Rakesh Kumar [a], Leonard I. Wiebe and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta,
Edmonton, Alberta, Canada T6G 2N8

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A novel class of 5-(1-azido-2-haloethyl)arabinouridines **4-6** was synthesized by the regiospecific addition of halogenoazides (XN_3: X = Cl, Br, I) to the vinyl substituent of 5-vinylarabinouridine (**7**). The title 5-(1-azido-2-haloethyl)arabinouridines **4-6** were previously shown to exhibit significant *in vitro* antiviral activity against herpes simplex virus type 1, varicella zoster virus and cytomegalo virus.

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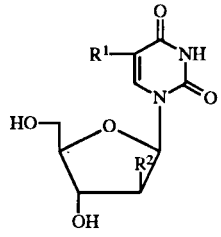
Introduction.

New methods for the synthesis of arabinouridines that possess novel two-carbon moieties at the C-5 position, which exhibit potent and selective antiviral activity, represents an important aspect of antiviral drug design. Among the many 5-substituted uracil nucleosides that have been investigated, 5-(2-chloroethyl)-2'-deoxyuridine (**1**) is one of the most potent and selective in its action against herpes simplex virus type 1 [1]. Thus, 5-(2-chloroethyl)-2'-deoxyuridine is effective against systemic herpes simplex type 1 infection and encephalitis in mice at a five-to-fifteen fold lower dose than (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (**2**) [2]. Although 5-azidomethyl-2'-deoxyuridine (**3**) is a potent inhibitor of herpes simplex virus type 1, it is not specific for virally infected cells [3]. Recently, we reported the *in vitro* antiviral activities for the hitherto unknown 5-(1-azido-2-haloethyl)arabinouridines **4-6** which inhibited herpes simplex type 1 induced cytopathicity in human skin embryo fibroblast (fifty percent inhibitory concentration = 0.46-1.8 μ*M* range), and varicella zoster virus (fifty percent inhibitory concentration = 0.08-0.234 μ*M* range) and cytomegalo virus (fifty percent inhibitory concentration = 1.45-10.4 μ*M* range) induced cytopathicity in human embryonic lung fibroblast, cell cultures [4]. The 5-(1-azido-2-haloethyl) substituents of the 5-(1-azido-2-haloethyl)-arabinouridines **4-6** can be considered to be hybrids of the 5-(2-haloethyl) and 5-azidomethyl moieties. We now report the synthesis of this novel class of 5-(1-azido-2-haloethyl)-arabinouridines **4-6**.

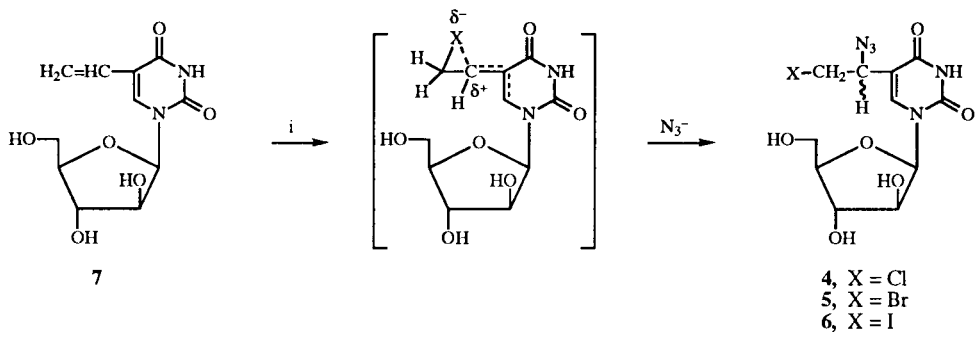


1, $R^1 = -CH_2CH_2Cl$, $R^2 = H$
2, $R^1 = (E)\text{-}CH{=}CH\text{-}Br$, $R^2 = H$
3, $R^1 = -CH_2N_3$, $R^2 = H$
4, $R^1 = -CH(N_3)CH_2Cl$, $R^2 = OH$
5, $R^1 = -CH(N_3)CH_2Br$, $R^2 = OH$
6, $R^1 = -CH(N_3)CH_2I$, $R^2 = OH$

Chemistry.

The target 5-(1-azido-2-haloethyl)arabinouridines **4-6** were synthesized by reaction of 5-vinylarabinouridine (**7**) with either *N*-chlorosuccinimide, *N*-bromosuccinimide, or iodine monochloride and sodium azide in 49%, 38% and 36% yields, respectively, as illustrated in Scheme 1. The 5-(1-azido-2-haloethyl)arabinouridines exist as a mixture of two diastereomers (1:1 ratio) which differ in configuration (*R* and *S*) at the 1-carbon atom of the 5-(1-azido-2-haloethyl) substituent. This regiospecific addition is consistent with reports that unsymmetrical olefins, capable of halonium ion formation, were found to favor an unsymmetrical bridged intermediate of the type illustrated in Scheme 1 even in solvents having a high dipole moment [5-7]. Attempts to separate the two diastereomers of the

Scheme 1 [a]



7

4, X = Cl
5, X = Br
6, X = I

[a] Reagents and conditions: i, *N*-chlorosuccinimide, sodium azide, 1,2-dimethoxyethane-water, 0°, two hours (**4**); *N*-bromosuccinimide, sodium azide, 1,2-dimethoxyethane-water, 0°, one hour (**5**); iodine monochloride, acetonitrile, 25°, two hours (**6**).

5-(1-azido-2-haloethyl)arabinouridines **4-6** by flash column chromatography, or the multiple development thin layer chromatography technique, were unsuccessful.

EXPERIMENTAL

Nuclear magnetic resonance spectra (^{1}H nmr) were recorded on a Bruker AM-300 spectrometer. Preparative thin-layer chromatography was performed using Whatman PLK5F plates, 1.0 mm in thickness, and silica gel column chromatography was carried out using Merck 7734 (60-200 mesh) silica gel. 5-Vinylarabinouridine (**7**) was prepared according to a reported method [8].

5-(1-Azido-2-chloroethyl)arabinouridine (**4**).

N-Chlorosuccinimide (40 mg, 0.3 mmole) was added slowly with stirring to a precooled (-5°) suspension, prepared by mixing a solution of 5-vinylarabinouridine (70 mg, 0.275 mmole) in 1,2-dimethoxyethane (25 ml) with a solution of sodium azide (65 mg, 1 mmole) in water (0.15 ml). The reaction was allowed to proceed at 0° for two hours with stirring and the solvent was removed *in vacuo*. The resulting residue was purified by preparative silica gel thin layer chromatography using chloroform-methanol (9:1, v/v) as development solvent to afford 5-(1-azido-2-chloroethyl)arabinouridine as a viscous oil (47 mg, 49%); ^{1}H nmr (deuteromethanol) (mixture of two diastereomers in a ratio of 1:1): δ 3.5-3.7 (m, 2H, CH_2Cl), 3.7-4.0 (m, 3H, H-4', H-5'), 4.08-4.14 (m, 1H, H-3'), 4.16-4.22 (m, 1H, H-2'), 4.7-4.8 (m, 1H, CHN$_3$), 6.14 and 6.16 (two d, $J_{1',2'}$ = 3.0 Hz, 1H total, H-1'), 7.98 and 8.02 (two s, 1H total, H-6).

Anal. Calcd. for $C_{11}H_{14}ClN_5O_6$: C, 37.99; H, 4.05; N, 20.14. Found: C, 38.10; H, 4.05; N, 19.79.

5-(1-Azido-2-bromoethyl)arabinouridine (**5**).

N-Bromosuccinimide (53 mg, 0.3 mmole) was added in aliquots with stirring to a precooled (-5°) suspension, prepared by mixing a solution of 5-vinylarabinouridine (70 mg, 0.275 mmole) in 1,2-dimethoxyethane (25 ml) with a solution of sodium azide (65 mg, 1 mmole) in water (0.15 ml). The initial yellow color produced upon addition of each *N*-bromosuccinimide aliquot quickly disappeared. After all of the *N*-bromosuccinimide had been added, the reaction was allowed to proceed at 0° for one hour with stirring. Removal of the solvent *in vacuo* gave a residue which was purified by silica gel column chromatography using chloroform-methanol (92:8, v/v) as eluant to afford 5-(1-azido-2-bromoethyl)arabinouridine as a viscous syrup (41 mg, 38%); ^{1}H nmr (deuteromethanol) (mixture of two diastereomers in a ratio of 1:1): δ 3.60-3.78 (m, 2H, CH_2Br), 3.8-3.9 (m, 2H, H-5'), 3.94-4.02 (m, 1H, H-4'), 4.10-4.15 (m, 1H, H-3'), 4.18-4.25 (m, 1H, H-2'), 4.75-4.82 (m, 1H, CHN$_3$), 6.17 and 6.20 (two d, $J_{1',2'}$ = 3.0 Hz, 1H total, H-1'), 8.0 and 8.02 (two s, 1H total, H-6).

Anal. Calcd. for $C_{11}H_{14}BrN_5O_6$: C, 33.68; H, 3.59; N, 17.86. Found: C, 33.70; H, 3.99; N, 17.74.

5-(1-Azido-2-iodoethyl)arabinouridine (**6**).

Iodine monochloride (50 mg, 0.3 mmole) was added slowly with stirring during a five minute period to a suspension of sodium azide (65 mg, 1 mmole) in dry acetonitrile (10 ml) at ice-bath temperature with stirring. This mixture was stirred for an additional five minutes, a solution of 5-vinylarabinouridine (70 mg, 0.275 mmole) in dry acetonitrile (40 ml) was added, the reaction mixture was warmed to 25° and the reaction was allowed to proceed at 25° for two hours with stirring. The resulting red-brown reaction mixture was poured onto ice-water (25 ml), this mixture was extracted with ethyl acetate (3 x 50 ml), and the ethyl acetate extract was washed with 5% aqueous sodium thiosulfate (10 ml). Drying the ethyl acetate fraction (sodium sulfate), removal of the solvent *in vacuo* and purification of the resulting residue by elusion from a silica gel column using chloroform-methanol (97:3, v/v) as eluant afforded 5-(1-azido-2-iodoethyl)arabinouridine as a viscous oil (44 mg, 36%); ^{1}H nmr (deuteromethanol) (mixture of two diastereomers in a ratio of 1:1): δ 3.5-3.7 (m, 2H, CH_2I), 3.8-3.95 (m, 2H, H-5'), 3.96-4.03 (m, 1H, H-4'), 4.13-4.19 (m, 1H, H-3'), 4.21-4.27 (m, 1H, H-2'), 4.66-4.72 (m, 1H, CHN$_3$), 6.18 and 6.20 (two d, $J_{1',2'}$ = 3.0 Hz, 1H total, H-1'), 8.01 and 8.03 (two s, 1H total, H-6).

Anal. Calcd. for $C_{11}H_{14}IN_5O_6$: C, 30.08; H, 3.21; N, 15.94. Found: C, 30.08; H, 3.36; N, 15.97.

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REFERENCES AND NOTES

[a] Current address: Department of Medical Microbiology and Immunology, Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada T6G 2H7.

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