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A NEW, DIRECT METHOD FOR INTRODUCTION OF INDOLYL GROUPS AT THE 5-POSITION OF URIDINE. PHOTOCHEMICAL SYNTHESIS OF MODEL COMPOUNDS FOR NUCLEIC ACID-PROTEIN ADDUCTS[1]

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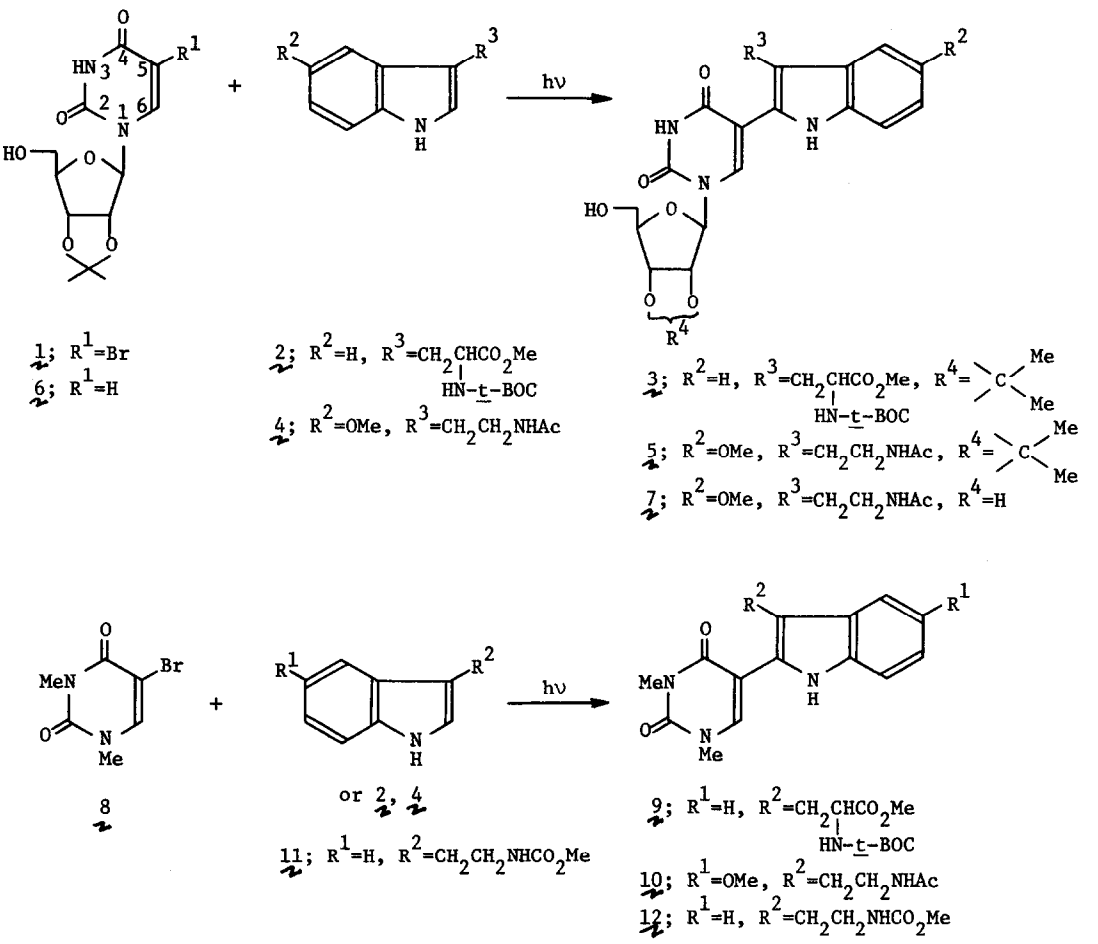
Uridine and related nucleosides substituted by various functional group at the pyrimidine C-5 position represent an intriguing class of compounds. Many methods have been developed for their synthesis and the biological properties, e.g. as antiviral agents, of their analogues have been widely studied.[2,3] Most of the methods consist of a nucleophilic displacement in 5-halogenopyrimidine nucleosides by heteroatom nucleophiles.[3] However, there are very few examples for forming carbon-carbon bonds at the C-5 position.[3,4] In our systematic study on the model reactions for the photoinduced nucleic acid-protein cross-linking, we have reported that N^b-acetyltryptophan methyl ester undergoes a photoreaction with 5-bromouridine to give the coupled product at the C-5 position of the pyrimidine nucleoside in a highly regiospecific fashion.[5] In this communication, we wish to report that biologically important indolic compounds such as melatonin and tryptamine derivatives readily undergo a photo-cross-coupling reaction with 5-bromouridine or 5-bromo-1,3-dimethyluracil to provide new 5-substituted uracil and uridine derivatives of potential biological significance.

As we reported earlier,[5] acetone-sensitized irradiation of 2',3',O-isopropylidene-5-bromouridine (1) (1.4 mM) in acetone-acetonitrile (1 : 3) in the presence of N^b-t-BOC-tryptophan methyl ester (2) (2.8 mM) gave rise to the coupled product 3[6] in good yield (80%). Under similar conditions, acetone-sensitized irradiation of 1 with melatonin (4) provided none of the coupled product, but gave a complex mixture of photoproducts derived from 4. However, direct irradiation of 1 (1.7 mM) and 4 (3.2 mM) in acetonitrile with 254-nm light resulted in the formation of the coupled product 5[6] (13%) together with the debrominated product 6 (35%).[7] Similarly, photolysis of 4 (2.1 mM) and 5-bromouridine (1.1 mM) in acetonitrile with 254-nm light provided 7[6] (15%) and uridine (72%).



1; R^1=Br
6; R^1=H

2; R^2=H, R^3=CH_2CHCO_2Me (HN-t-BOC)
4; R^2=OMe, R^3=CH_2CH_2NHAc

3; R^2=H, R^3=CH_2CHCO_2Me (HN-t-BOC), R^4=C(Me)(Me)
5; R^2=OMe, R^3=CH_2CH_2NHAc, R^4=C(Me)(Me)
7; R^2=OMe, R^3=CH_2CH_2NHAc, R^4=H

8

11; R^1=H, R^2=$CH_2CH_2NHCO_2Me$

9; R^1=H, R^2=CH_2CHCO_2Me (HN-t-BOC)
10; R^1=OMe, R^2=CH_2CH_2NHAc
12; R^1=H, R^2=$CH_2CH_2NHCO_2Me$

Similar types of photo-cross-coupling reactions have been observed with 5-bromo-1,3-dimethyluracil (8). Acetone-sensitized irradiation of 2 (4.4 mM) and 8 (2.1 mM) in acetonitrile gave 9[6] (41%), whereas direct irradiation of 4 (3.7 mM) and 8 (1.9 mM) provided 10[6] (6%) and 1,3-dimethyluracil (32%). Neither acetone-sensitized irradiation (method A) nor direct irradiation with 254-nm light (method B) provided the cross-coupled product between N^b-methoxycarbonyltryptamine (11) and the 5-bromouracil derivatives. This difficulty, however, was overcome by using electron-transfer photosensitizers[9] (method C). Thus, irradiation of 11 (3.3 mM) and 5-bromo-1,3-dimethyluracil (8) (1.6 mM) in acetone-acetonitrile (1 : 3) in the presence of 2,3-dimethoxynaphthalene (0.7 mM) as an electron-donating photosensitizer gave rise to the coupled product 12[6] (37%). The electron-donating sensitizer can be replaced by 2-methoxynaphthalene or 1,4-dimethoxynaphthalene.[10]

The present reaction provides a convenient and useful method for the synthesis of 5-substituted uracil and uridine which are otherwise difficultly accessible. It might, however, be worthwhile to point out that free tryptophan and tryptamine does not undergo such a coupling reaction by any of the methods (A,B,C). Only N^b-protected tryptophan and tryptamine can undergo such a couping reaction.[11]

Table Photoproducts and their spectral data

Substrate	Method[a]	Product (%)[b]	Spectral data[c]
1 + 2	A	3 (80)	Mp 129-132 °C (dec); UV (CH_3CN) 213 nm (log ε 4.36), 266 (3.99), 291 (3.85), 332 (3.61); ^1H NMR (acetone-d_6) δ 1.29 (s, 9 H), 1.35 (s, 3 H), 1.55 (s, 3 H), 3.31 (d, J = 7.8 Hz , 2 H), 3.52-3.94 (brs, 2 H, NH and OH), 3.61 (s, 3 H), 3.82 (m, d on addition of D_2O, J = 3.6 Hz, 2 H), 4.25 (td, J = 3.0, 3.2 Hz, 1 H), 4.57 (td, J = 7.8, 7.8 Hz, 1 H), 4.95 (dd, J = 6.4, 3.0 Hz, 1 H), 5.08 (dd, J = 3.0, 6.4 Hz, 1 H), 6.11(d, J = 3.0 Hz, 1 H), 6.30(brd, J = 7.8 Hz, 1 H), 6.99-7.70(m, 4 H), 8.23(s, 1 H), 10.20(brs, 1 H, NH).
1 + 4	B	5 (13)	Mp 108-113 °C; UV (CH_3CN) 219 nm (log ε 4.33), 274 (3.91), 307 (3.86), 330 (3.82); ^1H NMR (acetone-d_6) δ 1.36 (s, 3 H), 1.55 (s, 3 H), 1.86 (s, 3 H), 2.97 (t, J = 7.8 Hz, 2 H), 3.30-3.66 (m, t on addition of D_2O, J = 7.8 Hz, 2 H), 3.73-3.91 (brs, 2 H), 3.81 (s, 3 H), 4.23 (td, J = 3.2, 3.4 Hz, 1 H), 4.41-4.89 (brs, 3 H, OH and NH), 4.96 (dd, J = 6.4, 3.2 Hz, 1 H), 5.12 (dd, J = 3.2, 6.4 Hz, 1 H), 6.16 (d, J = 3.2 Hz, 1 H), 6.76 (dd, J = 8.4, 2.4 Hz, 1 H), 7.13 (d, J = 2.4 Hz, 1 H), 7.31 (d, J = 8.4 Hz, 1 H), 8.21 (s, 1 H), 10.09 (brs, 1 H, NH).
5-Bromo-uridine + 4	B	7 (15)	Viscous oil; UV (EtOH) 226 nm (log ε 4.05), 271 (3.82), 296 (3.70), 325 (3.52); ^1H NMR (CD_3OD) δ 1.87 (s, 3 H), 2.95 (t, J = 8.0 Hz, 2 H), 3.28-3.55 (m, 2 H), 3.79 (brs, 2 H), 3.84 (s, 3 H), 4.07 (m, 1 H), 4.22 (dd, J = 5.0, 3.2 Hz, 1 H), 4.34 (dd, J = 4.4, 5.0 Hz, 1 H), 6.06 (d, J = 4.4 Hz, 1 H), 6.78 (dd, J = 2.2, 8.4 Hz, 1 H), 7.10 (d, J = 2.2 Hz, 1 H), 7.25 (d, J = 8.4 Hz, 1 H), 8.23 (s, 1 H).
8 + 2	A	9 (41)	Mp 97-98 °C; UV (CH_3CN) 226 nm (log ε 4.44), 266 (3.97), 288 (3.98), 326 (3.73), ^1H NMR ($CDCl_3$) δ 1.39 (s, 9 H), 3.28 (d, J = 7.8 Hz, 2 H), 3.43 (s, 6 H), 3.59 (s, 3 H), 4.42 (td, J = 7.8, 7.8 Hz), 5.41 (d, J = 7.8 Hz, 1 H), 6.96-7.50 (m, 4 H), 8.15 (s, 1 H), 10.41 (s, 1 H).
8 + 4	B	10 (6)	Mp 112-113 °C; UV (CH_3CN) 222 nm (log ε 4.34), 268 (3.94), 306 (3.72); ^1H NMR (CD_3OD) δ 1.86 (s, 3 H), 2.55-2.76 (m, 2 H), 3.12-3.34 (m, 2 H), 3.39 (s, 3 H), 3.45 (s, 3 H), 3.75 (s, 3 H), 6.90 (s, 1 H), 7.03 (d, J = 8.6 Hz, 1 H), 7.34 (d, J = 8.6 Hz, 1 H),

			7.50 (s, 1 H).
8 + 11	C	13 (37)	Mp 163-168 °C (dec); UV (CH_3CN) 224 nm (log ε 4.33), 261 (3.98), 291 (3.95), 339 (3.71); ^1H NMR ($CDCl_3$) δ 2.97-3.21 (m, 2 H), 3.25 -3.44 (m, 2 H), 3.44 (s, 3 H), 3.64 (s, 3 H), 3.68 (s, 3 H), 5.16 (brs, 1 H), 6.99-7.58 (m, 4 H), 10.19 (s, 1 H, NH).

[a] A; Acetone-sensitized irradiation with 100-W high-pressure mercury lamp using glass filter (> 300-nm). B; Direct irradiation with low-pressure mercury lamp using Vycol filter (> 250-nm). C; 2,3-Dimethoxynaphthalene-sensitized irradiation with 100-W high-pressure mercury lamp (Pyrex filter).

[b] Isolated yield based on the reacted 5-bromopyrimidines.

[c] Satisfactory mass spectra (high resolution) were obtained for all new compounds.

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(6) The products were isolated by thick-layer chromatography (silica gel). The structure of the product was assigned on the basis of spectral data[5] (see Table).

(7) Photochemical debromination of 5-bromouracil with 254-nm light is well known.[8]

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(9) D. R. Arnold and A. J. Maroulis, J. Am. Chem. Soc., 99, 7356 (1977), and references therein.

(10) In the absence of 11, irradiation (> 320-nm) of an equimolar solution of 8 and 2,3-dimethoxynaphthalene gave the corresponding coupled product (42%). Photo-cross-coupling with other electron-rich aromatics will be reported elsewhere.

(11) This is probably due to the intramolecular electron-transfer (or quenching) between the indolyl group and the side-chain amino group. In fact, addition of n-butylamine to the reaction system (1 and 2) inhibited the cross-coupling reaction. Mechanistic aspects of this new type of photoreaction will be reported in forthcoming paper.