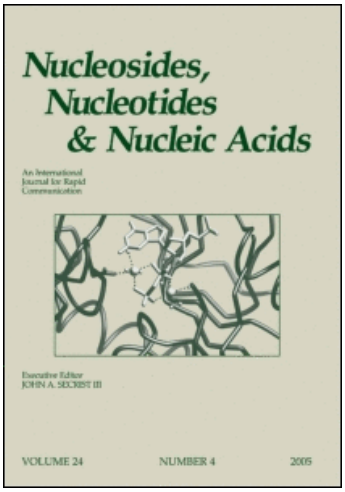

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PHOTOCHEMICAL SYNTHESIS OF 6-ARYLURIDINES[1)]

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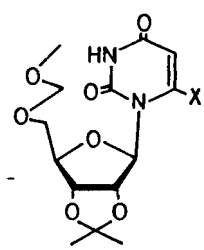
Abstract: Synthesis of 6-aryluridines was effected by photochemical arylation of 6-iodo-2',3'-O-isopropylidene-5'-O-methoxymethyluridine.

Our recent publications on the lithiation of nucleosides[2-7)] have proved the effectiveness of this tactic for the modification of base moieties both in terms of simplicity and generality. Thus, various types of 6-substituted uridines were prepared by the metallation of 2',3'-O-isopropylidene-5'-O-methoxymethyluridine (1) with lithium diisopropylamide (LDA) and successive reactions with electrophiles.[2)]

Some limitations involved in the above reaction can be compensated by a nucleophilic addition-elimination reaction of a compound having a suitable leaving group at the C-6 position, as has been shown in the preparation of 6-azido- and 6-alkylthiouridines.[8,9)]



1 X= H
2 X= SPh
3 X= SePh
4 X= I
5 X= Ph

With an intention to synthesize 6-aryluridines, we initially examined the addition-elimination reaction of 2-4 by using phenyllithium as a nucleophile. However, the main product in these reactions was 1. 6-Phenyluridine derivative 5 was isolated only in the reaction of 2 (3.5 eq of PhLi, in THF, below -70 °C, 3 h), but the yield of 5 was low (18%). This

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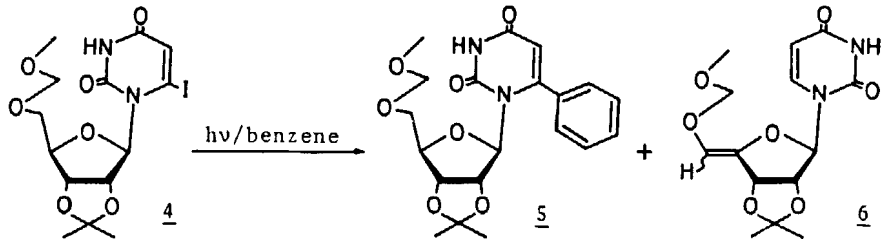
prompted us to investigate the photochemical synthesis of 6-aryluridines from 6-iodo-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (4). While this work was in progress, a brief communication[10] appeared in which a photochemical reaction of 4 prepared by our method[11] with N-phenylpyrrole has been described. We are not aware of any other report on the arylation of uridine at the C-6 position.[12]

When 4 was irradiated in benzene for 9 h with a 400 W high-pressure Hg lamp equipped with a Pyrex filter, 5 was produced in 12% yield. Another product isolated in this reaction showed H-6 (δ 7.32 ppm, doublet), which was coupled

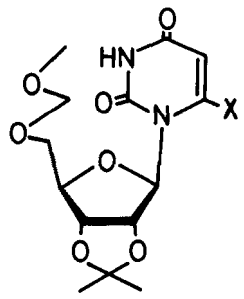


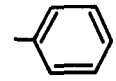
4 5 6

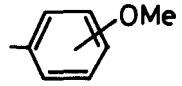
with H-5 (δ 5.78 ppm, double doublet), in its PMR spectrum measured in $CDCl_3$. In addition, it was void of a signal corresponding to H-4'. On the basis of these PMR data and those reported for 1-(5-deoxy-2,3-O-isopropylidene-β-D-erythro-pent-4-enofuranosyl)uracil,[13] the structure of this product was determined as 6 (8%). Its MS spectrum (m/z 327: M+1, m/z 311: M-Me, m/z 112: B+1) was also in accord with this structure.

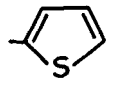
Addition of Et_3N (1 mol eq to 4) in the above phenylation gave a higher yield of 5 (43%) and the formation of 6 was not observed in this case. When the reaction was carried out in the presence of Et_3N by using MeCN as a co-solvent, the reaction time required for disappearance of the starting material was reduced to 4 h, but 5 was isolated only in 5% yield together with 1 (26%).

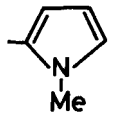
Trapping of the C-6 radical generated from 4 was further examined with other solvents in the absence or presence of MeCN. These results are summarized in Tables 1 and 2. As



5 X = 

7 X = 

8 X = 

9 X = 

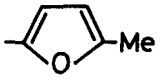
10 X = 

Table 1 Synthesis of 6-Aryluridines in the presence of 1 eq of Et_3N

Solvent	React. Time(h)	Product	Isolated yield(%)
benzene	9	5	43
anisole	3	7	54
thiophene	7	8	20
N-methylpyrrole	13	9	62
2-methylfuran	13	10	18

Table 2 Synthesis of 6-Aryluridines in the presence of MeCN and 1 eq of Et_3N

Solvent	MeCN/Solvent*	React.Time(h)	Products†
benzene	1	4	5(5%), 1(26%)
anisole	1	8	7(18%), 1(14%)
thiophene	3	3	8(10%), 1(9%), 4(4%)
N-methylpyrrole	3	3	9(13%), 4(28%)

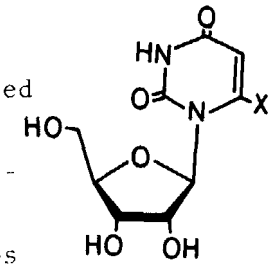
* ratio in v/v
† isolated yields are shown in parenthese

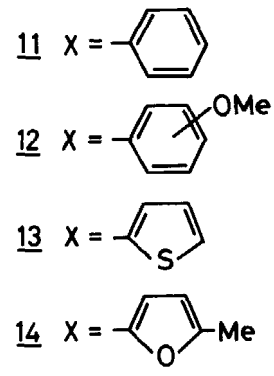
can be seen from these results, higher yields of 6-arylated products were obtained when the reactions were carried out in the absence of MeCN.

From the PMR spectra of 8, 9, and 10, it became clear that all the reactions with heteroaromatic solvents had occurred at the α-position.[14] In the reaction with anisole, the PMR spectrum of the product (7) indicated the presence of two regioisomers, which could not be separated even after deprotection or by the successive acetylation.

Another PMR feature of these products deserves a short comment, since introduction of an aryl group to the C-6 position decreased the differences in the chemical shift between the isopropylidene methyl signals, Δδ Me value,[15] as shown in Table 3.

We have already observed that a 6-substituted uridine having a "C^6-C-Ar" structure, where the aryl ring can bend to the endo isopropylidene methyl group, shows a considerably reduced Δδ Me value.[16] However, the above PMR results of 6-aryluridine derivatives suggest that, quite unexpectedly from examination of a molecular model, even a "C^6-Ar" structure in the uracil moiety can cause a change of the Δδ Me value.





The 6-arylated products were subjected to deprotection with 50% aqueous trifluoroacetic acid to give their free nucleosides (11-14). In the case of deprotection of 9, an intractable mixture of products resulted presumably due, in part, to the glycosidic bond cleavage provoked by its protonated species.

In conclusion, the usefulness of a 6-iodouridine derivative was exemplified herein by its photochemical arylation. 5-Substituted 6-aryluridines can certainly be pre-

Table 3 PMR chemical shifts (δ: ppm) of isopropylidene Me signals in $CDCl_3$

Compd.	endo-Me	exo-Me	Δδ Me (ppm)
1	1.59	1.36	0.23
4	1.57	1.35	0.22
5	1.38	1.30	0.08
8	1.45	1.32	0.13
9	1.45	1.32	0.13
10	1.51	1.35	0.16

pared in a similar manner, since their 6-iodo derivatives are now easily accessible by the lithiation method.[17]

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. PMR spectra were measured with a JEOL JNM-FX 100 NMR spectrometer by using TMS (tetramethylsilane) as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer. Column chromatography was carried out on silica gel (Wakogel® C-200). TLC was performed on silica gel (precoated silica gel plate F_{254}, Merck).

General procedure for photoarylation of 4 —— Irradiation of 4 (200 mg) was carried out, with a Shigemi 400 W high-pressure mercury lamp equipped with a Pyrex filter, in an appropriate solvent (80 ml) and Et_3N (0.06 ml) under Ar atmosphere. After evaporation of the solvent, each product was purified by preparative TLC.

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-phenyluridine (5)—— This compound was obtained as colorless oil.

PMR ($CDCl_3$) δ: 1.30 (3H, s, isop.Me), 1.38 (3H, s, isop.Me), 3.37 (3H, s, $CH_2OC\underline{H}_3$), 3.79 (2H, m, CH_2-5'), 4.16 (1H, m, H-4'), 4.68 (2H, s, $C\underline{H}_2OCH_3$), 4.86 (1H, dd, H-3'), 5.23 (1H, dd, H-2'), 5.52 (1H, d, J= 1.5 Hz, H-1'), 5.65 (1H, s, H-5), 7.50 (5H, s, phenyl), 9.49 (1H, br, NH). MS m/z: 404 (M^+), 389 (M-Me), 188 (B+1).

1-(2,3-O-Isopropylidene-5-O-methoxymethyl-β-D-erythro-pent-4-enofuranosyl)uracil (6)—— This compound was obtained as a foam. PMR ($CDCl_3$) δ: 1.38 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 3.49 (3H, s, $CH_2OC\underline{H}_3$), 4.76 (1H, d, J= 1.5 Hz, H-5'), 5.19 (1H, d, J= 6.3 Hz, H-2'), 5.29 (2H, s, $C\underline{H}_2OCH_3$), 5.41 (1H, dd, H-3'), 5.53 (1H; s, H-1'), 5.78 (1H, dd, H-5), 7.32 (1H, d, H-6), 8.73 (1H, br, NH). MS m/z: 327 (M+1), 311 (M-Me), 112 (B+1).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-(methoxy-phenyl)uridine (7)——This compound, a mixture of two regio-isomers, was obtained as foam. Partial PMR data which show the presence of two regioisomers are given below. PMR ($CDCl_3$) δ: 3.34 and 3.38 (3H, each as s, $CH_2OC\underline{H}_3$), 3.82 and 3.88 (3H, each as s, OMe), 4.64 and 4.68 (2H, each as s, $C\underline{H}_2OCH_3$), 9.43 and 9.55 (1H, each as br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-(thien-2-yl)uridine (8)—— This compound was obtained as a foam. PMR ($CDCl_3$) δ: 1.32 (3H, s, isop.Me), 1.45 (3H, s, isop.Me), 3.38 (3H, s, $CH_2OC\underline{H}_3$), 3.79 (2H, m, CH_2-5'), 4.19 (1H, m, H-4'), 4.68 (2H, s, $C\underline{H}_2OCH_3$), 4.89 (1H, dd, H-3'), 5.24 (1H, dd, H-2'), 5.81 (1H, s, H-5), 5.84 (1H, d, J= 1.5 Hz, H-1'), 7.17, 7.46, and 7.53 (3H, each as dd, thienyl), 9.24 (1H, br, NH). MS m/z: 410 (M^+), 194 (B+1).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-(N-methyl-pyrrol-2-yl)uridine (9)—— This compound was obtained as a foam. PMR ($CDCl_3$) δ: 1.32 (3H, s, isop.Me), 1.45 (3H, s, isop.Me), 3.36 (3H, s, $CH_2OC\underline{H}_3$), 3.63 (3H, s, N-Me), 3.79

(2H, m, CH_2-5'), 4.15 (1H, m, H-4'), 4.66 (2H, s, $C\underline{H}_2OCH_3$), 4.86 (1H, dd, H-3'), 5.22 (1H, dd, H-2'), 5.56 (1H, d, J= 1.5 Hz, H-1'), 5.66 (1H, d, H-5), 6.23, 6.45, and 6.81 (3H, each as dd, Ar), 9.94 (1H, br, NH). MS m/z: 407 (M^+), 392 (M-Me), 191 (B+1). High resolution MS m/z: 407.1695 (M^+) Calcd. for $C_{19}H_{25}N_3O_7$ 407.1683.

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-(5-methylfuran-2-yl)uridine (10)—— This compound was obtained as a foam. PMR ($CDCl_3$) δ: 1.35 (3H, s, isop.Me), 1.51 (3H, s, isop.Me), 2.39 (3H, s, Ar-Me), 3.36 (3H, s, $CH_2OC\underline{H}_3$), 3.80 (2H, m, CH_2-5'), 4.41 (1H, m, H-4'), 4.67 (2H, s, $C\underline{H}_2OCH_3$), 4.92 (1H, dd, H-3'), 5.25 (1H, dd, H-2'), 5.94 (1H, d, H-5), 5.99 (1H, d, J= 1.0 Hz, H-1'), 6.18 and 6.96 (2H, each as d, Ar), 9.99 (1H, br, NH). MS m/z: 408 (M^+), 192 (B+1).

6-Phenyluridine (11)—— Compound 5 (100 mg) in 50% TFA (5 ml) was stirred for 48 h at room temperature. Evaporation of the solvent followed by short-column chromatography on silica gel(5% EtOH in $CHCl_3$) gave 11(50 mg, 63%) as a foam. PMR (CD_3OD) δ: 3.73 (3H, m, CH_2-5' and H-4'), 4.29 (1H, dd, H-3'), 4.74 (1H, dd, H-2'), 5.25 (1H, d, J= 4.0 Hz, H-1'), 5.58 (1H, s, H-5), 7.53 (5H, s, Ph).

Compound 11 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 446.1372 (M^+) Calcd. for $C_{21}H_{22}N_2O_9$ 446.1317. UV absorption in MeOH: max 265 nm, min 238 nm.

6-Methoxyphenyluridine (12)——Compound 7 (180 mg) in 50% TFA (5 ml) was stirred for 17 h at room temperature. Evaporation of the solvent followed by short-column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 12 (121 mg) as colorless oil which was a mixture of two regioisomers.

Compound 12 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 476.1469 (M^+) Calcd. for $C_{22}H_{24}N_2O_{10}$ 476.1422.

6-(Thien-2-yl)uridine (13)—— Compound 8 (70 mg) in 50% TFA (3 ml) was stirred for 4 h at room temperature. Evaporation of the solvent followed by short-column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 13 (35 mg, 60%). Crystallization from acetone-hexane gave an analytical sample (mp 111-114 °C). Anal. Calcd. for $C_{13}H_{14}N_2O_6S \cdot 1/3$ acetone: C, 48.64; H, 4.67; N, 8.11. Found: C, 48.75; H, 4.67; N, 8.16. UV absorption in MeOH: max 292 nm (ε 9300), min 247.5 nm (ε 6400). PMR (CD_3OD) δ: 2.15 (2H, s, acetone), 3.76 (3H, m, CH_2-5' and H-4'), 4.31 (1H, dd, H-3'), 4.76 (1H, dd, H-2'), 5.55 (1H, d, J= 3.5 Hz, H-1'), 5.75 (1H, s, H-5), 7.19, 7.54, and 7.69 (3H, each as dd, Ar).

6-(5-Methylfuran-2-yl)uridine(14)——Compound 10 (40 mg) in 50% TFA (2 ml) was stirred for 16 h at room temperature. Evaporation of the solvent followed by short-column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 14 (23 mg, 73%). Crystallization from acetone-hexane gave an analytical sample (mp 282-287 °C). Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.84; H, 4.98; N, 8.64. Found: C, 52.11; H, 5.12; N, 8.59. UV absorption in MeOH: max 315 nm (ε 15000), shoulder 281 nm (ε 7500) and 271 nm (ε 7100), min 241.5 nm (ε 2500). PMR (CD_3OD) δ: 2.39 (3H, d, J= 1.0 Hz, Ar-Me), 3.78 (3H, m, CH_2-5' and H-4'), 4.34 (1H, dd, H-3'), 4.78 (1H, dd, H-2'), 5.71 (1H, d, J= 3.5 Hz, H-1'), 5.87 (1H, s, H-5), 6.28 (1H, dd, Ar), 7.10 (1H, d, Ar).

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