BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 3922—3924 (1970)

The Preparation of Halo-nucleosides

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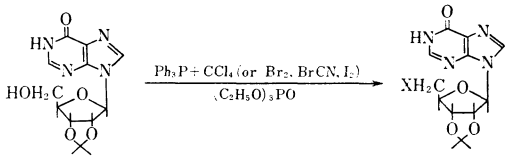
(Received April 6, 1970)

Attempts at the synthesis of halo-nucleosides have been made by the reaction of *p*-toluenesulfonyl nucleosides with an alkali-metal halide.[1,2] The present authors have also reported that 5′-chloro-5′-deoxy-2′,3′-*O*-isopropylidene nucleosides can be prepared *via* 5′-dichlorophosphoryl derivatives by the direct treatment of 2′,3′-*O*-isopropylidene nucleosides with phosphoryl chloride.[3] Recently, it has been reported that the reaction of suitably-protected nucleosides with methyltriphenoxy-phosphonium iodide affords iodo-nucleosides.[4,5] On the other hand, the conversion of some alcohols into chlorides with triphenylphosphine and carbon tetrachloride has been investigated.[6]

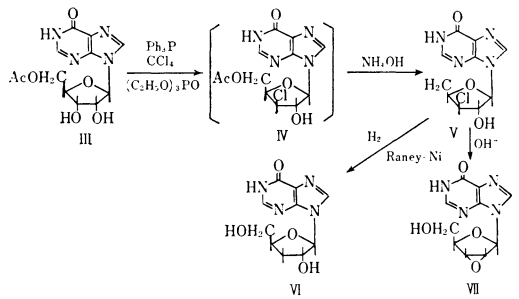
We have studied the preparation of a halo-nucleoside with triphenylphosphine and a suitable halogen source, such as carbon tetrachloride, bromine, cyanogen bromide, or iodine. For example, when 2′,3′-*O*-isopropylideneinosine(I) was treated in triethyl phosphate with three equiv. of triphenylphosphine in an excessive amount of carbon tetrachloride while being heated, 5′-chloro-5′-deoxy-2′,3′-*O*-isopropylideneinosine (IIa) was formed in a quantitative yield. The other halogen derivatives (IIb and IIc) were obtained in good yields by treatment with bromine, cyanogen bromide, or iodine and an equimolar amount of triphenylphosphine. The reactivity was extremely dependent on the kind of halogen source; the reaction with cyanogen bromide proceeded very rapidly at room temperature, while that with iodine required large excess of the reagent and an elevated reaction temperature. When dimethylformamide was used as a solvent in place of triethyl phosphate, the reactions did not proceed.



I II

a : X=Cl
b : X=Br
c : X=I

When 5′-*O*-acetylinosine(III) was treated similarly with triphenylphosphine and carbon tetrachloride, only the 3′-chloro derivative(IV) was obtained. The lack of the formation of the 2′-isomer may be due to the steric hindrance of the neighbouring purine base, which does not allow a rear-side attack by bulky phosphonium chloride at the *C*-2′ position. The hydrolysis of the reaction product with methanolic ammonium hydroxide afforded 3′-chloro-3′-deoxy-*β*-D-xylofuranosyl-hypoxanthine (V), together with a small amount of 2′,3′-anhydro-*β*-D-ribofuranosylhypoxanthine (VII).



III IV V VI VII

The NMR spectrum of V indicates that the substitution may have occurred at the *C*-3′ atom. The signals of the 2′-, 3′-, and 4′-protons shifted considerably downfields with respect to those of inosine (Table 1), while the chemical shift of the 1′-proton remained almost constant. Additional proof for the 3′-substitution was obtained from the fact that V afforded the 3′-deoxy compound (VI), the structure of which was characterized by the NMR spectrum (Table 1), on catalytic hydrogenation with Raney-nickel. The substituted chlorine atom was established to have the *β* configuration and so to be easily convertible to the epoxy compound (VII) under the basic conditions.[7] The structure of VII was proved to be that of the 2′,3′-anhydro compound of ribofuranosylhypo-

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Table 1. Chemical shifts and coupling constants[g)]

Proton	Inosine(I)[2)] (multiplicity[d)], J_{Hz})	3′-Chloro deriv. (VI)[a)]	3′-Deoxy inosine (VII)[b)]	2′,3′-Anhydro deriv. (VIII)[c)]
1′	5.92[e)] (d; 5.6)	5.89 (d; 3.7)	5.87 (d; 2.0)	6.28 (s)
2′	4.52 (d, d, d; 4.4, 4.4, 6.0)	4.74 (d, d; 3.7, 3.7)	4.2—4.6 (m)	4.65 (d; 2.4)
3′	4.18 (d, d, d; 3.6, 4.4, 5.0)	—4.5 (not resolved)	—2.0 (m)	4.42 (d; 2.4)
4′	3.99 (d, t; 3.6, 3.7)		4.2—4.6 (m)	4.49 (t; 5.4)
5′	3.65 (m)[f)]	3.75 (d; 4.5)	3.61 (m)	3.71 (d; 5.4)
2′-OH	5.47 (d; 6.0)	5.0 (broad)	5.65 (d; 4.0)	—
3′-OH	5.18 (d; 5.0)	—	—	—
5′-OH	5.07 (t; 5.3)	5.0 (broad)	5.00 (t; 5.4)	—

a) DMSO-d_6-$CDCl_3$, 100 MHz.
b) DMSO-d_6, 100 MHz.
c) D_2O, 60 MHz.
d) d, t indicates doublet of triplets and so on.
e) Chemical shifts are shown from internal TMS and DSS (D_2O solution).
f) This signal is appeared as AB part of ABX system on 5′-OH decoupling; $J_{5'a5'b}=12.0$, $J_{4'a5'b}=4.0$ Hz.
g) All parameters were obtained by the first order approximation. The assignments were established on the basis of the decoupling experiments.

xanthine (inosine) by the disappearance of $J_{1',2'}$ and $J_{3',4'}$.

Experimental

5′-Chloro-2′,3′-*O*-isopropylideneinosine (IIa). Triphenylphosphine (7.86 g, 0.03 mol) in carbon tetrachloride (80 m*l*) was added to a solution of 2′,3′-*O*-isopropylideneinosine (3.08 g, 0.01 mol) in anhydrous triethyl phosphate (40 m*l*). The mixture was heated at 100°C with stirring for 5 min. After cooling, the reaction mixture was poured into carbon tetrachloride (100 m*l*). A precipitate was collected on a filter, washed with cold water until the filtrate became neutral, and dissolved in chloroform (20—30 m*l*). After the solution had stood for about 30 min, the resulting precipitate was separated and recrystallized from methanol to give 2.8 g (85.8%) of IIa as colorless needles. Their IR spectrum and the melting point of the crystals were identical with those of the authentic sample.

5′-Bromo-5′-deoxy-2′,3′-*O*-isopropylideneinosine (IIb). *Method I.* To a solution of triphenylphosphine (7.8 g, 0.03 mol) in anhydrous triethyl phosphate (40m *l*), 2′,3′-*O*-isopropylideneinosine (3.08g, 0.01 mol) was added. Bromine was then added until the excessive addition of two drops gave the solution with an orange tint. The mixture was then heated at 80°C for 15 min. After cooling, the reaction mixture was poured into carbon tetrachloride (100 m*l*), and the resulting precipitate was collected on a filter. The precipitate was washed with cold water until the washings became neutral, and then with ethanol; then it was recrystallized from methanol to give 1.8 g (48.8%) of IIb, as colorless needles; mp 194°C (dec).

Found: C, 42.36; H, 4.19; N, 14.91; Br, 21.28%. Calcd for $C_{13}H_{15}N_3O_4Br$: C, 42.06; H, 4.07; N, 15.09; Br, 21.53%.

Method II. Cyanogen bromide (3.18 g, 0.03 mol) was used instead of bromine. The reaction proceeded exothermally. After the reaction mixture had been allowed to stand for about 5 min without heating, the solution was worked up in the manner described above (Method I) to give 2.2 g (59.6%) of IIb.

5′-Iodo-5′-deoxy-2′,3′-*O*-isopropylideneinosine (IIc). In a way similar to that used in the case of the 5′-chloro derivative (IIa), 2′,3′-*O*-isopropylideneinosine (3.08 g, 0.01 mol) in anhydrous triethyl phosphate (40 m*l*) was treated with triphenylphosphine (26.23 g) and iodine (25.38 g) for 30 min. After cooling, the solution was poured into ether (200 m*l*). The ether-insoluble materials were dissolved in chloroform (50 m*l*), and the solution was washed repeatedly with cold water until the washings became neutral. The chloroform layer was evaporated to dryness under reduced pressure at 40°C. The dark-reddish residue was redissolved in methanol (10 m*l*) and chromatographed on a column of neutral alumina in benzene. After the column had then been eluted successively with benzene and ether, 10% methanol-ether was passed through the column to elute IIc, the methanolic eluate was evaporated to dryness under reduced pressure, and the residue was crystallized from methanol to give 2.5 g (59.8%) of IIc as colorless plates; mp 195°C. (dec.).

Found: C, 37.38; H, 3.75; N, 13.15%. Calcd for $C_{13}H_{15}N_4O_4I$: C, 37.34; H, 3.62; N, 13.40%.

3′-Chloro-3′-deoxy-β-D-xylofuranosylhypoxanthine (V). To a solution of triphenylphosphine

(23.5 g, 0.09 mol) and carbon tetrachloride (66 m*l*) in triethyl phosphate (160 m*l*) was added 5′-*O*-acetylinosine (9.33 g, 0.03 mol). The mixture was refluxed at 110°C with stirring for 6 hr. After cooling, the solution was poured into ether (1 *l*). The ether-insoluble materials were dissolved in chloroform (300 m*l*), and the solution was extracted five times with an equivolume of cold water. The extractions were collected and evaporated to dryness under reduced pressure at 40°C. The residue was treated with 25 m*l* of concentrated ammonium hydroxide in 100 m*l* of methanol for 4 hr with ice-cooling and stirring. The solution was then evaporated under reduced pressure at 30°C, and the residue was dissolved in water (100 m*l*). A water-insoluble material was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The dark-reddish residue was dissolved again in methanol (30 m*l*) and chromatographed similarly as in the case of the 5′-iodo derivative (IIc); 1.6 g (18.7%) of V was then obtained by recrystallization from aqueous methanol; colorless needles; mp 220°C (dec.).

Found: C, 41.88; H, 4.09; N, 19.77; Cl, 12.24%. Calcd for $C_{10}H_{11}N_4O_4Cl$: C, 41.90; H, 3.87; N, 19.55; Cl, 12.37%.

3′-Deoxyinosine (VI). To a solution of V (1.51 g, 0.006 mol) in a mixture of triethylamine (2.52 m*l*, 0.006 mol) and aqueous 50% methanol (120 m*l*) was added Raney-nickel; hydrogen was then allowed to pass through the suspension with shaking under atmospheric pressure at room temperature for 8 hr. The catalyst was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was washed with ethanol, and subsequently recrystallized from ethanol-water (8 : 1) to give 0.79 g (59.9%) of VI; colorless needles; mp 200°C.

Found: C, 47.38; H, 4.85; N, 22.02%. Calcd for $C_{10}H_{12}O_4N_4$: C, 47.62; H, 4.80; N, 22.22%.

2′,3′-Anhydro-β-D-ribofuranosylhypoxanthine (VII). The compound V (1 g) was dissolved in concentrated ammonium hydroxide and the solution was kept at room temperature for a week. The solvent was then removed under reduced pressure, and the residue was crystallized from water to give 0.6 g (68.9%) of VII; columns; mp 210°C (dec).

Found: C, 47.93; H, 4.31; N, 22.26%. Calcd for $C_{10}H_{10}O_4N_4$: C, 48.00; H, 4.03; N, 22.39%.

The authors wish to thank Mr. Masatsune Kainosho for his measurement of the NMR spectra and for his valuable discussions.