Summary

1. The penetration of water and solutes though the intestinal barrier *in vitro* was investigated with the technique described by Smyth & Taylor. Sulfisomezole concentration in the fluid transported to the serosal surface was higher than that in the mucosal solution. This phenomenon was not observed with sulfathiazole or sulfaguanidine.

2. The uphill transport of sulfisomezole was demonstrated with the technique of Wilson & Wiseman employing everted sacs.

3. In experiments with the technique of Smyth & Taylor the level of sulfathiazole or sulfaguanidine concentration in the transported fluid was maintained approximately constant through the changes of the transport rate of fluid. On the other hand the increase of sulfisomezole concentration in the transported fluid corresponded to the increase of the transport rate of fluid, although the relationship between them was not linear.

4. No particular correlation was observed between the penetration of sulfisomezole and that of sodium ion.

5. It was suggested that the uphill transport of sulfisomezole was explainable from the view-point of pH-partition hypothesis and that 2,4-dinitrophenol might decrease the penetration of sulfisomezole after disturbing the mechanism of physiological pH maintenance at the absorptive surface.

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201. Takuzo Nishimura, Bunji Shimizu, and Issei Iwai : Studies on Synthetic Nucleosides. IV.*1 A New Synthetic Method of Pyrimidine and Purine Ribosides.

(*Research Laboratories, Sankyo Co., Ltd.**2)

In previous papers of this series,*1,1) the authors have synthesized trimethylsilyl derivatives of pyrimidines and purines and introduced a new synthetic method for glucose nucleosides by fusing the silyl compounds with α-acetobromoglucose, followed by removal of protecting groups. The glycosidations, in these cases, have took place at 1- or 9-position of pyrimidine or purine bases, respectively, giving the same type of derivatives as natural nucleosides. Analogously, condensation of trimethylsilylpyrimidines (Ia~c) and -purines (Va, b) with 2,3,5-tri-O-benzoylribosyl chloride (II) in place of α-acetobromoglucose gave benzoylated ribose nucleosides in good yields, which readily furnished the corresponding nucleosides.

Ribofuranosylpyrimidines

Three methods have been previously reported for the synthesis of uridine (IVa).

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*1 Part III. T. Nishimura, B. Shimizu : Agr. Biol. Chem., 28, 224 (1964).

*2 2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo (西村卓三, 清水文治, 岩井一成).

1) Part I, II. T. Nishimura, I. Iwai : This Bulletin, **12**, 352, 357 (1964).

Howard, *et al.*[2] prepared Ⅳa by deamination of cytidine (Ⅳc) which was synthesized from acetobromoribofuranose and 2,4-diethoxypyrimidine[3] followed by treatment with methanolic ammonia. The second method reported by G. Shaw, *et al.*[4] prepared uridine by ring closure of β-ethoxy-N-ethoxycarbonylacrylamide and tri-O-benzoylribofuranosylamine and followed by debenzoylation of the cyclization product. Furthermore, a reinvestigation of heterocyclic mercury derivatives applied to synthesis of pyrimidine nucleosides was made by Fox, *et al.*[5] : 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-ethoxy-2(1*H*)-pyrimidinone, also an intermediate for synthesis of cytidine and uridine, had been obtained in good yield by condensation of chloromercury salt of 4-ethoxypyrimidine and Ⅱ.

Primidine bases were readily trimethylsilylated with hexamethyldisilazane or trimethylchlorosilane in presence of triethylamine and the above method has been extensively used by Birkofer, *et al.*[6] for preparation of heterocyclic trimethylsilyl derivatives. Thus obtained bis (trimethylsilyl) uracil (Ia) and Ⅱ were condensed by heating at 190° and subsequent removal of the remaining trimethylsilyl group by treatment with aqueous ethanol gave crystalline 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)uracil (Ⅲa) in 58% yield. Debenzoylation with sodium methoxide in boiling methanol yielded 1-β-D-ribofuranosyluracil (uridine, Ⅳa).

The new route has a great advantage in that the protecting group (trimethylsilyl) is very easily removed by treatment of reaction mixture with aqueous ethanol without catalyst.

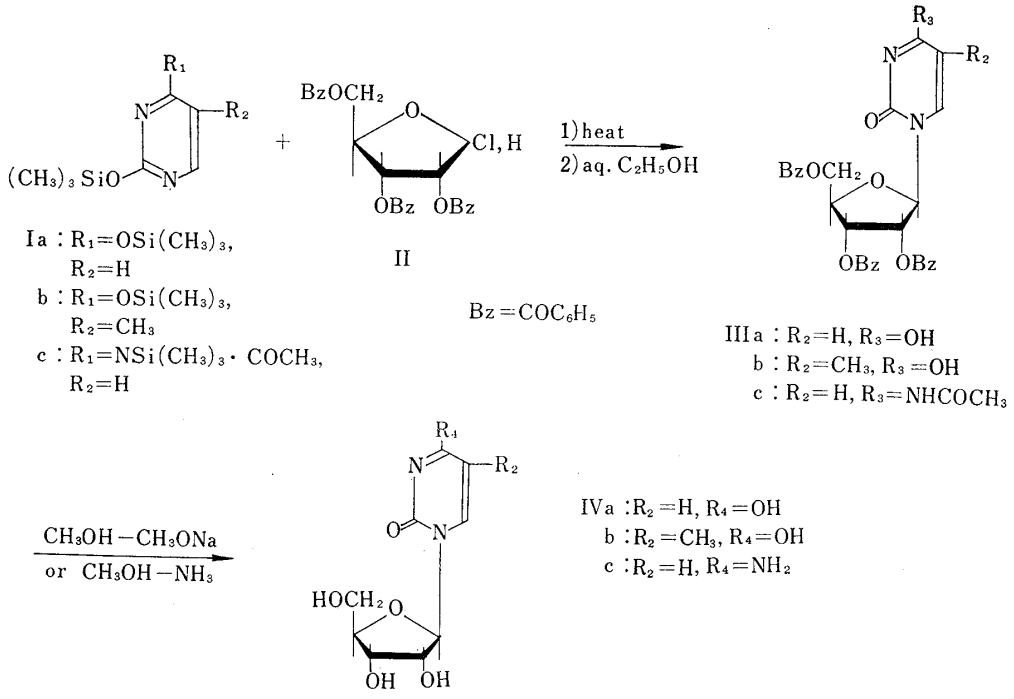


Chart 1.

In addition to tribenzoyluridine, a product (Ⅲa′) melting at 205° was obtained in 8.5% yield; the elementary analysis was identical with that of tribenzoyluridine. Debenzoylation of Ⅲa′ with sodium methoxide in refluxing methanol gave a nucleoside, which did

2) G. A. Howard, B. Lythgoe, A. R. Todd : J. Chem. Soc., **1947**, 1052.
3) G. E. Hilbert, T. B. Johnson : J. Am. Chem. Soc., **52**, 2001 (1930).
4) G. Shaw, R. N. Warrener, M. H. Maguire, R. K. Ralph : J. Chem. Soc., **1958**, 2294.
5) J. J. Fox, N. Yung, I. Wempen, I. L. Doerr : J. Am. Chem. Soc., **79**, 5060 (1957).
6) L. Birkofer, P. Richter, A. Ritter : Chem. Ber., **93**, 2804 (1960).

not reduce Fehling's solution and readily afforded a isopropylidene derivative. Its ultraviolet absorption spectra in various pH values were closely similar to those of uridine. Furthermore, it rapidly consumed one mole of sodium metaperiodate per mole without liberating formic acid. Thus it was concluded that the new nucleoside was 1-α-D-ribofuranosyluracil.

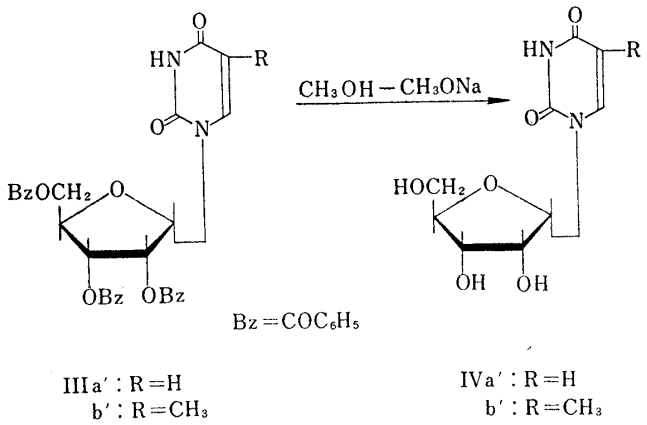


Chart 2.

Recently, Farkaš[7] stated that anomers of 1-D-ribofuranosylthymine or -5-methylcytosine[8] failed to obey Hudson's rules of Isorotation, namely the α-anomer of ribosylthymine was more laevorotatory than the β-isomer. A similar relationship was observed in the anomeric pairs of ribopyranosyl and xylopyranosylthymine.[9] In fact the optical rotation of α-uridine (−68°) was also negative while that of β-isomer was positive (+4°).

After removing IIIa and IIIa', the mother liquor was chromatographed on silica gel. Nitrogen containing fractions were collected and evaporated to dryness to give a small amount of an amorphous product, in which elementary analysis and molecular weight determination were suggestive of bis(tribenzoylribosyl)uracil. The ultraviolet absorption spectra of a debenzoylated product with methanolic ammonia were similar to those of 1,3-dimethyluracil.[10] However, the free nucleoside is very unstable, as indicated by a varying ultraviolet absorption curve of an aqueous solution kept at room temperature. No further experiments for structural assignment were made.

Thus it was shown that Ia afforded anomeric mixture of benzoylated ribofuranosyluracils by reacting with the syrupy tribenzoylribosyl chloride. But the O-riboside[11] sometimes formed by mercury procedure was not detected.

The reaction mechanism in this fusion method is not obvious but would differ from that of the mercury procedure in which one type of nucleoside has been obtained using the syrupy ribosyl chloride.[5,12]

The syntheses of ribosylthymine have been carried out by Roberts, *et al.*[8] and Fox, *et al.*[12] using the Hilbert-Johnson's and mercury procedure, respectively. However, enzymic behaviors, melting points and optical rotations of the two products differed. Subsequently, the above compounds have been confirmed to be 1-α- and 1-β-D-ribofuranosylthymine from their chemical, physical and biological properties.[7]

Bis(trimethylsilyl)thymine (Ib) was condensed with II by the same procedure as with IIIa. After treatment of a condensed mixture with aqueous ethanol, the unreacted sugar fragment was removed by treating with hexane and then the residue was debenzoylated with methanolic sodium methoxide to give 1-D-ribosylthymine in 50% yield (based on the reacted silylthymine). Fractional crystallizations from ethanol afforded 1-α- and 1-β-D-ribofuranosylthymine (IVb, IVb'), in which melting points, optical rotations and ultraviolet maxima[13] showed good agreement with values previously reported.[7,12]

7) Jiří Farkaš, L. Kaplan, J. J. Fox : J. Org. Chem., **29**, 1469 (1964). We are grateful to the authors for giving us the reprint of the paper.
8) M. Roberts, D. W. Visser : J. Am. Chem. Soc., **74**, 668 (1952).
9) T. Naito, T. Kawakami : This Bulletin, **10**, 627 (1962).
10) D. Shugar, J. J. Fox : Biochim. Biophys. Acta, **9**, 199 (1952).
11) T. Ukita, H. Hayatsu, Y. Tomita : This Bulletin, **11**, 1068 (1963).
12) J. J. Fox, N. Yung, J. Davoll, G. B. Brown : J. Am. Chem. Soc., **78**, 2117 (1956).
13) J. J. Fox, D. Shugar : Biochim. Biophys. Acta, **9**, 369 (1952).

The above configurational assignments of anomeric ribosyluracils and -thymines were confirmed by nuclear magnetic resonance analysis. Direct assignment of the configuration of ribose nucleosides can not obtain by nuclear magnetic resonance unless coupling constant is enough low.[14,15] In fact, $J_{1',2'}$ of α-isomers of ribosyluracil and -thymine were similar to those of β-isomers. Leonard, *et al.*[16] have stated that if ribofuranose ring was constrained by fusion with a second ring, $J_{1',2'}$ of β-nucleoside was reduced. The coupling constants between $H_{1'}$ and $H_{2'}$ of 2',3'-isopropylidene derivatives of Ⅳa and Ⅳb were very similar to those of 2',3'-cyclic AMP[17] and 2',3'-isopropylidene adenosine.[16] However in the case of the α-isomers synthesized above, coupling constants between $H_{1'}$ and $H_{2'}$ were unaffected by isopropylidenation (Table I).

Table I. Chemical Shifts and Coupling Constants of the Anomeric Ribofuranosyluracils and -thymines and their Isopropylidene Derivatives in D_2O

	$H_{1'}(J_{1',2'})$	$H_{2'}(J_{2',3'})$	$H_{3'}(J_{3',4'})$	$H_{4'}$	$H_{5'}$	CH_3 protons of isopropylidene group	H or CH_3 proton at C_5	H_6
α-Ribosyluracil	−143 (4.0)						−125 (8.5)	−241
2',3'-Isopropylidene-α-ribosyluracil	−148 (4.0)	−79 (0)	−77 (0)	−50	−1	+141, +143	−130 (8.0)	−244
β-Ribosyluracil	−129 (4.0)						−129 (8.0)	−247
2',3'-Isopropylidene-β-ribosyluracil	−132 (2.7)	−82 (7.0)	−70 (3.5)	−37	−3	+132, +143	−131 (8.5)	−248
α-Ribosylthymine	−146 (4.0)						+113	−237
2',3'-Isopropylidene-α-ribosylthymine	−151 (4.0)	−80 (0)	−79 (0)	−52	−1	+143, +145	+111	−237
β-Ribosylthymine	−129 (4.0)						+110	−238
2',3'-Isopropylidene-β-ribosylthymine	−130 (2.7)	−81 (7.0)	−77 (3.5)	−33	−4	+133, +145	+115	−237

The spectra were taken with Varian Associates A-60 spectrometer.
The positions of the signals in the spectra were measured in c.p.s. from dioxane as the internal standard.
J values are in c.p.s.

Thus it was shown that the determination of the configuration of β-nucleosides can be made from nuclear magnetic resonance spectra of isopropylidene derivatives, but 2',3'-cyclic α-nucleosides were not suitable for configurational analysis. Generally, the conformational determination of a sugar ring in an unsubstituted nucleoside is rather difficult since the peaks due to $H_{2'}$, $H_{3'}$ and $H_{4'}$ overlap giving multiplet. However the isopropylidene derivatives of the β-ribosides gave well-resolved peaks. Using the Karplus type equation,[18] dihedral angles of $H_{1'}$-C-C-$H_{2'}$, $H_{2'}$-C-C-$H_{3'}$ and $H_{3'}$-C-C-$H_{4'}$ could be calculated from $J_{1',2'}$, $J_{2',3'}$ and $J_{3',4'}$, respectively. These results indicate that the sugar rings of isopropylidene-β-ribosides are slightly puckered. However the peaks due to $H_{3'}$ of isopropylidene-α-isomers were not split and calculated dihedral angles of $H_{2'}$-C-C-$H_{3'}$ and $H_{3'}$-C-C-$H_{4'}$ are approximately 90°. Jardetzky[17] has reported that even though a five-membered ring was maximally puckered, the dihedral angles of $H_{2'}$-C-C-$H_{3'}$ and $H_{3'}$-C-C-$H_{4'}$ were 60° and 75°, respectively. Furthermore, the second fused ring (isoprop ylidene group) will reduce the dihedral angle comparing with an unsubstituted furanose ring. From these considerations, it is difficult to understand that signals due to $H_{3'}$ of isopropylidene-α-isomers appeared as singlets.

14) R. U. Lemieux, J. W. Lown : Can. J. Chem., **41**, 889 (1963).
15) L. Goldman, J. W. Marsico : J. Med. Chem., **6**, 413 (1963).
16) N. J. Leonard, R. A. Laursen : J. Am. Chem. Soc., **85**, 2026 (1963).
17) C. D. Jardetzky : *Ibid.*, **84**, 62 (1962).
18) M. Karplus : J. Chem. Phys., **30**, 11 (1959).

Hilbert-Johnson's method for synthesis of cytidine (Ⅳc)[2] had been unique until Fox, *et al.*[5] successfully applied the mercury method to synthesis of pyrimidine nucleosides. Cytidine has been prepared in good yields *via* the condensation of N-acetylcytosinemercury or chloromercury-4-ethoxy-2(1*H*)-pyrimidinone with Ⅱ.

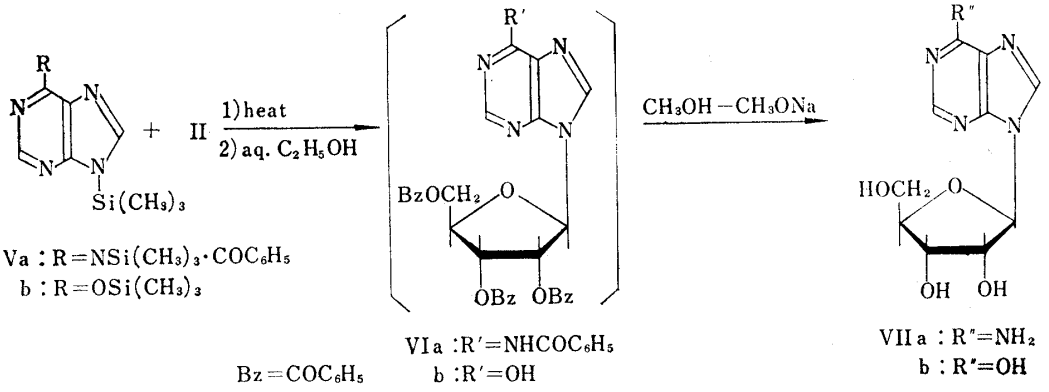
Bis(trimethylsilyl)-N-acetylcytosine (Ic) was condensed with Ⅱ analogously as with Ⅲ. The reaction mixture was purified on a silica gel column and then deacylated with methanolic ammonia. The formation of Ⅳc was detected by paper chromatography and ultraviolet absorption spectrum. The product was isolated in a crystalline state as the picrate, which showed no depression on admixture with an authentic cytidine picrate. The sample dried at room temperature *in vacuo* was a monohydrate as reported by Davoll, *et al.*[19] In addition to Ⅳc, a small amount of crystalline product was obtained (m.p. 211~214°), which was not confirmed yet.

We have already shown that the yield of synthetic glucopyranosylcytosine was lower than those of glucopyranosyluracil or -thymine.[1] In this case also, the yield of cytidine was rather low and undesirable by-products were observed by thin-layer chromatography.

Adenosine and Inosine

Adenosine (Ⅶa) has been synthesized by Davoll, *et al.* starting from acetochlororibose and silver salt of 2,8-dichloroadenine,[20] and its structure has been confirmed synthetically by condensation of an aminopyrimidine derivative and ribose.[21] Subsequent use of the chloromercury salt of 6-benzamidopurine greatly improved the yield of Ⅶa.[22]

When bis(trimethylsilyl)-N-benzoyladenine (Va) was heated with equimolar quantities of Ⅱ at 150~160°, brownish adduct was obtained. Removal of protecting groups and chromatography on anion exchange column (Dowex 1 OH^-) gave Ⅶa. In Part Ⅲ of this series, it was shown that fusion of Va with α-acetobromoglucose and then removal of protecting groups gave anomeric mixture of 9-D-glucopyranosyladenine. In this case also, formation of α-adenosine was presumed but could not be isolated.



Va : R=NSi(CH3)3·COC6H5
b : R=OSi(CH3)3

Bz=COC6H5

VIa : R'=NHCOC6H5
b : R'=OH

VIIa : R''=NH2
b : R''=OH

Chart 3.

Generally, hypoxanthine nucleosides have been obtained by deamination of adenine nucleosides with nitrous acid.[23,24] The authors have already shown that trimethylsilyl derivatives of hypoxanthine (Vb) gave 9-β-D-glucopyranosylhypoxanthine by condensation

19) J. Davoll, B. Lythgoe, A. R. Todd : J. Chem. Soc., **1946**, 833.
20) *Idem* : *Ibid.*, **1948**, 967.
21) G. W. Kenner, C. W. Taylor, A. R. Todd : J. Chem. Soc., **1949**, 1620.
22) J. Davoll, B. A. Lowy : J. Am. Chem. Soc., **73**, 1650 (1951).
23) E. Fischer, B. Helferich : Ber., **47**, 210 (1914).
24) J. M. Gulland, E. R. Holiday : J. Chem. Soc., **1936**, 765.

with α-acetobromoglucose followed by deacylation. This method was successfully applied to the synthesis of inosine (VIIb); Vb and II were fused and purified by chromatography. Debenzoylation and acetylation gave crystalline triacetylinosine in 18% yield based on reacted Vb. The product was confirmed by melting point, mixed melting point, ultraviolet characteristics and elementary analysis.

Experimental

1-(2,3,5-Tri-O-benzoyl-D-ribofuranosyl)uracil (IIIa, IIIa′)——A mixture of 2.56 g. of Ia and II, which was prepared from 5.04 g. of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose with dry ethereal hydrogen chloride,[25] was heated at 190° for 40 min. After cooling, the reaction mixture was dissolved in aq. EtOH, and the solvent evaporated to a brown gum under reduced pressure. The gum was dissolved in 80 ml. of hot benzene. Insoluble uracil (0.38 g.) was recovered by filtration. The filtrate on standing in the cold overnight furnished 1.3 g. of 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)uracil (IIIa) as needles melting at 144~145°. Considerable product remained in the mother liquors which were chromatographed as follows. On a column (2.5 cm. diameter × 20 cm.) packed with silica gel, the above mother liquors were placed, the column washed with benzene and the solvent was changed to $CHCl_3$. Fractions containing nucleoside derivatives were collected and evaporated. A residue was treated with benzene to yield 0.8 g. of crystals. The crude crystalline material was purified by fractional crystallization. By treatment with warm benzene, sparingly soluble clusters were removed by filtration. Evaporating and cooling the mother liquor gave needles. Recrystallizations of the needles from benzene afforded additional 1.0 g. of IIIa, m.p. 144~145° (corr.), $[\alpha]_D^{29}$ −48° (c=1.9, $CHCl_3$). Total yield of IIIa was 2.3 g. (58%, based on reacted Ia). *Anal.* Calcd. for $C_{30}H_{24}O_9N_2$: C, 64.74; H, 4.35; N, 5.03. Found: C, 64.52; H, 4.39; N, 5.10.

The sparingly benzene soluble clusters were collected and recrystallized from benzene containing EtOH. Pure IIIa′ (0.35 g.) was obtained, m.p. 203~205° (corr.), $[\alpha]_D^{29}$ −83° (c=1.9, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{24}O_9N_2$: C, 64.74; H, 4.35; N, 5.03. Found: C, 64.43; H, 4.42; N, 4.89.

1-α-D-Ribofuranosyluracil (IVa′)——1-(2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl)uracil (400 mg.) was suspended in 100 ml. of abs. MeOH saturated with dry ammonia at 0°. The suspension was set aside in refrigerator for 2 days. The crystals gradually dissolved giving a clear solution. After evaporation of the solvent, the residue was taken up in H_2O and repeatedly extracted with $CHCl_3$ in order to remove benzamide. The aqueous solution was evaporated to dryness under reduced pressure. The residue was dissolved in about 10 ml. of abs. EtOH and then a large amount of petr. ether was added. The precipitate was collected and dried giving 130 mg. of IVa′: UV: $\lambda_{max}^{H_2O}$ 264 mμ (ε 10,050) (pH 2.9~6.2), 263 mμ (pH 11); $[\alpha]_D^{25}$ −68° (c=1.0, H_2O).

By paper chromatography in BuOH-AcOH-H_2O (4:1:5), a single spot was obtained (Rf 0.17).

Metaperiodate titration was carried out according to the method of Lythgoe and Todd.[26] The nucleoside (49 mg.) was dissolved in 10 ml. of H_2O, treated with 3 ml. of 0.2565*M* sodium metaperiodate, diluted with H_2O to 25 ml. and set aside at room temperature. After oxidation, unchanged metaperiodate was estimated iodometrically. After 24 hr., IVa′ consumed 0.92 moles of oxidant per mole without the liberation of formic acid.

2′,3′-Isopropylidene-1-α-D-ribofuranosyluracil[*3]——To a mixture of 0.95 ml. of dry acetone, 0.41 ml. of ethyl orthoformate and 1.0 ml. of abs. EtOH containing 30 mg. of HCl was suspended 100 mg. of IVa′. α-Uridine dissolved to give a clear solution for about 5 min. After the solution was kept at room temperature for 20 min., the solvent was evaporated to dryness *in vacuo* at 10°. The residue was dissolved in abs. EtOH and then evaporated. This procedure was repeated three times to remove last traces of HCl. A crystalline residue was purified by recrystallizations from H_2O to give 75 mg. of 2′,3′-isopropylidene-α-uridine; m.p. 201~202.5° (corr.), UV: $\lambda_{max}^{H_2O}$ 262 mμ (ε 10,300), $[\alpha]_D^{26}$ −166.5 (c=2.1, MeOH). *Anal.* Calcd. for $C_{12}H_{16}O_6N_2$: C, 50.70; H, 5.67; N, 9.86. Found: C, 50.58; H, 5.81; N, 9.87.

1-β-D-Ribofuranosyluracil (uridine IVa)——The solution of IIIa (0.56 g.) and sodium methoxide (0.2 g.) in 3 ml. of abs. MeOH was refluxed for about 30 min. After cooling, Na^+ ion was removed from reaction mixture by treating with Dowex 50 (H^+) resin. The solution was evaporated to dryness. The residue was twice recrystallized from 99% EtOH to give 0.21 g. of IVa, m.p. 165~166° (corr.); $[\alpha]_D^{30}$ +4.6° (c=5.3, H_2O), UV: $\lambda_{max}^{H_2O}$ 262 mμ (ε 10,300). *Anal.* Calcd. for $C_9H_{12}O_6N_2$: C, 44.26; H, 4.95; N, 11.47. Found: C, 44.12; H, 5.08; N, 11.53.

*3 Isopropylidenation was carried out according to the procedure reported by T. Kato, T. Mori, N. Muramatsu, T. Meguro, M. Yoshikawa, T. Ichikawa, T. Takenishi, Y. Tsuchiya (Annual Meeting of Agricultural Chemical Society of Japan, Tokyo, Apr. 1963).

25) H. M. Kissman, C. Pidacks, B. R. Baker: J. Am. Chem. Soc., **77**, 18 (1955).
26) B. Lythgoe, A. R. Todd: J. Chem. Soc., **1944**, 592.

1-D-Ribofuranosylthymine (IVb, IVb′)——Bis(trimethylsilyl)thymine (Ib, 2.70 g.) and II, which was prepared by treating 5.04 g. of 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose with 100 ml. of dry ethereal hydrogen chloride, was dissolved in 50 ml. of dry benzene. After evaporation of the solvent, the residue was heated at 190° for 45 min. The reaction mixture was treated with about 50 ml. of hot aq. EtOH. After evaporation of the solvent, the residue was dissolved in benzene and 0.25 g. of unreacted thymine was recovered by filtration. To the filtrate was added large amounts of hexane and supernatant was removed by decantation. After this procedure was repeated twice, a gummy residue was dissolved in 80 ml. of abs. MeOH containing 0.2 g. of sodium methoxide. The solution was heated under reflux for an hour. The mixture was cooled and evaporated to dryness *in vacuo*. A residue was taken up in H_2O, the aqueous solution was washed with ether repeatedly and then applied to the top of a column packed with Dowex 50 resin (H^+ form, 3.5 cm. × 8 cm.). The column was washed with H_2O. UV absorbing fraction was evaporated and a residue was treated with abs. EtOH to give 1.05 g. (50%) of a crystalline material which was a mixture of anomeric 1-D-ribofuranosylthymines. The separation and isolation of IVb and IVb′ were carried out by the procedure reported by Farkaš, *et al.*[7]

Thus 0.36 g. of 1-α-D-ribofuranosyltymine was obtained, m.p. 174~175° (corr.), UV : $\lambda_{max}^{H_2O}$ 267 mμ (ε 10,000) (pH 3.7~6.2), 266 mμ (pH 10.6~12.0). The specific rotation was $[\alpha]_D^{26}$ −52.3° (c=1.60, MeOH). *Anal.* Calcd. for $C_{10}H_{14}O_6N_2$: C, 46.51; H, 5.47; N, 10.85. Found : C, 46.33; H, 5.47; N, 10.99.

Furthermore, 0.64 g. of 1-β-D-ribofuranosylthymine was obtained, m.p. 183~184.5° (corr.), UV : $\lambda_{max}^{H_2O}$ 267 mμ (ε 9,700) (pH 3.9~6.2), 266 mμ (pH 10.6~12.1), $[\alpha]_D^{27}$ −10.0 (c=4.0, H_2O). *Anal.* Found : C, 46.65; H, 5.44; N, 10.78.

2′,3′-Isopropylidene-1-α-D-ribofuranosylthymine was prepared by the same procedure described above. From 95 mg. of IVb′, 70 mg. of its isopropylidene derivative was obtained, m.p. 212~213° (corr.), UV : $\lambda_{max}^{H_2O}$ 268 mμ (ε 10,000), $[\alpha]_D^{30}$ −131.7° (c=1.3, MeOH). *Anal.* Calcd. for $C_{13}H_{18}O_6N_2$: C, 52.34; H, 6.08; N, 9.39. Found : C, 51.93; H, 6.02; N, 9.51.

1-β-D-Ribofuranosylcytosine Picrate (cytidine picrate)——Bis(trimethylsilyl)-N-acetylcytosine (Ic, 1.8 g.) was condensed as described above with II prepared from 3.02 g. of 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose. By treatment of reaction mixture with aq. EtOH, 0.3 g. of N-acetylcytosine was recovered. The product was purified by column chromatography on silica gel using $CHCl_3$. The resulting acylated nucleoside was hydrolyzed with methanolic ammonia for 3 days in refrigerator. The solution was evaporated to dryness : the residue was dissolved in H_2O and repeatedly washed with ether. By paper chromatographic analysis, formation of IVc was confirmed. After evaporation of the aqueous phase the resulting thick gum was dissolved in EtOH and treated with 0.46 g. of picric acid in EtOH. The solvent was concentrated to dryness. The residue was recrystallized twice from H_2O giving 0.28 g. of cytidine picrate; m.p. 182~185.5° (corr.), undepressed on admixture with a picrate prepared from natural cytidine. *Anal.* Calcd. for $C_{15}H_{16}O_{12}N_6 \cdot H_2O$: C, 36.74; H, 3.48; N, 17.14. Found : C, 36.73; H, 3.68; N, 17.32.

Adenosine (VIIa)——Bis(trimethylsilyl)-N-benzoyladenine (3.83 g.) and equimolar amounts of II were condensed at 150~160° for 3.5 hr. The reaction mixture treated with aq. EtOH was debenzoylated with methanolic sodium methoxide. After removal of Na^+ ion by treatment with IRC 50, the debenzoylated product was dissolved in 0.01*M* $HCOONH_4$ solution (pH 11.0) and the solution applied to a column which packed with Dowex 1 resin in OH^- form (3.5 cm × 26 cm.). The product was eluted with 0.01~0.03*M* HCOOH-NH_4OH buffer, the pH being gradually changed from 11.0 to 9.1. Fractions were checked in spectrophotometer, UV absorbing fractions collected and evaporated to dryness under reduced pressure. The residue was crystallized from H_2O giving 0.18 g. of VIIa. The adenosine obtained was confirmed by its failure to depress the melting point of an authentic sample. At the stage of debenzoylation, 0.3 g. of adenine was recovered. *Anal.* Calcd. for $C_{11}H_{13}O_4N_5$: C, 44.94; H, 4.90; N, 26.21. Found : C, 44.62; H, 4.90; N, 26.12.

2′,3′,5′-Tri-O-acetylinosine——Bis(trimethylsilyl)hypoxanthine (2.0 g.) and equimolar amounts of II were condensed at 150~160° for 1.5 hr. After treatment of condensation mixture with aq. EtOH, the mixture was worked up with $CHCl_3$. Unreacted hypoxanthine (0.47 g.) was recovered. Evaporating the $CHCl_3$ solution and the washing the residue with ether gave 3.18 g. of a foaming resin like product, which was treated with boiling methanolic sodium methoxide. The reaction mixture was treated with IRC 50 (H^+) and evaporated to dryness. The residue was acetylated for 45 min. with a boiling mixture of 30 ml. of dry pyridine and 15 ml. of Ac_2O. The solvent was removed under reduced pressure furnishing thick syrup, which taken up with $CHCl_3$. The solution was repeatedly washed with H_2O, dried with Na_2SO_4 and evaporated. The residue was crystallized from EtOH giving crystalline triacetylinosine. An additional amount of the product was obtained by chromatographic purification ($CHCl_3$-silica gel) of the mother liquors. The combined crude products were recrystallized from EtOH to afford 0.17 g. of triacetylinosine; m.p. 238~240° (corr.); $[\alpha]_D^{28}$ −31.9 (c=3.3, $CHCl_3$). *Anal.* Calcd. for $C_{16}H_{18}O_8N_4$: C, 48.73; H, 4.60; N, 14.21. Found : C, 48.45; H, 4.51; N, 14.43.

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Summary

A new synthetic method of pyrimidine and purine ribosides was introduced. Condensation of tribenzoylribofuranosyl chloride with trimethylsilyl derivatives of pyrimidines and purines and then deacylation furnished natural ribose nucleosides in good yields. In the syntheses of uridine and ribofuranosylthymine, α-isomers were also isolated and the determinations of the structures were described.

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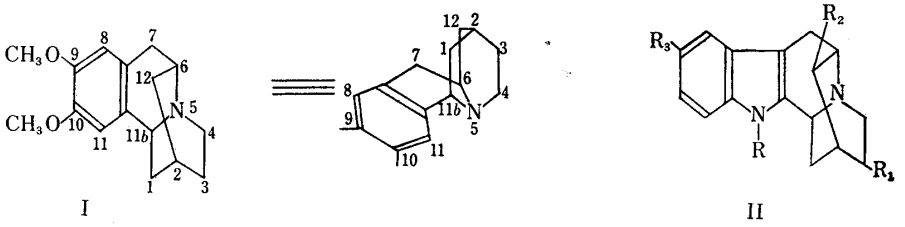
202. Naoto Yoneda : Synthesis of 9,10-Dimethoxy-1,2,3,4,6,7-hexahydro-2,6-methano-11*bH*-benzo[*a*]quinolizine.

(*Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd.*[*1])

In this paper is described a synthesis of the title compound (I), as a preliminary to the synthesis of 2,6-methano-indolo[2,3-*a*]quinolizine derivative (II), which forms the fundamental skeleton of sarpagine (II) (R=H; R_1= >CH-CH_3; R_2=CH_2OH; R_3=OH) and cognate Rauwolfia bases.

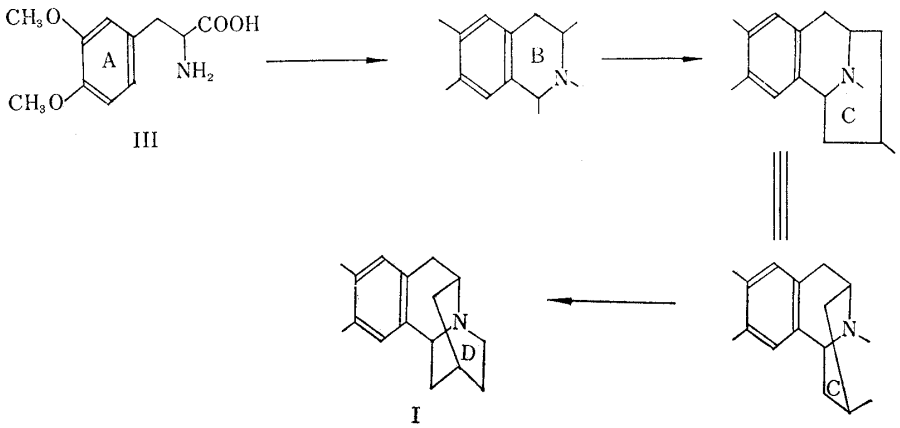


I II

Chart 1.

An unsuccessful attempt of I has already been described by Arata and Sugasawa.[1]

The scheme of the present synthesis starting from *dl*-3-(3,4-dimethoxyphenyl)alanine (III) is outlined in the following Chart 2.



III I

Chart 2.

*1 Toda-machi, Kita-adachi-gun, Saitama-ken (米田直人).

1) Y. Arata, S. Sugasawa : This Bulletin, **9**, 104 (1961).