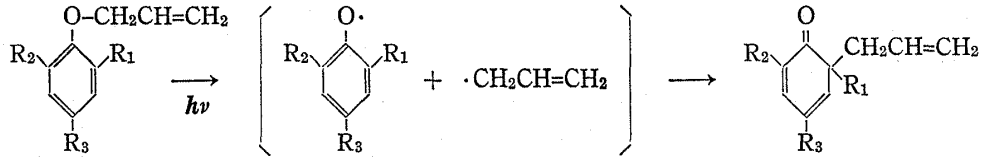

Ia : $R_1=R_2=R_3=H$
Ib : $R_1=R_2=H$; $R_3=Me$
Ic : $R_1=R_2=Me$; $R_3=H$

The above data, especially the detection of phenoxy radicals provides the first direct evidence for the presence of the radical mechanism in the photo-rearrangement of allyl phenyl ethers, though in our experimental conditions allyl radicals or 2,5-cyclohexadienones could not be observed.

Faculty of Pharmaceutical Sciences
Hokkaido University
Kita-12, Nishi-6, Kita-ku, Sapporo

KEIJI HEMMI
SHUNJI NARUTO
KEN-ICHI HIRAO
OSAMU YONEMITSU

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Direct Synthesis of 2,5′-Anhydro Pyrimidine Nucleosides

Anhydronucleosides are useful intermediates for the chemical transformation of nucleosides and nucleotides. Although a large number of pyrimidine anhydronucleosides has been prepared,[1] the syntheses of 2,5′-anhydro pyrimidine nucleosides developed so far seem to be rather complicated. Recently Wada and Mitsunobu reported[2] that the treatment of 2′,3′-O-isopropylideneuridine with triphenylphosphine (I) and diethyl azodicarboxylate (II)[3] in tetrahydrofuran afforded 2′,3′-O-isopropylidene-2,5′-anhydrouridine in an excellent yield. According to them,[4] however, under the same conditions uridine was not transformed into 2,5′-anhydrouridine but into a 1:1 adduct of uridine with I. The authors happened to find that (O)-2,5′-, (S)-2,5′- and (N)-2,5′-anhydro pyrimidine nucleosides (IVa, IVb and VI) could be synthesized directly from uridine (IIIa), 2-thiouridine (IIIb),[5] and isocytidine (V)[6] by treating them with I and II and adding a little amount of water to the reaction mixture.

Uridine (IIIa) was treated with 1.8 equivalents of triphenylphosphine (I) and diethyl azodicarboxylate (II) in dioxane at room temperature for 3 hours, followed by addition of 0.1 volume of water to the reaction mixture. The mixture was then heated under reflux for 30 minutes. After the work-up the product, 2,5′-anhydrouridine (IVa), was obtained in 67% yield: mp 213—214° (decomp.) (from aq. EtOH): *Anal.* Calcd. for $C_9H_{10}O_5N_2$: C, 47.81; H, 4.42; N, 12.38. Found: C, 47.68; H, 4.28; N, 12.35. It was positive to the periodate-

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5) *a*) D.M. Brown, D.B. Parihar, A. Todd and S. Varadarajan, *J. Chem. Soc.*, **1958**, 3028; *b*) T. Ueda and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **18**, 1076 (1970).
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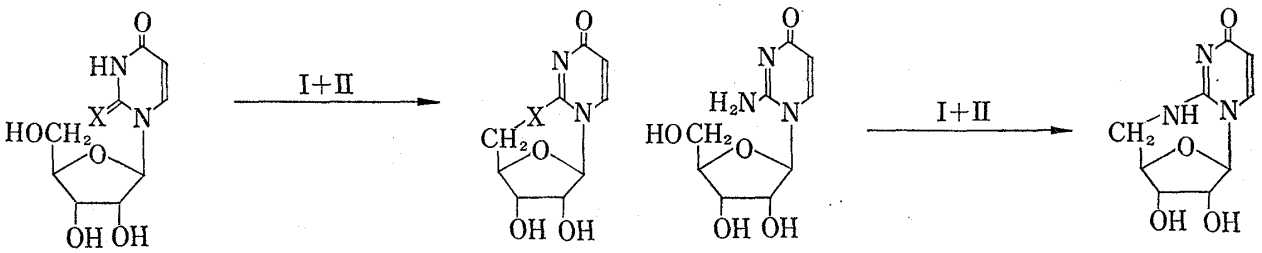
benzidine spray test,[7] and its ultraviolet (UV) spectrum ($\lambda_{max}^{H_2O}$ 240 nm, ε 12000) was similar to that of 2′,3′-O-isopropylidene-2,5′-anhydrouridine.[2,6] Ammonolysis of IVa with methanolic ammonia afforded isocytidine,[6] and treatment of IVa with liquid hydrogen sulfide[5b] in aqueous pyridine afforded 2-thiouridine.[5] Nuclear magnetic resonance (NMR) spectrum of IVa was in good accordance with those expected for the structure IVa (Table I): the signals were characteristic of the anomeric 1′- and geminal 5′-protons of anhydronucleosides and similar cyclic compounds.[5b,8]

Table I. NMR Chemical Shift of 2,5′-Anhydronucleosides

	Compound IVa	Compound IVb	Compound VI
C_1'-H (ppm)	5.57(s)	5.56(d)	5.46(s)
$J_{1',2'}$ (Hz)	—	1.5	—
C_5'-Ha (ppm)	4.13(q)	3.04(q)	3.10(q)
$J_{4',a}$ (Hz)	1.2	3.0	2.0
C_5'-Hb (ppm)	4.50(q)	3.40(q)	3.29(q)
$J_{4',b}$ (Hz)	1.5	2.8	2.5
$J_{a,b}$ (Hz)	13.0	14.0	13.5

NMR spectra were taken on a Hitachi R-20B recording spectrometer (60 M Hz) in *d*-DMSO-D_2O. TMS was employed as an internal standard.

Similarly, the treatment of 2-thiouridine (IIIb) and isocytidine (V) with I, II and water afforded the corresponding (S)-2,5′-, and (N)-2,5′-anhydronucleosides. The product, (S)-2,5′-anhydro-1-(5-deoxy-β-D-ribofuranosyl)-2-thiouracil (IVb), was obtained in 78% yield: mp 164—165° (decomp.) (from aq. EtOH): *Anal.* Calcd. for $C_9H_{10}O_4N_2S$: C, 44.63; H, 4.16; N, 11.57. Found: C, 44.52; H, 3.96; N, 11.44. UV spectrum ($\lambda_{max}^{H_2O}$ 244 nm, ε 17000) was closely similar to that of its 2′,3′-O-isopropylidene derivative.[5b] From the compound (V),(N)-2,5′-anhydro-1-(5-deoxy-β-D-ribofuranosyl)-isocytosine (VI)[9] was obtained in 76% yield: mp 222—224° (decomp.): *Anal.* Calcd. for $C_9H_{11}O_4N_3$: C, 48.00; H, 4.92; N, 18.66. Found: C, 47.99; H, 4.89; N, 18.89. UV spectra ($\lambda_{max}^{H_2O}$ 221 nm, ε 25000; $\lambda_{max}^{H_2O\,(pH2)}$ 258 nm, ε 6200) were closely similar to those of N^2-methylisocytidine.[10] Compounds IVb and VI were positive



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9) According to recent private communication, the compound VI was independently prepared by T. Ueda and J. Yamashita, Faculty of Pharmaceutical Sciences, Hokkaido University.
10) The N^2-methylisocytidine was prepared from 2,5′-anhydrouridine (IVa) with methylamine by a method that of the ammonolysis.

to the periodate-benzidine test.[7] Their NMR spectra were characteristic for the structures IVb and VI (Table I). In addition, 2′,3′-O-isopropylidene derivatives of (S)-2,5′, and (N)-2,5′-anhydronucleosides (IVb and VI) were also prepared from 2′,3′-O-isopropylidene derivatives of IIIb and V in a similar way.

So far as is known, the work reported here is the first specifically designed to synthesize 2,5′-anhydro pyrimidine nucleosides directly from pyrimidine nucleosides. The studies of cleavage reaction of (S)-2,5′-and (N)-2,5′-anhydronucleosides are being undertaken.

Research Laboratory,
Yamasa Shoyu Co., Ltd.
Cho-shi, Chiba

Susumu Shibuya
Akira Kuninaka
Hiroshi Yoshino

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Syntheses and Properties of Formyl Sarcosine[1]-LH-RH and N-Methyl-L-pGlu[1]-LH-RH[1)]

In the course of our investigations on the structure-activity relationship of luteinizing hormone-releasing hormone (LH-RH), pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2, acylated Gly[1]-LH-RH such as formyl Gly[1]-LH-RH was revealed to retain some biological activity in spite of the lack of the N-terminal pyrrolidone ring structure.[2)] Time course study based on the serum level of luteinizing hormone (LH) after the administration of formyl Gly[1]-LH-RH in rats suggested shorter life time of this compound than that of LH-RH in animal body (Fig. 1). In an attempt to suppress the rapid inactivation, we synthesized formyl Sar[1]-LH-RH, in which methyl group was introduced to the nitrogen atom of formyl glycine part, and found a marked increase in LH-releasing activity (Table I). A prolonged high LH-level in serum was also observed distinctly (Fig. 1). This result prompted us to synthesize N-methyl-L-pGlu[1]-LH-RH, and its LH-releasing activity remained at a half level of the natural LH-RH.

These analogs, formyl Sar[1]-LH-RH and N-methyl-L-pGlu[1]-LH-RH, were synthesized as follows. The protected nonapeptide amide, Z-His-Trp-Ser(Bu^t)-Tyr(Bu^t)-Gly-Leu-Arg(Tos)-Pro-Gly-NH_2 (I), synthesized according to the same procedure described in our previous communication,[2)] was decarbobenzoxylated by hydrogenolysis and coupled with formyl sarcosine *p*-nitrophenyl ester to give the protected decapeptide amide (II) [mp 165—167°, $[\alpha]_D^{20}$ −33.3° (c=0.47 in MeOH), *Anal.* Calcd. for $C_{69}H_{97}O_{15}N_{17}S \cdot 1.5H_2O$: C, 56.62; H, 6.89; N, 16.27. Found: C, 56.90; H, 6.97; N, 15.58]. Deprotection of II with anhydrous hydrogen fluoride,[3)] followed by purification with column partition chromatography on Sephadex G-25

1) The amino acid residues (except glycine and sarcosine) mentioned in this communication are of the L-configuration. The abbreviations used to denote amino acids, peptides and peptide derivatives are those recomended by IUPAC-IUB Commission on Biochemical Nomenclature, *Biochemistry*, **5**, 2485 (1966); **6**, 362 (1967).
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