Synthesis of New Nucleosides Containing a Fused Cyclopropane Ring 1-{(1*R*,3*R*,5*R*)-2-Oxabicyclo[3.1.0]hexan-3-yl}-thymine and -uracil

By TAKESHI ADACHI, TAMEO IWASAKI, MUNEJI MIYOSHI, and ICHIZO INOUE*

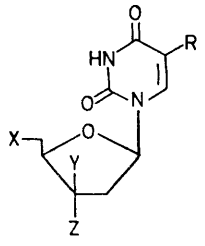
(*Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co. Ltd.*, 16-89, *Kashima-3-chome, Yodogawa-ku, Osaka* 532, *Japan*)

Summary 1-{(1*R*,3*R*,5*R*)-2-Oxabicyclo[3.1.0]hexan-3-yl}-thymine and -uracil have been obtained by the cathodic reduction of 3′,5′-dideoxy-3′,5′-di-iodothymidine and 2′,3′,5′-trideoxy-3′,5′-di-iodouridine, respectively.

IN recent years, modification of the sugar unit of nucleosides has been studied extensively in connection with a search for antimicrobiological and antineoplastic agents. However, few studies have been reported on the synthesis of nucleosides containing a cyclopropane ring group within the sugar part of the nucleoside.[1] We have recently reported a convenient method for the introduction of 2′,3′-unsaturation into the sugar unit of nucleosides by electrolysis of vicinal bromo esters.[2] We have further studied the electrolysis of various halogenated sugar nucleosides in which another leaving group, such as halogen, mesyloxy, or acetoxy, is located in different positions on the furanose ring.

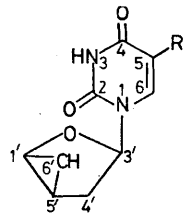
Here we report an electrochemical synthesis of 1-{(1*R*,3*R*,5*R*)-2-oxabicyclo[3.1.0]hexan-3-yl}-thymine (**2a**) and

-uracil (**2b**), new nucleosides containing a fused cyclopropane ring, from 3′,5′-dideoxy-3′,5′-di-iodothymidine (**1a**)[3] and 2′,3′,5′-trideoxy-3′,5′-di-iodouridine (**1b**),[3] respectively. It has been shown by Rifi and Covitz that a cyclopropane ring can be formed by electrochemical reduction



(1)

	R	X	Y	Z
a;	Me	I	H	I
b;	H	I	H	I
c;	Me	Cl	Cl	H
d;	H	Cl	Cl	H
e;	Me	I	H	$MeSO_3$



(2)

a; R = Me

b; R = H

of $\alpha\gamma$-dihalides.[4] The applicability of the method was first examined by determining the polarographic half-wave potentials of the halides (**1a**—**e**). The di-iodides (**1a**) and (**1b**) showed more anodic half-wave potentials, −1·13 and −1·08 V. *vs.* S.C.E., respectively than the dichlorides (**1c**) and (**1d**),[5] suggesting that the iodides would be better substrates for electrolysis. The controlled potential electrolysis of (**1a**) at a reduction potential (−1·15 V. *vs.* S.C.E.) near the polarographic wave was carried out below 10 °C in a three-compartment cell using a mercury pool cathode under dry nitrogen gas, with tetraethylammonium tosylate–dimethylformamide solution (0·25M) as electrolyte.

Compound (**2a**) was obtained after chromatography on silica gel with $CHCl_3$–MeOH (95 : 5) as eluant; 36% yield, m.p. 163—164 °C, λ_{max} (MeOH) 267·5 nm (ϵ 9·040); $[\alpha]_D^{28}$ +36° (*c* 0·5, MeOH); δ ($CDCl_3$, relative to Me_4Si) 0·6—1·05 (2H, m, 6′-H_2), 1·5—2·14 (2H, m, 4′-H^b and 5′-H), 1·95 (3H, s, 5-Me), 2·5—3·04 (1H, m, 4′-H^a), 3·9—4·25 (1H, m, 1′-H), 6·25 [1H, dd, *J* (3′-H, 4′-H^b) 3·5, *J* (3′-H, 4′H^a) 7 Hz, 3′-H], 7·22 (1H, s, 6-H), and 9·75—10·2 (1H, m, 3-H); *m/e* 208 (M^+), 127 (base residue +2H), and 83 (oxabicyclohexanyl residue). Compound (**2b**) was obtained similarly from (**1b**) in 31% yield, m.p. 180—182 °C, $[\alpha]_D^{28}$ +77·2 (*c* 0·285, MeOH); its u.v., n.m.r. (5-H at δ 5·73, $J_{5,6}$ 8 Hz), and mass spectra showed similar features to those of (**2a**). Similar treatment of 5′-deoxy-3′-*O*-methanesulphonyl-5′-iodothymidine (**1e**)[6] gave thymine in 81% yield as the only isolable product. Electrolysis of the dichlorides (**1c**) and (**1d**) also resulted in glycosidic cleavage.

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[1] D. Horton and C. G. Tindall, Jr., *Carbohydrate Res.*, 1971, **17**, 240; B. Fraser-Reid, *Accounts Chem. Res.*, 1975, **8**, 192.
[2] T. Adachi, T. Iwasaki, M. Miyoshi, and I. Inoue, *Nucleic Acids Res.*, 1976, Special Publication No. 2, 93.
[3] J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 1970, **35**, 2868.
[4] M. R. Rifi and F. H. Covitz, 'Introduction to Organic Electrochemistry,' Marcel Dekker, New York, 1974, Ch. 4, p. 209.
[5] H. P. C. Hogenkamp, *Biochemistry*, 1974, **13**, 2736.
[6] A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 1955, 816.