,50		7,73	5,75	AcO 2,20; NH 11,5
	d (6)	t (6)	2xd(4,6)	s^{xx} (3H)		d (8)	2xd(8,2)	MeO 3,25
4a	6,35	5,28	225----------275			7,85	5,85	MeO 3,15
	d (6)	d (6)	m (4H)			d (7)	d (7)	OH 6,18 d (5)
4b	6,42	5,35	245-------275		193-230	7,95	5,95	OH 6,22 d (4)
	d (6)	d (6)	m (2H)		m (2H)	d (7)	d (7)	
4c	6,40	5,35	240----------275			8,55	-	MeO 3,15
	d (6)	d (6)	m (4H)			s		OH 6,25 d (4)

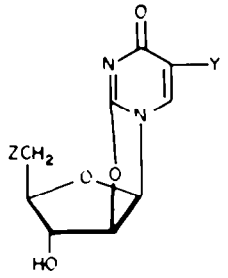
x multiplets are given in Hz

xx the singlet of the methylene group overlaps with the H-4' signal

quantitatively into the 5'-chloro derivatives on heating in DMF–H_2O in the presence of NaCl.

The 3-type compounds give similar spectra to the starting materials (Table 1); only the H-5' signals are shifted downfield (~ 4.5 ppm) in the ^{1}H-NMR spectra as a result of substitution at C-5'.

In further experiments, the behaviour of the 2' - halogeno - 5' - O - mesyl (**3a–3c**) and 2',5'-dihalogeno derivatives (**3d–3f**) towards methanolic sodium methoxide[1] was investigated. Codington *et al.*[7] obtained the thermodynamically more stable 2,2'-anhydrouridine derivative on treating 2',3',5' - tri - O - mesyluridine with sodium hydroxide in aqueous ethanol at 45–50°; but as the reaction with sodium methoxide can be carried out at room temperature, the more reactive 5'-groups might react, leading to 2,5'-anhydro derivatives. However, this reaction did not take place even for the 2' - chloro - 5' - O - mesyl derivative **3b**, where the 5'-group has a much stronger leaving character; Cl^- was displaced, giving the corresponding 2,2'-anhydro derivative[8] **4a** as the only product. The same compound (**4a**) was obtained from the 2' - bromo - 5' - O - mesyl derivative **3c**, whereas 5' - chloro - 2,2' - anhydrouridine (**4b**) was formed both from the 2',5'-dichloro (**3e**) and the 2' - bromo - 5' - chloro-derivative (**3f**). Halogen substitution on the pyrimidine ring had no influence on this reaction, since 2,2' - anhydro - 5' - O - mesyl - 5 - bromouridine (**4c**) was formed from the corresponding 5-bromo derivative **3a**.



4a: Y = H, Z = MsO
4b: Y = H, Z = Cl
4c: Y = Br, Z = MsO

The structure of 4 type compounds was unambiguously established from their spectra; as a consequence of the formation of the 2,2'-anhydro bridge, the original pyrimidyldionering was changed into a cross-conjugated 4-one structure. Therefore, the absorption of a conjugated acylimino group (νC=O: 1640 and νC=N: 1600 cm^{-1}) and that of the C=C bond at 1530 cm^{-1} appeared instead of the imide νNH and νC=O bands in the original IR spectra. Related changes occurred in the ^{1}H-NMR spectra; no NH signal could be detected and the original H-5 double doublet of the 3-type compounds appeared in the case of structure **4** as a doublet (5.75 ppm), due to the absence of the long-range coupling with the NH proton. On the other hand, substitution of the 2'-halogen by the oxygen of the anhydro bridge (with inversion) caused a downfield shift of the H-2' signal,[10] due to the neighbouring bridge-oxygen and coplanar pyrimidine ring. Because of deacylation of O-3', the corresponding H-3' signal was shifted upfield and overlapped with the multiplet of the H-4' and H-5' protons (Table 1).

EXPERIMENTAL

M.ps are uncorrected. TLC was carried out on Kieselgel G-coated microscope slides using EtOAc (A), EtOAc/CCl_4 2:1 (B), EtOAc/CCl_4 1:1 (C) and EtOAc/AcOH/pyridine/H_2O 30:10:3:6 (D) for elution. Detection was effected with 0.1 M $KMnO_4$ and M H_2SO_4 (1:1), and subsequent heating to 100°. Kieselgel 40 (0.063–0.200 mm) was used for column chromatography. All evaporations were carried out in a rotary evaporator under diminished pressure. ^{1}H-NMR spectra were recorded at 60 MHz with a Varian A-60D spectrometer, with TMS as internal standard. IR spectra were recorded in KBr pellets on a Perkin–Elmer 457 spectrometer. Optical rotations were determined in DMF solution at C = 1. Analytical data are given in Table 2.

2' - Chloro - 2' - deoxyuridine. A stirred slurry of 2,2'-anhydrouridine[5] (4.5 g) in dry chloroform (100 ml) was saturated at room temp. with HCl. Saturation and stirring was continued for 5 hr, when the HCl salt was filtered off and dried (5.2 g). A suspension of this salt in dry dioxane (670 ml) was heated at 75° until complete soln was obtained (5 hr), after which it was evaporated. The residue was recrystallized from EtOAc yielding 4.8 g (91.5%) 2' - chloro - 2' - deoxiuridine, m.p. 205–207° dec., lit.[6] m.p. 207–212° dec.

2' - Bromo - 2' - deoxyuridine. The HBr salt of 2,2'-an-

Table 2. Analytical data of compounds 1d, 2a, 2c, 3a–f and 4b, 4c

comp.	formula	Mwt		C	H	Br	Cl	N	S
1d	$C_{13}H_{15}BrN_2O_7$	391,19	Found:	39,87	3,90	19,39		7,04	
			required:	39,92	3,87	20,43		7,16	
2a	$C_{11}H_{12}Br_2N_2O_6$	428,05	Found:	31,01	2,88	37,32		6,52	
			required:	30,87	2,83	37,35		6,55	
2c	$C_{11}H_{13}BrN_2O_6$	349,15	Found:	37,78	3,91	22,71		7,94	
			required:	37,64	3,73	22,76		7,98	
3a	$C_{12}H_{14}Br_2N_2O_8S$	506,15	Found:	28,58	2,70	31,38		5,53	6,02
			required:	28,47	2,79	31,58		5,53	6,33
3b	$C_{12}H_{15}ClN_2O_8S$	382,79	Found:	37,68	4,10		9,35	7,43	8,42
			required:	37,66	3,95		9,26	7,32	8,38
3c	$C_{12}H_{15}BrN_2O_8S$	427,24	Found:	33,77	3,57	18,82		6,66	7,43
			required:	33,74	3,54	18,70		6,56	7,51
3d	$C_{11}H_{11}Br_2ClN_2O_5$	446,47	Found:	29,45	2,68	35,42	8,01	6,00	
			required:	29,60	2,48	35,80	7,94	6,27	
3e	$C_{11}H_{12}Cl_2N_2O_5$	323,14	Found:	40,86	3,76		21,90	8,25	
			required:	40,90	3,74		21,95	8,67	
3f	$C_{11}H_{12}BrClN_2O_5$	367,59	Found:	36,06	3,38	21,00	9,34	7,66	
			required:	35,95	3,29	21,74	9,65	7,62	
4b	$C_9H_9ClN_2O_4$	244,63	Found:	44,53	3,90		14,56	11,38	
			required:	44,20	3,71		14,50	11,45	
4c	$C_{10}H_{11}BrN_2O_7S$	383,16	Found:	31,88	3,00	20,81		7,20	8,33
			required:	31,34	2,89	20,85		7,31	8,37

hydrouridine was obtained, as described for the HCl salt, using HBr. The dried salt (6.1 g) was dissolved in trifluoroacetic acid (700 ml) and kept at room temp. for 5 days. The residue obtained on work-up was evaporated with EtOH and was then recrystallized from EtOH, yielding 5.2 g (85%) 2' - bromo - 2' - deoxyuridine, m.p. 184–186°, lit.[6] m.p. 186–190°.

1 - (*β - D - 3',5' - Di - O - acetyl - 2' - bromo - 2' - deoxy-ribofuranosyl*) - *uracil* (**1d**). A soln of 2' - bromo - 2' - deoxyuridine (3.1 g) in pyridine (30 ml) and Ac_2O (30 ml) was kept at room temp for 48 hr and was then evaporated. The residue was concentrated with EtOH (3 × 10 ml) and was then recrystallized from EtOH (15 ml), yielding **1d** (2.7 g, 69%), m.p. 124–126°, $[\alpha]_D^{20}$ + 6.9°, lit.[6] amorphous, $[\alpha]_D^{20}$ + 8.9° (*c* 0.4 EtOH).

Partial deacetylation of 3',5' - *di* - O - *acetyl compounds* **1a**, **1c** *and* **1d**. A suspension of the diacetyl compound in 0.1 M methanolic HCl (50 volume) was boiled after dissolution for 20 min. On cooling, the solution was neutralized with an ion-exchanger (Varian AD) and filtered. The crystalline slurry, obtained after evaporation, was filtered off and washed with MeOH. Recrystallization from MeOH gave **2a** (36%), m.p. 205–208°, R_f 0.5 (A), $[\alpha]_D^{20}$ −28.1°; **2b** (66%), m.p. 176–178°, R_f 0.6 (A), $[\alpha]_D^{20}$ +15.1°, lit.[4] m.p. 183–184°, $[\alpha]_D^{20}$ +13.7° (*c* 0.76 MeOH); and **2c** (58%), m.p. 156–158°, R_f 0.4 (A), $[\alpha]_D^{20}$ +21.2°, respectively.

Mesylation of compounds **2a–2c**. A soln of **2a–2c** in pyridine (10 volume) was treated with mesyl chloride (1.1 equiv). After 5 hr at room temp., the mixture was worked up the usual way to give, after recrystallisation from EtOH, **3a** (76%), m.p. 170–172°, R_f 0.7 (B), $[\alpha]_D^{20}$ −22.1°; **3b** (71%), m.p. 167–168°, R_f 0.7 (A), $[\alpha]_D^{20}$ +9.4° and **3c** (62%), m.p. 175–176°, R_f 0.4 (B), $[\alpha]_D^{20}$ +9.9°, respectively.

Synthesis of the 5'-*chloro compounds* **3d–3f**. Compound **3a–3c** was heated in a mixture of DMF (15 volume) and water (1.5 volume) containing NaCl (10 equiv) on a steam bath for 3 hr. The brown slurry was then evaporated and water was added to the residue, which was then filtered. The crude chloro compounds were either recrystallized from EtOH or purified by column chromatography (solvent A), yielding **3d** (90%), m.p. 192–194°, R_f 0.9 (B), $[\alpha]_D^{20}$ −29.9°; **3e** (76%), m.p. 158–160°, R_f 0.5 (C), $[\alpha]_D^{20}$ +3.5°, and **3f** (60%), m.p. 144–146°, R_f 0.8 (B), $[\alpha]_D^{20}$ +11.9°, respectively.

2,2' - *Anhydro* - 1 - (*β - D - 5' - O - mesyl-arabinofuranosyl*) - *uracil* (**4a**). A slurry of **3b** or **3c** in dry MeOH (10 volume) was treated with 1 equiv of methanolic 0.4 M NaOMe. The mixture was stirred at room temp. for 24 hr and was then evaporated. The residue was recrystallized from water (20 fold) to yield **4a** (55%), m.p. 208–210°, R_f 0.6 (D), $[\alpha]_D^{20}$ −50.7°, lit.[8] m.p. 215–216°, $[\alpha]_D^{20}$ −41.8° (*c*, 0.37 DMF).

2,2' - *Anhydro* - 1 - (*β - D - 5' - chloro - 5' - deoxy-arabinofuranosyl*) - *uracil* (**4b**). Treatment of **3e** or **3f** with methanolic NaOMe, as described for **4a**, afforded **4b** (67%), m.p. 195–196°, R_f 0.7 (D), $[\alpha]_D^{20}$ −70.6°.

2,2' - *Anhydro* - 1 - (*β - D - 5' - O - mesyl-arabinofuranosyl*) - 5 - *bromouracil* (**4c**). Treatment of **3a** or **3d** with methanolic NaOMe, as described for **4a**, afforded **4c** (63%), m.p. 190–192°, R_f 0.9 (D), $[\alpha]_D^{20}$ −92.4°.

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