**Trimethyl Ether of Natural η-Pyrromycinone**——A mixture of 20 mg. of natural η-pyrromycinone, 5 g. of anhyd. $K_2CO_3$, 20 g. of MeI and 20 ml. of acetone was refluxed for 11.5 hr. After removing the solvent, the residual mass was extracted with $CHCl_3$ (30 ml. × 3). The $CHCl_3$ extract was filtered and evaporated. Washing the residue with a small amount of ether, followed by recrystallization from MeOH, gave 22 mg. of bright yellow needles, m.p. 235~237°. *Anal.* Calcd. for $C_{25}H_{22}O_7$: C, 69.11; H, 5.10. Found: C, 68.62; H, 5.12.

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## Summary

η-Pyrromycinone (I), η-pyrromycinonic acid (XIII) and η-pyrromycinone trimethyl ether (IX) were synthesized by a series of reactions shown in Chart 1. The syntheses provide unequivocal confirmations for their structures.

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## 105. Takuzo Nishimura and Bunji Shimizu: Studies on Synthetic Nucleosides. V.*1 Anomeric Pyrimidine Nucleosides of D-Arabinose and D-Lyxose.

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Previous papers of this series[1] have described the facile synthesis of glucose and ribose nucleosides by the fusion of acyl halogeno sugars with trimethylsilylated pyrimidines or purines followed by removal of the protecting groups. In addition, it has been shown that the method introduced gave not only β- but α-nucleosides having 1′,2′-*cis* configuration. Such type of compounds have scarcely been prepared[2] and are of interest in biological studies.

The "silyl method" has now been applied to the synthesis of anomeric pyrimidine nucleosides of arabinose and lyxose which have opposite hydroxyl configuration to ribose or glucose at 2′-carbon atom. The spectral and chromatographic properties and the determinations of the structures of the nucleosides prepared are reported. Methyl 2,3,5-tri-O-benzoyl-α-D-arabinofuranoside, which was prepared according to the procedure of Wright and Khorana,[3] was converted to 2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl bromide (III) in good yield. Bis(trimethylsilyl)uracil (I)[1] and III were condensed by heating together at 190° for 40 minutes. After treatment of the reaction mixture with aqueous ethanol, the product was chromatographed on silica gel and the required tribenzoylarabinofuranosyluracil was obtained in 50% yield. Trituration of the tribenzoate with ethanol yielded fine needles (IVb). Tribenzoate was debezoylated

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*1 Part IV: This Bulletin, **12**, 1471 (1964).

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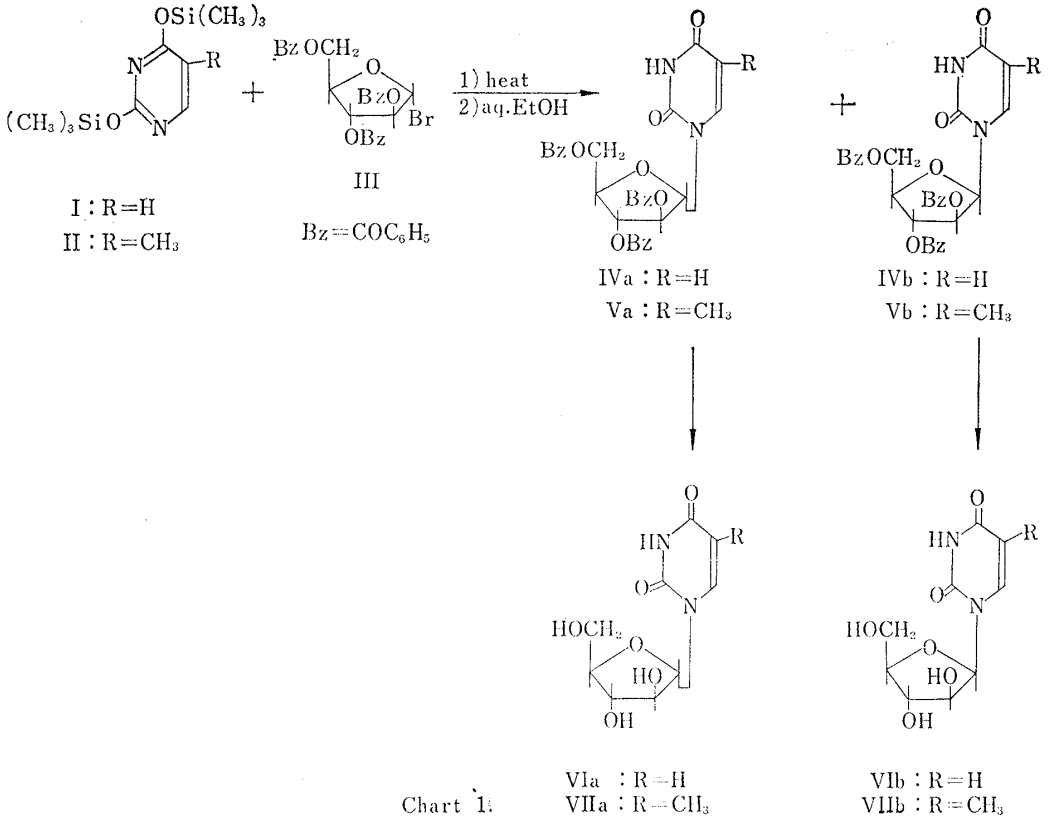
1) Part I, II. T. Nishimura, I. Iwai: This Bulletin, **12**, 352, 357 (1964). Part III. T. Nishimura, B. Shimizu: Agr. Biol. Chem., **28**, 224 (1964). Part IV. T. Nishimura, B. Shimizu, I. Iwai: This Bulletin, **12**, 1471 (1964).

2) R. S. Wright, G. M. Tener, H. G. Khorana: J. Am. Chem. Soc., **80**, 2004 (1958).

3) R. S. Wright, H. G. Khorana: *Ibid.*, **80**, 1994 (1958).




I : R=H
II : R=$CH_3$

III

Bz=$COC_6H_5$

IVa : R=H
Va : R=$CH_3$

IVb : R=H
Vb : R=$CH_3$

VIa : R=H
VIIa : R=$CH_3$

VIb : R=H
VIIb : R=$CH_3$

Chart 1.

with sodium methoxide in boiling methanol affording 1-$\beta$-D-arabinofuranosyluracil in 90% yield (VIb). The melting point, optical rotation and ultraviolet absorption characteristics of the product were identical with those of the nucleoside (spongouridine) isolated from Carribean sponges by Bergmann, *et al.*[4] or prepared by acid hydrolysis of $O^2$ : 2′-cyclouridine.[5]

After the separation of IVb, the mother liquor was evaporated and the residue was debenzoylated with sodium methoxide by the usual manner to yield a very hygroscopic product (VIa), which appeared homogeneous on paper chromatogram, but showed a small contamination with VIb in nuclear magnetic resonance spectra (Table I). The structure of VIa was assigned by the following verifications. The ultraviolet absorption characteristics in various pHs were identical with those of the spongouridine.[4] The compound (VIa) slowly consumed one mole of metaperiodate per mole and the specific rotations of the dialdehydes produced by periodate oxidation of VIa and $\alpha$-uridine (in Part IV) were similar (Table III).

From these results, the structure of the amorphous product (VIa) was assumed to be 1-$\alpha$-D-arabinofuranosyluracil. The relative ratio of VIa and VIb was estimated to be 1.0~1.5:1.0 by nucler magnetic resonance measurement.

The final confirmation of VIa was effected by comparison with the authentic sample prepared from chloromercury-4-ethoxy-2(1*H*)-pyrimidinone (VIII) and III by a modification of the method of Fox, *et al.*,[6] in which the nucleosides having 1′,2′-*trans* configuration have predominantly been obtained. Condensation of VIII with III in boiling xylene gave two major products which were separated by column chromatography on silica gel to give 2-(tri-O-benzoyl-D-arabinofuranosyl)oxy-4-ethoxypyrimidine (IX) in the first eluate

4) W. Bergmann, D.C. Burke : J. Org. Chem., **20**, 1501 (1955); Angew. Chem., **67**, 127 (1955).
5) D.M. Brown, A.R. Todd, S. Varadarajan : J. Chem. Soc., **1956**, 2388.
6) J.J. Fox, N. Yung, I. Wempen, I.L. Doerr : *Ibid.*, **79**, 5060 (1957).

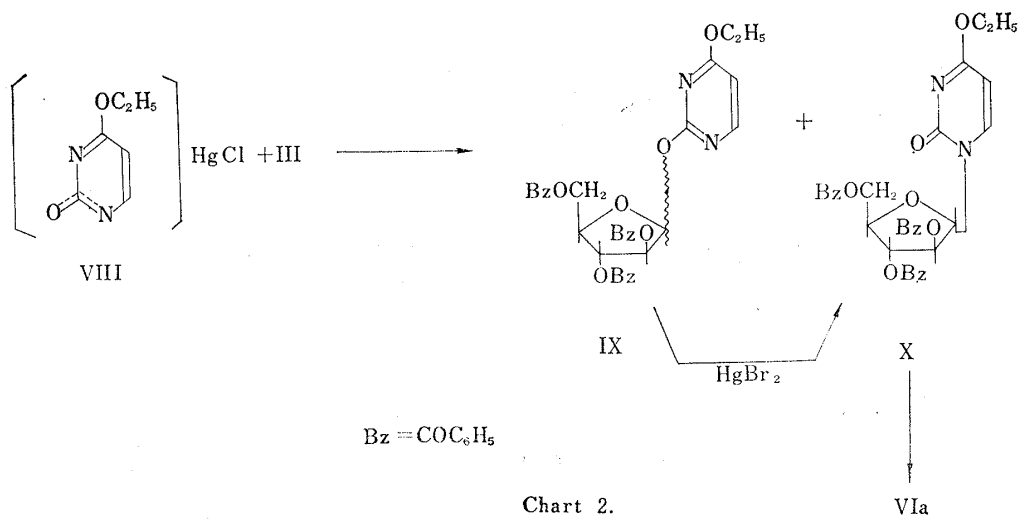



Chart 2.

and 1-(2,3,5-tri-O-benzoyl-$\alpha$-D-arabinofuranosyl)-4-ethoxy-2(1*H*)-pyrimidinone (X) in the second. Treatment of X with methanolic sodium methoxide simultaneously liberated the masking groups of the sugar moiety and the pyrimidine ring to afford 1-$\alpha$-D-arabinofuranosyluracil. By paper chromatography and nuclear magnetic resonance, the product was shown to be identical with the product (VIa) prepared by the silyl method. The benzoylated O-glycoside (IX) was converted into X in 40% yield by refluxing with mercuric bromide in xylene solution.[7]

Recently, Farkaš, *et al.*[8] have reported that the optical rotatory relationship of anomeric pyrimidine nucleosides did not obey the Hudson's Isorotation rules and $\alpha$-anomers were more leavorotatory than $\beta$-anomers In the case of arabinofuranosyluracil, a similar result was observed (Table I). This supports our configurational assingment of VIa and VIb.

Arabinofuranosylthymines were also prepared. Condensation of bis(trimethylsilyl)-thymine (II)[1] with III gave the benzoylated arabinofuranosylthymine in 42% yield, from which benzoyl groups were removed by the usual manner. The resulting product was proved to be a mixture of two components by paper chromatography and nuclear magnetic resonance analysis. By treatment of the mixture with ethanol, a crystalline product was obtained and recrystallized twice from aqueous ethanol to give pure VIIb. The physical properties of VIIb were found to be in good agreement with those of spongothymidine isolated by Bergmann, *et al.*[4] or prepared by the epimerization of 2′-hydroxy groups of $\beta$-D-ribofuranosylthymine through $O^2$ : 2′-cyclo derivatives.[9]

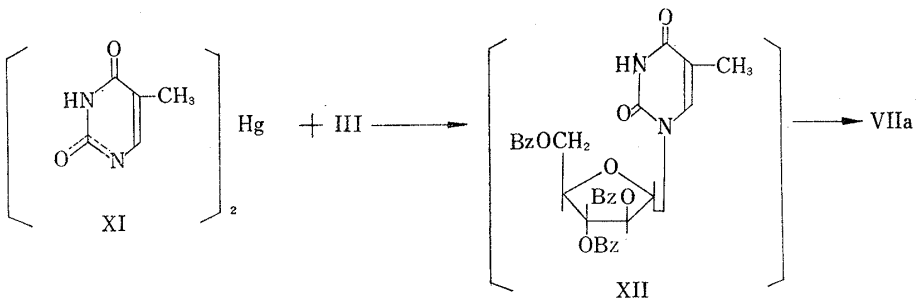
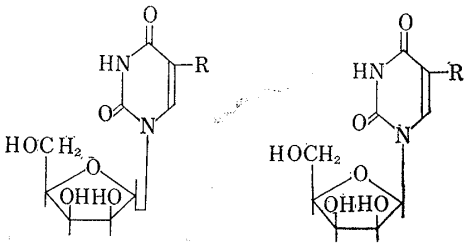



Chart 3.

7) T. Ukita, H. Hayatsu, Y. Tomita : This Bulletin, **11**, 1068 (1963).
8) J. Farkaš, L. Kaplan, J. J. Fox : J. Org. Chem., **29**, 1469 (1964).
9) J. J. Fox, N. Yung, A. Bendich : J. Am. Chem. Soc., **79**, 2775 (1957).



XIIIa : R=H
XIVa : R=$CH_3$

XIIIb : R=H
XIVb : R=$CH_3$

Chart 4.

On the other hand, after removal of Ⅶb by filtration, the filtrate was evaporated to dryness to yield a very hygroscopic product (Ⅶa). As shown in Table Ⅲ, Ⅶa consumes one mole of metaperiodate per mole and the similar optical rotation are obtained by periodate oxidation of Ⅶa and $\alpha$-ribofuranosylthymine (in Part Ⅳ). Furthermore, ultraviolet absorption maxima of Ⅶa in various pHs are nearly identical with those reported for spongothymidine.[10] The nucleoside is therefore described as 1-$\alpha$-D-arabinofuranosylthymine. Finally, the product (Ⅶa) is identified with the sample prepared from dithyminylmercury (Ⅺ) and Ⅲ by a modification of the method of Fox, *et al.*[11]

The configurational assignment of ribofuranosyl nucleosides by use of nuclear magnetic resonance spectra is generally difficult[1,12] since no significant difference between $J_{1',2'}$ of $\alpha$- and $\beta$-ribofuranosyl nucleosides has been observed. In case of the anomeric arabinofuranosyl nucleosides, the coupling constants between C-1′ and C-2′ protons were similar ($\alpha$-anomers : 4.0～5.0, $\beta$-anomers : 5.0～5.5 c.p.s.) and of no use to determine the configuration of the glycosidic linkage. However, the signals of C-1′ protons of 1′,2′-*cis* nucleosides appeared in lower field than those of 1′,2′-*trans* anomers. The same observation was obtained in anomeric lyxofuranosylpyrimidines (*vide infra*) and ribofuranosylpyrimidine (in Part Ⅳ). It is unobvious whether this fact is caused by difference of shielding effect or anisotropy between the anomers. By nuclear magnetic resonance, the independent determination of configuration of a nucleoside involving pentofuranose as a sugar moiety is still difficult, but it would be possible to distinguish the anomeric nucleosides by comparison of the chemical shift of their C-1′ protons. The results thus obtained are listed in Table I, Ⅱ. Furthermore, lyxofuranosyluracil and -thymine were also synthesized by the same procedures

Table I. Physical Properties of the Anomeric Arabinofuranosylpyrimidines

| Compound \ Method / Configuration | | Mercury method | Silyl method | |
|---|---|---|---|---|
| | | $\alpha$ | $\alpha$ | $\beta$ |
| 1-D-Arabinofuranosyluracil | m.p.[a] | —— | —— | 225～227.5° |
| | $[\alpha]_D$ | +22.4° ($H_2O$) | +34.0° ($H_2O$) | +126° ($H_2O$) |
| | UV $\lambda_{max}^{pH\,7.0}$ | 263 | 263 | 263 |
| | C.S.[b] ($J_{1',2'}$) | −127 (4.0) | −127 (4.0) | −145 (5.0) |
| | Rf[c] | 0.22 | 0.23 | 0.28 |
| 1-D-Arabinofuranosylthymine | m.p.[a] | —— | —— | 246～248° |
| | $[\alpha]_D$ | +40.0° ($H_2O$), +75.5° (pyridine) | +39.0° ($H_2O$), +81.0° (pyridine) | +98.0° ($H_2O$), +90.0° (pyridine) |
| | UV $\lambda_{max}^{pH\,7.0}$ | 268 | 268 | 269 |
| | C.S.[b] ($J_{1',2'}$) | −127 (5.0) | −127 (5.0) | −145 (5.5) |
| | Rf[c] | 0.33 | 0.33 | 0.38 |

*a*) All melting points are corrected.
*b*) Chemical shift of C-1′ proton from dioxane in c.p.s.
*c*) See experimental part.

10) J. J. Fox, D. Shugar : Biochim. Biophys. Acta, **9**, 369 (1952).
11) J. J. Fox, N. Yung, J. Davoll, G. B. Brown : J. Am. Chem. Soc., **78**, 2117 (1956).
12) C. D. Jardetzky : J. Am. Chem. Soc., **82**, 229 (1960); R. V. Lemieux, J. W. Lown : Can. J. Chem., **41**, 890 (1963).

as those for arabinofuranosylpyrimidines. The corresponding 2,3,5-tri-O-acetyllyxofuranosyl chloride whose synthetic route gave exclusively furanose derivative,[13] was coupled with I or II and then the protecting groups were removed to afford anomeric 1-D-lyxofuranosyluracils (XIIIa, XIIIb) and -thymines (XIVa, XIVb). The structures and the configuration of the products were assigned on the bases of ultraviolet and nuclear magnetic resonance spectra, the uptakes of metaperiodate and the optical rotations of the dialdehydes produced by periodate oxidation (Tables II, III). Moreover, 1-$\alpha$-D-lyxofuranosyluracil was characterized by comparison with the sample prepared by the mercury procedure. Relationships of optical rotations or chemical shifts of C-1′ protons between the anomers of lyxofuranosylpyrimidines were similar to those of the arabinose nucleosides anomers (Table II).

TABLE II. Physical Properties of the Anomeric Lyxofuranosylpyrimidines

| Compound \ Configuration | | $\alpha$ | $\beta$ |
|---|---|---|---|
| 1-D-Lyxofuranosyluracil | m.p.[a] | 203～204.5° | 200.5～202°[14] |
| | $[\alpha]_D$ | +62.5° ($H_2O$) | +107° ($H_2O$) |
| | UV $\lambda_{max}^{pH\,7.0}$ ($\varepsilon$) | 263 (11, 100) | 263 (10, 500) |
| | C. S.[b] ($J_{1',2'}$) | −130 (7.5)[d] | −144 (6.0) |
| | Rf[c] | 0.15 | 0.21 |
| 1-D-Lyxofuranosylthymine | m.p.[a] | 203～203.5° | 184～186°[15] |
| | $[\alpha]_D$ | +80.0° ($H_2O$) | —— |
| | UV $\lambda_{max}^{pH\,7.0}$ ($\varepsilon$) | 268 (10, 500) | 269 (10, 000) |
| | C. S.[b] ($J_{1',2'}$) | −131 (7.0) | −144 (6.0) |
| | Rf[c] | 0.30 | 0.39 |

*a*),*b*),*c*) See Table I.
*d*) $J_{1',2'}$ was not exactly measured because it was superimposed on the doublet of C-5 proton.

## Experimental

Paper chromatography was carried out on Toyo Roshi No. 51 paper using a solvent; butanol-water (86:14) by the descending technique. Spots were visualized under UV light.

**2,3,5-Tri-O-benzoyl-$\alpha$-D-arabinofuranosyl Bromide (III)**——Methyl 2,3,5-tri-O-benzoyl-$\alpha$-D-arabinofuranoside was converted into the bromide (III) according to the direction of Wright and Khorana.[3] The gummy product was crystallized by treatment with dry ether and recrystallized twice from ether-hexane (4:3) to give a 73% yield of 2,3,5-tri-O-benzoyl-$\alpha$-D-arabinofuranosyl bromide, m.p. 102.5～103.5° (corr.), $[\alpha]_D^{29}$ +87.9° (c=1.0, $CH_2Cl_2$).

**1-(2,3,5-Tri-O-benzoyl-$\alpha$-D-arabinofuranosyl)-4-ethoxy-2(1*H*)-pyrimidinone (X)**——Chloromercury-4-ethoxy-2(1*H*)-pyrimidinone (2.36 g.) and III (3.30 g.) were condensed in boiling xylene by the usual manner. After cooling, the precipitate was filtered off and large amounts of petr. ether added to the filtrate. The resulted precipitate was dissolved in benzene and chromatographed on a column of silica gel (60 g.). The column was developed using the following solvent systems. Fraction 1, 600 ml. of benzene; Fraction 2, 500 ml. of benzene-ethyl acetate (95:5); Fraction 3, 400 ml. of benzene-ethyl acetate (95:5) and 350 ml. of benzene-ethyl acetate (90:10).

Evaporation of Fraction 1 gave unidentified sugar fragments. From Fraction 2, a resinous product was obtained and rechromatographed on silica gel using the same solvent systems to give 1.16 g. of IX (*Anal.* Found: C, 65.88; H, 4.72; N, 4.57). Treatment of IX with mercuric bromide in boiling xylene yielded 1-(2,3,5-tri-O-benzoylarabinofuranosyl)-4-ethoxy-2(1*H*)-pyrimidinone in 40% yield. Melting point of this product was not depressed by admixture with the sample from Fraction 3. After evaporation of Fraction 3, a resulted resin was triturated with methanol to give crystals. Recrystallization from methanol yielded 0.67 g. of pure X, m.p. 133～136° (corr.), $[\alpha]_D^{30}$ −54.5° (c=3.0, $CHCl_3$). *Anal.* Calcd. for $C_{32}H_{28}O_9N_2$: C, 65.75; H, 4.83; N, 4.79. Found: C, 65.54; H, 4.82; N, 4.74.

13) H. Zinner, H. Brandner, G. Rembarz: Chem. Ber., **89**, 800, 1507 (1956).
14) R. Fecher, J.F. Godington, J.J. Fox: J. Am. Chem. Soc., **83**, 1889 (1961).
15) J.J. Fox, J.F. Godington, N.C. Yung, L. Kaplan, J.O. Lampen: *Ibid.*, **80**, 5155 (1958).

**Anomeric 1-(2,3,5-Tri-O-benzoyl-D-arabinofuranosyl)uracils (IVa and IVb) by Silyl Method**——A mixture of 1.28 g. of bis(trimethylsilyl)uracil and 2.63 g. of III was heated at 190° for 40 min., and then the brownish gummy product was dissolved in aqueous ethanol. After evaporation of the solvent, the residue was taken in benzene and the solution filtered. To the filtrate were added large amount of petr. ether, and the resulted precipitate was collected and chromatographed on silica gel (40 g.). The column was developed using the following solvent systems: Fraction 1, 2 L. of benzene; Fraction 2, 0.5 L. of benzene-chloroform (80:20); Fraction 3, 0.5 L. of benzene-chloroform (70:30); Fraction 4, 0.5 L. of benzene-chloroform (60:40); Fraction 5, 1.5 L. of benzene-chloroform (55:45); Fraction 6, 1 L. of benzene-chloroform (50:50). Fraction 5 and 6 were collected and evaporated to yield 1.38 g. of a resin. Trituration of that resin with ethanol gave a crystalline product which was recrystallized from ethanol to afford 0.39 g of 1-(2,3,5-tri-O-benzoyl-β-D-arabinofuranosyl)uracil (IVb), m.p. 202~203° (corr.) $[\alpha]_D^{26}$ +72.0° (c=2.0, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{24}O_9N_2$: C, 64.74; H, 4.35; N, 5.03. Found: C, 64.58; H, 4.28; N, 4.92. After removal of IVb, the mother liquor was evaporated to yield 0.97 g. of crude 1-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)uracil (IVa).

**1-α-D-Arabinofuranosyluracil (VIa). From X**——To a solution of 20 mg. of sodium methoxide in 30 ml. of abs. methanol was added 400 mg. of X. The solution was refluxed for 45 min. and then evaporated to dryness. The aqueous solution of the residue was washed three times with ether and treated with small portions of Dowex-50 resin ($H^+$). The resulting solution was adsorbed on a column of Dowex-1 resin ($CO_3''$, 2.6 cm. i.d. × 14 cm.). By elution using 0.05*M* $NaHCO_3$-$Na_2CO_3$ buffer (pH 11.0), a small amount of product was obtained. From the UV absorption spectrum ($\lambda_{max}$ 273 mμ), this compound was thought to be 1-arabinofuranosyl-4-ethoxy-2(1*H*)-pyrimidinone,[16] although no further experiment for determination of its structure was carried out. Then, pH of the solvent was lowered to 10.2, and a strongly UV absorbing fraction was collected. This fraction was treated with Dowex-50 resin ($H^+$) and the aqueous eluate evaporated to dryness *in vacuo*. It yielded 115 mg. of 1-α-D-arabinofuranosyluracil, UV $\lambda_{max}^{H_2O}$ mμ (pH): 263 (3.2), 263 (7.0), 263 (9.55), 265 (14.0). $[\alpha]_D^{28}$ +22.4° (c=1.9, $H_2O$), Rf 0.22.

**From IVa**——Crude IVa (500 mg.) was treated with sodium methoxide in boiling methanol as described above. After removal of methyl benzoate and sodium ion as in the above experiment, the aqueous solution of the product was adsorbed on a column containing Dowex-1 resin ($OH^-$). After being washed well with water, the column was eluted with water saturated with carbon dioxide. The eluate which showed UV absorption was evaporated to dryness to give 207 mg. of the product (VIa) which showed a single spot on paper chromatogram (Rf 0.23). This product was identical in NMR spectra and paper chromatogram with the authentic sample prepared from X. However, that the optical rotation of the product is higher ($[\alpha]_D^{27}$ +34.0°, c=2.4, $H_2O$) than that of the sample from X shows some contamination with β-anomer. UV $\lambda_{max}^{H_2O}$ mμ (pH): 263 (3.2), 263 (7.0), 263 (9.5), 265 (14.0).

**1-β-D-Arabinofuranosyluracil (VIb)**——1-(2,3,5-Tri-O-benzoyl-β-D-arabinofuranosyl)uracil (200 mg.) was debenzoylated with sodium methoxide in refluxing methanol, and the resulted methyl benzoate and sodium ion were removed. A crude product was recrystallized from methanol to give 79 mg. of 1-β-D-arabinofuranosyluracil, m.p. 225~227.5° (corr.), $[\alpha]_D^{27}$ +126° (c=1.0, $H_2O$), Rf 0.28. UV $\lambda_{max}^{H_2O}$ mμ (ε, pH): 263 (11,100, 3.2), 263 (11,100, 7.0), 263 (9,300, 9.6), 267 (9,300, 14.0). Melting point and optical rotation showed good agreement with the reported values for the authentic sample prepared from natural source.[4] *Anal.* Calcd. for $C_9H_{12}O_6N_2$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.25; H, 4.78; N, 11.37.

**1-α-D-Arabinofuranosylthymine (VIIa) by Mercury Procedure**——Dithyminylmercury (1.42 g.) and III (3.3 g.) were condensed in boiling xylene by the procedure of Fox, *et al.* The crude tribenzoate (XII) was hydrolyzed using sodium methoxide as described for VIa (from IVa) and an amorphous product (1.08 g., VIIa) was obtained, UV $\lambda_{max}^{H_2O}$ mμ (ε, pH): 268 (9,830, 3.2), 268 (9,830, 7.0), 268 (8,570, 9.6), 270 (7,650, 14.0), $[\alpha]_D^{28}$ +40.0° (c=1.9, $H_2O$), +75.5° (c=1.6, pyridine), Rf 0.33.

**Anomeric 1-D-Arabinofuranosylthymines (VIIa and VIIb) by Silyl Method**——Bis(trimethylsilyl)-thymine (1.15 g.) and III (2.19 g.) were condensed together by the same procedure as with anomeric tribenzoylarabinofuranosyluracils. After chromatographic purification on silica gel, 1.13 g. of the mixture of Va and Vb was obtained. Hydrolysis of the above mixture (500 mg.) with sodium methoxide in methanol followed by the removal fo sodium ion with Dowex-50 resin gave 0.25 g. of an anomeric mixture of 1-D-arabinofuranosylthymine. This mixture which contained α- and β-anomer in 2.7:1.0 ratio, was triturated with ethanol to give a crude β-anomer in crystalline state. Recrystallization from aqueous ethanol yielded 40 mg. of 1-β-D-arabinofuranosylthymine (VIIb), m.p. 246~248° (corr.), $[\alpha]_D^{28}$ +90.0° (c=0.8, pyridine), +98.0° (c=0.1, $H_2O$), UV $\lambda_{max}^{H_2O}$ mμ (ε, pH): 269 (10,300, 3.2), 269 (10,300, 7.0), 269 (9,300, 9.6), 272 (9,000, 14.0), Rf 0.38. *Anal.* Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.20; H, 5.56; N, 10.76.

The mother liquor of VIIb was evaporated to dryness and the residue purified on a column containing Dowex-1 resin ($OH^-$) as described above to afford the required 1-α-D-arabinofuranosylthymine (yield 140 mg.), $[\alpha]_D^{27}$ +81.0° (c=2.6, pyridine), +39.0° (c=2.0, $H_2O$), UV $\lambda_{max}^{H_2O}$ mμ (pH): 268 (3.2), 268 (7.0), 268 (9.5),

16) D. Shugar, J. J. Fox: Biochim. Biophy. Acta, **9**, 199 (1952).

270 (14.0), Rf 0.33. Identification of the product with the sample prepared from XII was effected by paper chromatography and NMR spectrum.

**1-α-D-Lyxofuranosyluracil (XIIIa) by Mercury Procedure**——2,3,5-Tri-O-acetyl-D-lyxofuranosyl chloride and chloromercury-4-ethoxy-2(1*H*)-pyrimidinone were condensed together as described for X. By chromatography on silica gel (benzene-$CHCl_3$) the crude triacetate was obtained in 64% yield. Hydrolysis of the product (250 mg.) was effected by usual procedure. Passing the aqueous solution of the product through a column containing Dowex-1 resin gave 150 mg. of crude XIIIa. This was recrystallized from a mixture of methanol and ethanol (1:3) to give 47 mg. of 1-α-D-lyxofuranosyluracil, m.p. 203~204.5° (corr.), $[\alpha]_D^{27}$ +62.5° (c=1.0, $H_2O$), UV $\lambda_{max}^{H_2O}$ mμ (ε, pH): 263 (11,000, 3.2), 263 (11,000, 7.0), 264 (10,000, 9.6), 266 (8,800, 14.0), Rf=0.15. *Anal.* Calcd. for $C_9H_{12}O_6N_2$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.24; H, 5.12; N, 11.27.

**Anomeric 1-D-Lyxofuranosyluracils (XIIIa and XIIIb) by Silyl Method**——Tri-O-acetyl-D-lyxofuranosyl chloride (0.5 g.) was coupled with equimolar amounts of I by heating at 190°. Treatment of a condensed mixture with petr. ether and chromatography on silica gel (benzene-$CHCl_3$) yielded 0.32 g. of a resin which was deacetylated by sodium methoxide in methanol. After removal of methyl acetate by evaporation and sodium ion as described for the corresponding arabinose nucleosides, the product was dissolved in methanol and then ethanol was added. From 260 mg. of the acetate, the α-anomer (66 mg.) was obtained in crystalline form, m.p. 201~203° (corr.), $[\alpha]_D^{27}$ +62.5° (c=1.0, $H_2O$). Melting point showed no depression by admixture with the sample prepared by mercury procedure.

The mother liquor was concentrated and set aside in the cold to afford the crude β-anomer (XIIIb). Recrystallization from methanol-ethanol yielded 19 mg. of the pure XIIIb, m.p. 200.5~202° (corr.), $[\alpha]_D^{27}$ +107° (c=1.0, $H_2O$). UV $\lambda_{max}^{H_2O}$ mμ (ε, pH): 263 (10,500, 3.2), 263 (10,500, 7.0), 264 (10,300, 9.5), 266 (9,000, 14.0), Rf 0.21. Physical constants were found in good agreement with the reported ones.[14] *Anal.* Calcd. for $C_9H_{12}O_6N_2$: C, 44.26; H, 4.95; N, 11.47. Found: C, 43.99; H, 5.12; N, 11.52.

**Anomeric 1-D-Lyxofuranosylthymines (XIVa, XIVb) by Silyl Method**——Condensation of tri-O-acetyl-lyxofuranosyl chloride (0.60 g.) and II (0.51 g.) was carried out as already described. Crude 1-(tri-O-acetyl-D-lyxofuranosyl)thymine (0.30 g.) was obtained. Hydrolysis of the triacetate (0.23 g.) and purification on Dowex-1 ($OH^-$) column gave 0.118 g. of anomeric mixture of 1-D-lyxofuranosylthymine (XIVa and XIVb). The mixture was dissolved in minimum amount of hot abs. ethanol and the solution set aside at room temperature to give the crude α-anomer as colorless needles. After removal of the needles, the crude β-anomer was obtained from the filtered solution on standing in refrigerator overnight. Additional amounts of XIVa and XIVb were obtained by evaporation of the mother liquor and fractional crystallizations of the residue as mentioned above. Thus obtained anomeric lyxofuranosylthymin eswere separately recrystallized three times from abs. ethanol.

α-anomer (XIVa): Yield 50 mg., m.p. 203~204.5°, $[\alpha]_D^{27}$ +80.0° (c=1.2, $H_2O$), UV $\lambda_{max}^{H_2O}$ mμ (ε, pH): 268 (10,500, 3.2), 268 (10,500, 7.0), 269 (10,100, 9.5), 270 (8,200, 14.0), Rf 0.30. *Anal.* Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.36; H, 5.60; N, 10.85.

β-anomer (XIVb): Yield 25 mg., m.p. 184~186° (corr.), UV $\lambda_{max}^{H_2O}$ mμ (ε, pH): 269 (10,000, 3.2), 269 (10,000, 7.0), 270 (10,000, 9.5), 270.5 (8,500, 14.0), Rf 0.39. *Anal.* Found: C, 46.21; H, 5.43; N, 10.52.

**Periodate Oxidation Studies**——a) Arabinofuranosylpyrimidine (11~26 mg.) was dissolved in 20~50 ml. of 0.005*M* sodium metaperiodate. At intervals, aliquats were removed and the consumption of metaperiodate was measured by the method of Lythgoe, *et al.*[17] The consumption of metaperiodate by lyxofuranosylpyrimidine was spectrophotometrically estimated by the method of Dixon, *et al.*[18]

Table III. Periodate Oxidation

| Compound | Moles of periodate consumed (hr.) | $[\alpha]_{340}$ of the dialdehyde produced (hr.) |
|---|---|---|
| α-Uridine | | −152° (0.3) |
| VIa | 0.94 (72) | −161 (24) |
| VIIIa | 1.01 (0.25) | −160 (0.3) |
| α-Ribosylthymine | | −147 (0.5) |
| VIIa | 1.02 (72) | −136 (19) |
| XIVa | 1.12 (0.25) | −147 (0.3) |
| β-Uridine | | +50.0 (0.3) |
| XIIIb | 0.97 (0.25) | +51.0 (0.3) |
| β-Ribosylthymine | | +62.2 (0.3) |
| VIIb | | +65.0 (24) |
| XIVb | 1.12 (0.25) | +63.5 (0.5) |

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18) J. S. Dixon, D. Lipkin: Anal. Chem., **26**, 1092 (1954).

b) The nucleoside (10~25 mg.) was dissolved in 1.0 ml. of 0.2*M* sodium metaperiodate and set aside at room temperature. Final rotation at 340 mμ was measured (based on the starting material) (Table Ⅲ).

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## Summary

Anomeric arabinofuranosyl and lyxofuranosyl nucleosides are synthesized by fusion of acylhalogenosugars with trimethylsilyl derivatives of uracil and thymine followed by removal of the protecting groups. The α-anomers of the nucleosides are found to be identical with the samples prepared by the mercury procedures. Relationships of optical rotations and nuclear magnetic resonance spectra between the anomers are described.

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# 106. Hideo Nakao: Studies on Seven-membered Ring Compounds. XVIII.*1 Reactions of the Quaternary Ammonium Salts of Cycloheptimidazole Derivatives.

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As reported in the previous paper,*1 1-benzylcycloheptimidazol-2(1*H*)-one (I) was found to be an active analgesic and anti-inflammatory agent.[1] During our investigations on the better synthetic procedure of I, the quaternary ammonium salts of cycloheptimidazole derivatives have been found to show interest reactivity.

The reaction of cycloheptimidazol-2(1*H*)-one (Ⅱ) with benzyl chloride in the presence of sodium hydroxide in 50% ethanol afforded I and an orange-yellow crystalline product, $C_{21}H_{21}N_2Cl$ (A), m.p. 234° (decomp.) in about 80% and 8% yield, respectively. Treatment of A with sodium hydroxide afforded yellow crystals, $C_{21}H_{20}N_2$ (B), m.p. 84°. A was recovered on treatment of B with hydrochloric acid. Therefore, A was confirmed to be hydrochloride of B. Brasen, *et al.*[2] reported that 1-methylamino-7-methyliminocycloheptatriene showed absorption maxima at 263, 346, 360, and 418 mμ in its ultraviolet spectrum, and 1-benzylamino-7-benzyliminocycloheptatriene (Ⅲ) melted at 82°. The ultraviolet spectrum of B was similar to that of 1-methylamino-7-methyliminocycloheptatriene. Therefore, B was considered to be Ⅲ. Hydrolysis of B according to the Brasen's method[2] was unsuccessful. However, B was converted to 2-benzylaminotropone on treatment with formalin and formic acid in an attempt to prepare the methylated derivative. Likewise bromination[2] of 1-methylamino-7-methyliminocycloheptatriene, B was brominated to give a monobromo derivative, m.p. 132°, which

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