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Studies of Nucleosides and Nucleotides. LXXXII.[1] Cyclonucleosides. (39).[2] Synthesis and Properties of 2′-Halogeno-2′-deoxyadenosines

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9-(2′-O-Methanesulfonyl- or trifluoromethanesulfonyl-3′,5′-di-O-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (Ia, b) were reacted with lithium chloride or tetrabutylammonium halide to yield 2′-halogeno-2′-deoxy compounds (IIa—d). These halogeno compounds were deprotected with 80% acetic acid to give 2′-chloro-, 2′-bromo-, 2′-fluoro and 2′-iodo-2′-deoxyadenosine (IVa—d) in overall yields of 12—25% from the compound I. Ultraviolet absorption properties, ^{1}H and ^{13}C-nuclear magnetic resonance spectral properties were recorded on the compounds IVa—d.

Keywords—9-(2′-mesyl-3′,5′-di-O-tetrahydropyranyl-9-β-D-arabinofuranosyl)adenine; 9-(2′-O-trifluoromesyl-3′,5′-di-O-tetrahydropyranyl-9-β-D-arabinofuranosyl)adenine; tetraethylammonium chloride; tetra-*n*-butylammonium bromide; tetra-*n*-butylammonium fluoride; tetra-*n*-butylammonium iodide; UV; ^{1}H-NMR; ^{13}C-NMR

In connection to the biological importance of sugar-modified nucleosides, several researchers reported the synthesis of 2′-substituted 2′-deoxypurine nucleosides.[4–8] Among them, 2′-azidoadenosine revealed some anticancer activity[9] and poly(2′-azido-2′-deoxyadenylic acid) had quite similar physical properties with poly(adenylic acid), but not with poly(2′-deoxyadenylic acid).[10] Moreover, polynucleotides containing 2′-azido-2′-deoxyinosine, poly(Iz)[11] have been found to possess interferon-inducing activity when it was hybridized with poly(citidylic acid).[12]

We, therefore, investigated methods for synthesizing 2′-deoxy-2′-halogenoadenosines and results are reported in the present paper.

It was previously found[4,5] that the use of 9-(3′,5′-di-O-tetrahydropyranyl-2′-O-mesyl-β-D-arabinosyl)adenine (Ia) as a starting material was quite suitable for introducing an azido group to the $C_{2'}$-position in α-configuration. The compound (I) is rather easily obtainable from 8,2′-anhydro-8-oxy-9-β-D-arabinofuranosyladenine (8,2′-O-cycloadenosine),[13] which in turn could be synthesized from adenosine in four step reaction. All these steps do not involve laborious separation of α and β or positional isomers, such as 2′ and 3′ compounds. Thus, the compound (Ia) was treated with lithium chloride in DMF at 150°. However, the reaction proceeded rather slowly compared to the case of the azido ion. We then changed lithium chloride to tetraalkylammonium chloride, which was proved to be a suitable nucleophile in

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the substitution reaction.[14] For increasing the rate of the reaction, 2′-leaving group was also altered to trifluoromethylsulfonyloxy group, which has been used by Ranganasan[8] for the same type of reactions.

9-(2′-O-Trifluoromethanesulfonyl-3,5-di-O-tetrahydropyranyl-β-D-arabinofuranosyl)adenine (Ib) was obtained by treating 3′,5′-di-O-tetrahydropyranyl-araA[5] with NaH and trifluoromethanesulfonyl chloride at −60° for 1 hr. The yield was 54% and the structure was confirmed by elemental analysis and ultraviolet (UV) absorption properties. The compound (Ib) was then heated with tetraethylammonium chloride in DMF at 80° for 3 hr. The 2′-chloro compound (IIa) was obtained in a yield of 57.5%. For deprotection IIa was heated in 80% acetic acid at 50° for 5 hr and 2′-chloro-2′-deoxyadenosine (IIIa) was obtained in a yield of 40% as needles having mp 221—222°. Elemental analysis and UV absorption properties confirmed the structure of IIIa. As summarized in Table I, ^{1}H-nuclear magnetic resonance ^{1}H-(NMR) spectrum of IIIa showed a sign of $H_{2'}$ at 5.11 δ. The coupling constants $J_{1'-2'}$, and $J_{2'-3'}$, equal to 7 Hz and 4.5 Hz, respectively. These values may be consonant with α-ribo configuration of the sugar moiety of IVa. In ^{13}C-NMR (Table II) it reveals a C-2′ signal at δ −5.33 (from dioxane as standard). This fact may suggest that 2′-carbon is substituted with an electronegative atom.

TABLE I. ^{1}H-NMR of 2′-Halogeno-2′-deoxyadenosines (δ (ppm) from TMS)

2′-Substituents	H-8	H-2	H-N^6	H-1′	3′-OH	5′-OH	H-2′	H-3′	H-4′	H-5′
Cl	8.41 (s, 1H)	8.17 (s, 1H)	7.44 (s, 1H)	6.17 (d, 1H)	5.93 (d, 1H)	5.44 (q, 1H)	5.11 (q, 1H)	4.43 (q, 1H)	4.13 (m, 1H)	3.69 (m, 1H)
				$J_{H1'-H2'}=5$Hz	$J_{OH3'-H3'}=5$Hz		$J_{H2'-H3'}=4.5$Hz		$J_{H3'-H4'}=8$Hz	
Br	8.39 (s, 1H)	8.16 (s, 1H)	7.33 (s, 2H)	6.27 (d, 1H)	5.98 (b, 1H)	5.50 (q, 1H)	5.13 (q, 1H)	4.36 (m, 1H)	4.16 (m, 1H)	3.69 (m, 2H)
				$J_{H1'-H2'}=7.5$Hz	$J_{OH3'-H3'}=5$Hz		$J_{H2'-H3'}=5$Hz			
F	8.31 (s, 1H)	8.16 (s, 1H)	7.30 (s, 2H)	6.34 6.16 (d, 2 0.5H)	5.76 (q, 1.5H)	5.28	5.72 5.14 (m, 1.5H)			
				$J_{H1'-H2'}=3.5$Hz $J_{H1'-F}=16$Hz						
F (D_2O)							5.72 (q, 0.5H) 5.14 (q, 0.5H)	4.62 4.62 (octaplet, 1H)	4.03 (m, 1H)	3.68 (m, 2H)
							$J_{H2'-H3'}=4.5$Hz $J_{2'-F}=52$Hz	$J_{H3'-4H'}=9$Hz $J_{H3'-F}=17$Hz		
I	8.36 (s, 1H)	8.14 (s, 1H)	7.31 (s, 2H)	6.31 (d, 1H)	6.02 (d, 1H)	5.44 (m, 1H)	5.13 (q, 1H)	4.14 (m, 2H)		3.66 (m, 2H)
				$J_{H1'-H2'}=8.5$Hz	$J_{H3'-OH3'}=5$Hz		$J_{H2'-H3'}=4.5$Hz			

TABLE II. ^{13}C-NMR of 2′-Halogeno-2′-deoxyadenosines (δ (ppm) from dioxane)

2′-Substituents	C-2	C-4	C-5	C-6	C-8	C-1′	C-2′	C-3′	C-4′	C-5′
Cl	86.25	82.65	52.81	89.73	73.18	21.46	−5.33	3.90	19.90	−5.33
Br	86.25	82.71	52.86	89.78	73.24	21.94	−13.42	3.90	20.14	−5.07
F	86.30	82.44	52.76	89.82	73.01	19.47[a]	26.94[b]	2.06[c]	17.89	−5.81

a) $J_{C1'-F}=33.9$Hz. b) $J_{C2'-F}=26.94$Hz. c) $J_{C3'-F}=2.06$Hz.

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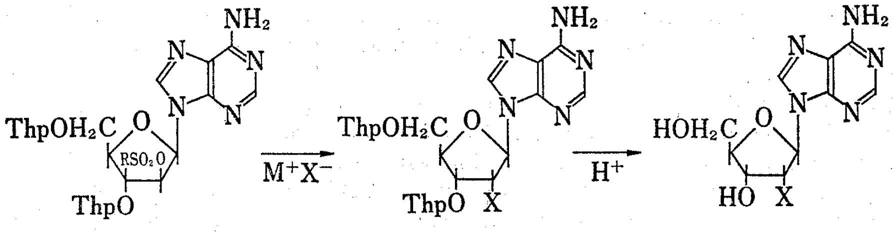
The compound Ib was then heated with tetra-*n*-butylammonium bromide in DMF at 70°. In this case reaction proceeded very slowly and the temperature was raised to 100°. After 5 hr heating the isolated yield of the product (IIb) was 55%. At 120° for 3 hr the yield was 58%. The 2′-bromo compound (IIb), isolated by thin-layer chromatography (TLC), was deprotected with 80% AcOH at 50° for 3 hr and 2′-bromo-2′-deoxyadenosine (IIIb), mp 225—226.5°, was obtained in a yield of 30%. Elemental analysis and UV absorption properties supported the structure of the compound IIIb to be correct. In ^{1}H-NMR (Table I) the compound IIIb reveals a H-2′ signal at δ 5.13 and coupling constants $J_{1'-2'}$ and $J_{2'-3'}$ equal to 7.5 and 5 Hz, respectively, suggesting a β-ribo configuration in the sugar moiety. ^{13}C-NMR (Table II) of IIIb showed C-2′ signal at δ −13.42, suggesting substitution of a strong electronegative atom at the 2′-carbon.

For obtaining 2′-fluoro compound, Ib was treated in tetrahydrofuran with tetra-*n*-butylammonium fluoride at 0° for 2 hr. Separation of 2′-fluoro compound (IIc) was performed by column chromatography on silica gel in a yield of 60%. Deprotection with 80% AcOH of IIc gave 2′-fluoro-2′-deoxyadenosine (IIc), mp 232—234°, in a yield of 37°. Elemental analysis and UV absorption properties supported the structure of IIIc to be correct. In ^{1}H-NMR the compound IIIc revealed signals of H-2′ at δ 5.72 and 5.14 after D_2O exchange of OH due to coupling with fluorine atom. Furthermore, H-1′ also coupled with fluorine to give $J_{1'\text{H}-\text{F}}$ equal to 16 Hz, usual H–H coupling constants $J_{1'-2'}$ and $J_{2'-3'}$ (after D_2O exchange) being 3.5 and 4.5 Hz, respectively. H-3′ is also coupled with fluorine to give $J_{\text{H}3'-\text{F}}$ equal to 17 Hz. These facts clearly showed that a fluorine atom was introduced to 2′-position. ^{13}C–NMR of the compound IIIc showed a very large low-field shift of C-2′ signal (26.74 ppm from dioxane). The coupling constants $J_{\text{C}2'-\text{F}}$ were as large as 187.8 Hz and even $J_{\text{C}1'-\text{F}}$ and $J_{\text{C}3'-\text{F}}$ were 34 and 16 Hz, respectively. These facts also supported the introduction of a fluorine atom at 2′-carbon. Finally, the compound Ib was heated with tetra-*n*-butylammonium iodide in DMF at 100° for 2 hr. 3′,5′-Di-O-tetrahydropyranyl-2′-iodo-2′-deoxyadenosine (IIb) was obtained as a glass, which was deprotected by heating in 80% acetic acid at 30° for 30 hr. By this procedure, 2′-iodo-2′-deoxyadenosine (IIId) was obtained in a yield of 25% as crystals having mp 202—203°. UV absorption properties and elemental analysis showed the structure of IIId to be correct. In ^{1}H-NMR spectrum (see Table I) H-2′ appeared at δ 5.44 and coupling constants and $J_{\text{H}2'-\text{H}3'}$ were 8.5 and 4.5 Hz, respectively. The configuration of these halogen atoms in α-position could also be predicted by S_N2 type mechanism for replacement at the 2′-carbon as shown in the case of azido compounds.[5]

2′-Chloro-, 2′-bromo- and 2′-fluoro adenosine were derivatized to 5′-diphosphates and polymerized to give poly(2-chloro-,[15] poly(2-bromo-[15] and poly(2-fluoro-2-deoxyadenylic acid)[16] and their properties have been investigated.



I II III

(Thp : tetrahydropyranyl)

Chart 1

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Experimental

General Methods——UV absorption spectra were taken with Hitachi 200-10 spectrophotometer. ^{1}H-NMR spectra were recorded on a Hitachi R-22 spectrometer (90 MHz, ambient probe temperature 34°). Chemical shifts were measured from an external TMS capillary. ^{13}C-NMR spectra were recorded on a Hitachi R-22-CFT (22.63 MHz, ambient prove temperature 32—35°). Spectrometer operation in the transform mode in connection with a Hitachi HITAC 1011 computer obtained from noise-decoupled spectra measured in DMSO-d_6 with dioxane (0.5%, v/v) as internal reference for 0.2 M solution, the precision is 0.05 ppm. Paper chromatography was performed on Toyo filter paper No. 51A in descending technique. Solvent used were: A, *n*-BuOH–H$_2$O (84: 16); B, iso-PrOH–conc. NH$_4$OH–H$_2$O (7: 1: 2), C, *n*-BuOH–AcOH: H$_2$O (%: 2: 3). TLC was performed on silica gel G.

8-2′-O-Trifluoromethanesulfonyl-3′,5′-di-O-tetrahydropyranyl-D-arabinofuranosyladenine (Ib)——3′,5′-Di-O-tetrahydropyranyl-arabinofuranosyladenine (3′,5′-di-O-Thp-araA)[4,5] (2 g, 4.6 mmol) was dissolved in tetrahydrofuran (THF) (55 ml) and cooled to 0°. NaH (360 mg, containing 50% mineral oil, 1.6 equiv.) was added with stirring. The solution was kept at 0° for 1 hr until evolution of H$_2$ ceased and then cooled to -5——-60° with dry ice-ethanol bath. Trifluoromethanesulfonyl chloride (0.92 ml, 2 equiv.) was added and the mixture was kept at the same temperature range for 1 hr. The reaction mixture was poured in 2% NaHCO$_3$ aq. (500 ml) and precipitates were collected by filtration. The precipitates was dried over P$_2$O$_5$ at 80° for 10 hr *in vacuo* to give 1.54 g (2.72 mmol, 59%) of Ib. mp was 145—149°. *Anal.* Calcd. for $C_{21}H_{28}F_3N_5O_8S$: C, 44.43; H, 4.98; N, 12.34. Found: C, 44.57; H, 5.05; N, 12.37. UV: $\lambda_{max}^{95\%\,EtOH}$ 258.5 nm, $\lambda_{max}^{pH\,2}$ 257.5 nm, $\lambda_{max}^{pH\,12}$ 258.5 nm.

2′-Chloro-2′-deoxy-3′,5′-di-O-tetrahydropyranyladenosine (IIa)——i) 2′-O-Mesyl-3′,5′-di-O-Thp-araA[5] (Ia) (450 mg, 0.88 mmol) was dissolved in DMF (50 ml). Lithium chloride (383 mg, 8.8 mmol) was added to the solution and heated at 150° for 2 hr. The solvent was evaporated *in vacuo* and the residue was extracted with CHCl$_3$–H$_2$O. The CHCl$_3$-layer was concentrated *in vacuo*. The residue was applied to a preparative TLC plate and developed in CHCl$_3$–EtOH (10: 1). A band migrating at *Rf* 0.31 was extracted with CHCl$_3$–EtOH (2: 1). CHCl$_3$–EtOH was evaporated and IIa was obtained as a hard glass (124.7 mg, 0.28 mmol, 31%).

ii) 2′-O-Trifluoromesyl-3′,5′-di-O-Thp-araA (Ib) (1.7 g, 3 mmol) was dissolved in DMF (100 ml), tetraethylammonium chloride (1.5 g, 3 equiv.) was added, and heated at 80° for 3 hr. The solvent was evaporated *in vacuo* and the residue was taken up in CHCl$_3$. Insoluble material was filtered off. The CHCl$_3$ solution was dried over Na$_2$SO$_4$ and concentrated. The solution was applied to a column of Silica gel G (70 g) and eluted in a CHCl$_3$–EtOH (3: 1). The compound IIa was obtained as a hard glass in a yield of 768 mg (1.73 mmol, 57.5%). This material was used for the deprotection reaction without further precipitation.

2′-Chloro-2′-deoxyadenosine (IVa)——Di-O-Thp-2′-chloro compound (IIa) (768 mg, 1.73 mmol) was dissolved in 80% AcOH (20 ml) and kept at room temperature overnight. The solvent was evaporated *in vacuo* and traces of AcOH were codistilled several times with added H$_2$O. The residue was dissolved in H$_2$O and washed twice with CHCl$_3$. H$_2$O was distilled off and the residue was recrystallized from H$_2$O. The compound IIIa was obtained in a yield of 195 mg (0.69 mmol, 40%). mp was 221—222°. *Anal.* Calcd. for $C_{10}H_{12}ClN_5O_3$: C, 42.03; H, 4.24; N, 24.52. Found: C, 41.78; H, 4.24; N, 24.30. UV: $\lambda_{max}^{H_2O}$ 259.1 nm (ε 14400), $\lambda_{max}^{pH\,2}$ 256.5 (ε 14700), $\lambda_{max}^{pH\,12}$ 259.5 nm (ε 15000). PPC: *Rf* (A), 0.62; *Rf* (B), 0.72; *Rf* (C), 0.68. TLC (CHCl$_3$–EtOH, 5: 1); *Rf* 0.36.

2′-Bromo-2′-deoxy-3′,5′-tetrahydropyranyladenosine (IIb)——2′-Trifluoromesyl-3′,5′-Thp-araA (Ib) (300 mg, 0.53 mmol) was dissolved in DMF (15 ml) and tetra-*n*-butylammonium bromide (512 mg, 1.59 mmol) was added. The mixture was heated at 120° for 3 hr. The solvent was evaporated *in vacuo*, the residue dissolved in CHCl$_3$ and the insoluble material was filtered off. CHCl$_3$ was evaporated to some extent and the solution was applied to a preparative TLC plate. The plate was developed with CHCl$_3$–EtOH (20: 1) 2 times. A band migrating at *Rf* 0.54 (starting material *Rf* 0.68) was extracted with CHCl$_3$–EtOH to give 168 mg (0.34 mmol, 58%) of the compound IIIb as a hard glass. This material was rendered to deprotection without further purification.

2′-Bromo-2′-deoxyadenosine (IIIb)——The compound IIIb (159 mg, 0.32 mmol) obtained as above was dissolved in 80% AcOH (5 ml) and heated at 50% for 3 hr. The solvent was evaporated *in vacuo* and traces of AcOH are removed by repeated evaporation with added H$_2$O. To the residue H$_2$O (20 ml) was added and the H$_2$O-layer was washed with CHCl$_3$ (10 ml). CHCl$_3$ was evaporated *in vacuo* to some extent and crystalline IIIb were collected by filtration. Yield was 31.3 mg (30%). mp 225—226.5°. *Anal.* Calcd. for $C_{10}H_{12}BrN_5O_3$: C, 36.38; H, 3.67; Br, 24.20, N, 21.22. Found: C, 36.45; H, 3.56; Br, 24.40; N, 21.02. UV: $\lambda_{max}^{H_2O}$ 259.5 nm (ε 15000), $\lambda_{max}^{pH\,2}$ 257 nm (ε 15200), $\lambda_{max}^{pH\,12}$ 260 nm (ε 15300). PPC: *Rf* (A), 0.63, *Rf* (B), 0.72, *Rf* (G), 0.72. TLC (CHCl$_3$–EtOH, 5: 1), *Rf* 0.36.

2′-Fluoro-2′-deoxy-3′,5′-tetrahydropyranyladenosine (IIc)——2′-Trifluoromesyl-3′,5′-Thp-araA (Ib) (1 g, 1.77 mmol) was dissolved in tetrahydrofuran (35 ml) and combined with a solution of tetra-*n*-butylammonium fluoride [8.8 mmol, 5 eq., made from (nBu)$_4$NBr (8.8 mmol) passed through Dowex 1×8 (fluoride form)] dissolved in tetrahydrofuran (5 ml) at 0°. The mixture was kept at 0° for 2 hr. The solvent was evaporated *in vacuo* the residue taken up in CHCl$_3$, and the insoluble material was filtered off. CHCl$_3$ was evaporated to some extent and the solution was applied to a column (ϕ2.75 × 13 cm) of Silica gel G. Elution with $CHCl_3$–EtOH (30: 1) gave 463.7 mg (1.06 mmol, 60%) of the compound IIc. mp 105—106°. TLC: ($CHCl_3$–EtOH, 5: 1) *Rf* 0.19. This material was used for further reaction without purification.

2′-Fluoro-2′-deoxyadenosine (IIIc)——The compound IIc (464 mg, 1.06 mmol) obtained as above was dissolved in 80% AcOH (20 ml) and the solution was kept at room temperature overnight. AcOH was evaporated *in vacuo* and traces of AcOH were codistilled several times with added H_2O. The residue was taken up in $CHCl_3$ and H_2O and the H_2O-layer was evaporated *in vacuo*. The residue was recrystallized from EtOH to give 105 mg (0.39 mmol, 37%) of 2′-fluoro-2′-deoxyadenosine, mp 232—234°. *Anal.* Calcd. for $C_{10}H_{12}FN_5O_3$: C, 44.60; H, 4.50; F, 7.06; N, 26.01. Found: C, 44.65; H, 4.66; F, 7.07; N, 25.72. UV: $^{H_2O}_{max}$ 259.5 nm (ε 14200), $\lambda^{pH\,2}_{max}$ 259 nm (ε 14400), $\lambda^{pH\,12}_{max}$ 260 nm (14100). PPC: *Rf* (A), 0.64, *Rf* (B), 0.64, *Rf* (C), 0.52. TLC: ($CHCl_3$–EtOH, 5: 1), *Rf* 0.19 (2′-chloro-2′-deoxyadenosine *Rf* 0.33).

2′-Iodo-2′-deoxyadenosine (IIId)——9-(2′-O-Trifluoromethyl-3′,5′-di-O-Thp-araA) (IIb) (850 mg, 1.5 mmol) was heated with $(nBu)_4$-N·I (2.6 g, 7 mmol) in DMF (50 ml) at 100° for 2 hr with exclusion of moisture. The solvent was evaporated *in vacuo*, the residue taken up in $CHCl_3$ and insoluble material was filtered off. $CHCl_3$ was evaporated *in vacuo* to give a glass, which contain a trace ammount of contaminat (probably tributylammonium iodide). The glass was dissolved in 80% AcOH (10 ml) and kept at 30° for 30 hr. The solvent was evaporated and the residue was crystallized from MeOH to give 114 mg (0.37 mmol, 25% from Ib) of the compound IIId. This material colorized at 200° and melted at 202—203°. *Anal.* Calcd. for $C_{10}H_{12}IN_5O_3$: C, 31.84; H, 3.21; I, 33.65; N, 18.57. Found: C, 31.96; H, 3.00; I, 33.50; N, 18.63. UV: $\lambda^{H_2O}_{max}$ 259 nm (ε 14100), $\lambda^{pH\,2}_{max}$ 256.5 nm (ε 14200), $\lambda^{pH\,12}_{max}$ 259 nm (ε 14600). Paper chromatography: *Rf* (A) 0.64, *Rf* (B) 0.73, *Rf* (C) 0.36. TLC ($CHCl_3$–EtOH, 5: 1) *Rf* 0.36.

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