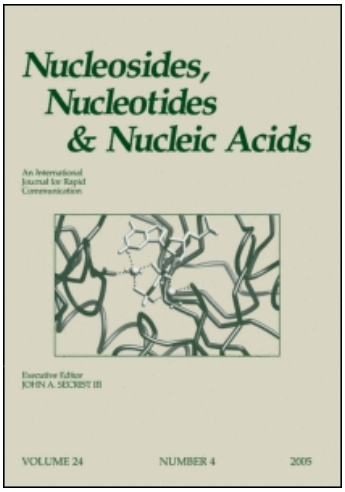
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Photochemical Synthesis of Phosphonopyrimidine and Phosphonopurine Ribonucleosides

Tokumi Maruyama[a]; Mikio Honjo[a]
[a] Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima, JAPAN

To cite this Article Maruyama, Tokumi and Honjo, Mikio(1988) 'Photochemical Synthesis of Phosphonopyrimidine and Phosphonopurine Ribonucleosides', Nucleosides, Nucleotides and Nucleic Acids, 7: 2, 203 — 211
To link to this Article: DOI: 10.1080/07328318808070204
URL: http://dx.doi.org/10.1080/07328318808070204

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

NUCLEOSIDES & NUCLEOTIDES, 7(2), 203-211 (1988)

PHOTOCHEMICAL SYNTHESIS OF PHOSPHONOPYRIMIDINE AND PHOSPHONOPURINE RIBONUCLEOSIDES

Tokumi Maruyama and Mikio Honjo*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, JAPAN

Downloaded At: 09:16 27 January 2011

Abstract. Photochemical reaction of 2',3'-di-O- or 2',3',5'-tri-O-protected 5-bromouridine (1), 8-bromoadenosine (4) and 8-bromoguanosine (10) with triethyl phosphite in a mixture of dimethylformamide (DMF) and acetonitrile, followed by deprotection, provided the corresponding diethyl phosphonate derivatives (3, 7 and 12).

In a previous paper,[1] we reported the synthesis of phosphonopyrimidine and phosphonopurine ribonucleosides, based upon treatment of lithiated species of 2',3',5'-tri-O-protected uridine and 6-chloropurine ribonucleoside with diethyl chlorophosphate, followed by deblocking and hydrolysis. This paper deals with an alternative method for the synthesis of these ribonucleosides by photoinduced coupling reaction.

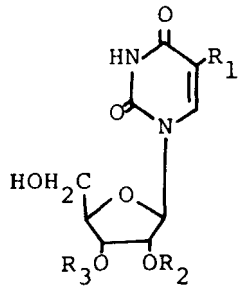
The photolysis of iodobenzene in the presence of trialkyl phosphites has been shown to yield dialkyl phenylphosphonates.[2] Photochemical reaction of 2',3'-O-isopropylidene-5-iodouridine with aromatic compounds has also been reported to give 2',3'-O-isopropylidene-5-aryluridine along with 2',3'-O-isopropylideneuridine.[3] Thus, we attempted photochemical synthesis of the title compounds by an attack of nucleoside radicals on trialkyl phosphites. Addition of

Copyright © 1988 by Marcel Dekker, Inc.

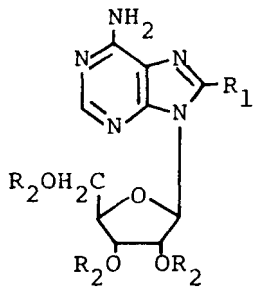
triethyl phosphite to a solution of 5-bromo-2',3'-O-isopropylideneuridine (1) in a mixture of DMF and acetonitrile, followed by irradiation with a low-pressure mercury lamp under argon gas afforded diethyl 2',3'-O-isopropylideneuridine-5-phosphonate (2a) and 2',3'-O-isopropylideneuridine (2b) in 56% and 5% yields, respectively, after purification with silica-gel column chromatography. The structure of 2a was assigned by the proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, which showed the presence of a pair of ethyl-proton signals due to the diethyl phosphonate group. Compound 2b was identified by comparison of the melting point and ultra-violet (UV) spectrum with those of an authentic sample of 2b. Deacetonation of 2a with 80% trifluoroacetic acid provided diethyl uridine-5-phosphonate (3) as colorless needles, whose melting point and UV spectrum were in accord with those of an authentic sample of the phosphonate (3).[1] A mechanism for the formation of 2a involves the following two steps. (i) The photoinduced 2',3'-O-isopropylideneuridine-5-yl radical reacts with triethyl phosphite yields the corresponding uridine-5-triethoxyphosphoranyl radical. (ii) The intermediate is subjected to disproportionation to give 2a and ethyl radical.

An analogous reaction of 2',3',5'-tri-O-acetyl-8-bromoadenosine (4) with triethyl phosphite provided a mixture containing diethyl 2',3',5'-tri-O-acetyladenosine-8-phosphonate (5). The major product 5 was isolated by silica-gel column chromatography in 63% yield, and the structure was established by the ^{1}H NMR and mass spectroscopies. The UV absorption maximum was bathochromically shifted by 20 nm, compared with that of adenosine. Treatment of 5 with methanolic ammonia at room temperature for 1 day gave, after purification with DEAE-cellulose column chromatography, a mixture of monomethyl (6a) and monoethyl (6b) esters of adenosine-8-phosphonic acid in a molar ratio of 2:1, which were detected by the ^{1}H NMR spectroscopy, while alcoholysis of 5 with ethanolic

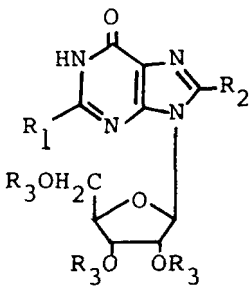
Downloaded At: 09:16 27 January 2011



1 R_1=Br, R_2,R_3=$C(CH_3)_2$
2a R_1=$P(O)(OC_2H_5)_2$, R_2,R_3=$C(CH_3)_2$
2b R_1=H, R_2,R_3=$C(CH_3)_2$
3 R_1=$P(O)(OC_2H_5)_2$, R_2=R_3=H



4 R_1=Br, R_2=$COCH_3$
5 R_1=$P(O)(OC_2H_5)_2$, R_2=$COCH_3$
6a R_1=$P(O)(OCH_3)OH$, R_2=H
6b R_1=$P(O)(OC_2H_5)OH$, R_2=H
7 R_1=$P(O)(OC_2H_5)_2$, R_2=H



8 R_1=H, R_2=$P(O)(OC_2H_5)_2$, R_3=$COCH_3$
9 R_1=R_3=H, R_2=$P(O)(OC_2H_5)_2$
10 R_1=NH_2, R_2=Br, R_3=$COCH_3$
11 R_1=NH_2, R_2=$P(O)(OC_2H_5)_2$, R_3=$COCH_3$
12 R_1=NH_2, R_2=$P(O)(OC_2H_5)_2$, R_3=H

ammonia at 10°C for 3 days afforded, after work-up, a trifluoroacetate of diethyl adenosine-8-phosphonate (7) as colorless needles in 46% yield. Deamination of 5 with nitrous acid yielded inosine counterpart (8) and deacetylation of 8 with methanolic ammonia gave diethyl inosine-8-phosphonate (9) as colorless needles in 43% yield. The difference in the behavior of 5 and 8 towards methanolic ammonia could be explained by dissociation of the N^1 proton in 8 followed by delocalization of the N^1 negative charge, and unfavorable nucleophilic attack of the reagent on the phosphorus atom.

Downloaded At: 09:16 27 January 2011

A similar photochemical reaction of 2',3',5'-tri-O-acetyl-8-bromoguanosine (10) and triethyl phosphite in acetonitrile provided diethyl 2',3',5'-tri-O-acetylguanosine-8-phosphonate (11) in 49% yield. Alcoholysis of 11 with methanolic ammonia afforded, after work-up, diethyl guanosine-8-phosphonate (12) as colorless needles in 60% yield. A similar difference in the behavior of 8 and 11 towards methanolic ammonia could also be explained as in the case of 5 and 8.

The synthesis of 7 or 12 by photoinduced coupling reaction is superior to the synthesis by proton-lithium[1,4] or halogen-lithium[5] exchange reaction so far as the unnecessity of protection of the adenine or guanine moiety is concerned.

Downloaded At: 09:16 27 January 2011

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus (hot stage type) and are uncorrected. The UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. The ^{1}H NMR spectra were recorded with a JEOL GX-400 (400MHz) spectrometer in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard and in D_2O with sodium 3-(trimethylsilyl)propionate as an internal standard, respectively. Photoreactions were performed with low pressure Hg lamp (a quartz filter) at a light intensity of 30W under argon gas. Paper electrophoresis (PE) was carried out at 22 V/cm using 0.01M phosphate buffer (pH 7.5).

Diethyl 2',3'-O-Isopropylideneuridine-5-phosphonate (2a).—— Triethyl phosphite (10 ml) was added to a solution of 5-bromo-2',3'-O-isopropylideneuridine (1) (2.00 g, 5.46 mmol) in a mixture of DMF (5 ml) and acetonitrile (25 ml). The solution was stirred and irradiated at room temperature for 6 days. After evaporation of the solvents, the residue was dissolved in AcOEt (10 ml), applied to a column of Silica gel G (∅2.5 X 40 cm) and eluted with AcOEt (1 l) to give the three main fractions. From the first fraction, 1

(0.48 g) was recovered. The second fraction was evaporated to dryness to give 2',3'-O-isopropylideneuridine (2b) (77 mg, 5 %). as white needles. mp 160 - 161.5° (lit.[6] 163.5 - 164°). UV λ_{max}^{MeOH}nm; 260. Evaporation of the third fraction gave a caramel (2a) (1.02 g, 56 %). UV λ_{max}^{MeOH}nm: 266. MS m/z: 405 (M^+-C_2H_5O). ^{1}H NMR ($CDCl_3$) δ : 9.90 (1H, br s, N^3-H), 8.50 (1H, d, J_{HCCP}= 13.3 Hz, H-6), 5.81 (1H, s-like, H-1'), 4.85 (2H, s-like, H-2', H-5'OH), 4.33 (1H, q, H-3'), 4.12 (4H, quintet, $POCH_2CH_3$), 3.6-4.1 (3H, m, H-4', H-5'), 1.55 and 1.33 (each 3H, s, $C(CH_3)_2$), 1.30 (6H, t, $POCH_2CH_3$).

Diethyl Uridine-5-phosphonate (3). —— A solution of 2a (1.02 g, 2.31 mmol) in 80 % trifluoroacetic acid (10 ml) was stirred at room temprtature for 10 min, concentrated to a syrup, and evaporated azeotropically with water The residue was partitioned between water (30 ml) and $CHCl_3$ (10 ml) and the aqueous solution was washed with $CHCl_3$ (10 ml). After evaporation of the aqueous layer to dryness, the resulting gum was triturated with EtOH (10 ml) to give colorless needles (751 mg, 81%). mp 162-164° (lit.[1] 161-163°). UV λ_{max}^{MeOH}nm: 265.5.

Diethyl 2',3',5'-Tri-O-acetyladenosine-8-phosphonate (5). —— Triethyl phosphite (20 ml) was added to a solution of 8-bromo-2',3',5'-tri-O-acetyladenosine (4) (6.00 g, 12.7 mmol) in acetonitrile (250 ml). The mixture was stirred and irradiated at 15° for 3 days. After evaporation to dryness, the residue was taken up in a small amount of $CHCl_3$, applied on a column of Silica gel G (∅ 4.0 X 30 cm), and eluted using a gradient of $CHCl_3$ (1.5 l) and $CHCl_3$-EtOH (10:1, 1.5 l). The desired fractions were combined and evaporated to dryness to give a pale-yellow caramel (4.23 g, 63 %). UV: λ_{max}^{MeOH}nm: 281, 270 (sh). MS m/z: 529 (M^+). ^{1}H NMR ($CDCl_3$) δ: 8.39 (1H, s, H-2), 6.78 (1H, d, $J_{1',2'}$= 4.03 Hz, H-1'), 6.34 (1H, q, $J_{2',3'}$= 6.23 Hz, H-2'), 6.21 (2H, br s, NH_2), 5.96 (1H, t, H-3'), 4,53 (1H, sestet, H-4'), 4.38 (2H, m, H-5'), 4.27 (4H, m, $POCH_2CH_3$), 2.14, 2.08, 2.04 (each 3H, s, $-OCOCH_3$), 1.39 (6H, t-like, $POCH_2CH_3$).

Downloaded At: 09:16 27 January 2011

Reaction of 5 with methanolic ammonia. —— A solution of 5 (600 mg, 1.13 mmol) in methanolic ammonia (saturated at 0°, 10 ml) was kept at room temperature for 24 hr. After evaporation to dryness, the residue was dissolved in water (5 ml) and the solution was chromatographed on a column of DEAE cellulose (bicarbonate, ∅ 2.7 X 12cm) using a gradient (1 l) of 0 - 0.1M triethylammonium bicarbonate (TEAB). The desired fractions were combined and evaporated to dryness. Water (30 ml) was added to the solid and the azeotropic mixture was evaporated. The residue was dissolved in water (10 ml) and the solution was passed through a column of Amberlite IR 120B (Na^+, ∅2.7 X 7 cm), which was washed with water (300 ml). The passings and washings were combined and evaporated to dryness to give a caramel (305 mg). UV: $\lambda_{max}^{0.05N\ HCl}$ nm: 266, $\lambda_{max}^{H_2O}$ nm: 268, $\lambda_{max}^{0.05N\ NaOH}$ nm: 268. The product showed a single UV absorbing spot on PE ($M_{5'\text{-AMP}}^{7}$ = 0.57), but ^1H NMR spectrum (D_2O) revealed that the product was a mixture of methyl (6a) and ethyl (6b) esters of adenosine- 8-phosphonic acid in a ratio of 2:1. δ: 8.22 (1H, s, H-2), 6.59 (0.3H, d, H-1' of 6b), 6.55 (0.7H, d, H-1' of 6a), 5.08(1H, m, H-2'), 4.52(1H, d, H-3'), 4.34 (1H, br s, H-4'), 4.01 (0.7H, m, $POCH_2CH_3$ of 6b), 3.95 (1H, d, H-5'a), 3.88 (1H, q, H-5'b), 3.66 (1.9H, d, $POCH_3$ of 6a), 1.27 (1H, t, $POCH_2CH_3$ of 6b).

Trifluoroacetate of Diethyl Adenosine-8-phosphonate (7). —— A solution of 5 (4.23 g, 8.00 mmol) in ethanol (60 ml) was saturated with ammonia at 0°. After standing at 10° for 3 days, the mixture was concentrated and chromatographed on a column of Silica gel G (∅4.0 X 30 cm) with a gradient of 5 - 12.5 % EtOH in $CHCl_3$ (3 l). The desired fractions were combined and evaporated to give a crude product (7) (2.13 g, 66 %) as a pale brown caramel, which showed a single UV absorbing spot by TLC ($CHCl_3$ - EtOH =4:1, Rf 0.57). Trifluoroacetic acid (1 ml) was added to a solution of crude 7 (1.00 g, 2.48 mmol) in water (10 ml). The mixture was concentrated to a small volume and triturated with EtOH (3 ml) to give white needles (0.89 g, 70 %). mp 125-127°.

Downloaded At: 09:16 27 January 2011

Anal. Calcd. for $C_{14}H_{22}N_5O_7P\ CF_3COOH\ H_2O$: C, 35.90, H, 4.70, N, 13.08. Found: C, 35.69, H, 4.45, N, 13.08. UV $\lambda_{max}^{0.1N\ HCl}$nm ($\varepsilon$): 270 (17400), $\lambda_{max}^{H_2O}$nm (ε): 280 (13200), 270 (sh, 12300), $\lambda_{max}^{0.1N\ NaOH}$nm ($\varepsilon$): 267 (14700). ^{1}H NMR (DMSO-d_6 + D_2O) δ: 8.35 (1H, s, H-2), 6.38 (1H, d, $J_{1',2'}$= 6.23 Hz, H-1'), 5.01 (1H, t, $J_{2',3'}$= 5.49 Hz, H-2'), 4.15 - 4.25 (5H, m, $POCH_2CH_3$, H-3'), 3.98 (1H, m, H-4'), 3.71(1H, q, $J_{5'a,4'}$= 4.03 Hz, $J_{5'a,5'b}$= 12.09 Hz, H-5'a), 3.55 (1H,q, $J_{5'b,4'}$= 4.39 Hz, H-5'b), 1.32 and 1.29 (each 3H, each t, $POCH_2CH_3$).

Diethyl Inosine-8-phosphonate (9). — Sodium nitrite (690 mg, 10 mmol) was added to a solution of 5 (2.02 g, 3.82 mmol) in 80 % acetic acid (10 ml). The mixture was stirred at room temperature overnight, then evaporated to dryness. The residue was partitioned between water (30 ml) and $CHCl_3$ (50 ml). The organic layer was washed with water (10 ml), dried over $MgSO_4$ and evaporated to afford a caramel (8). UV λ_{max}^{MeOH}nm: 262. Compound 8 was dissolved in methanolic ammonia (30 ml, saturated at 0°) and the solution was kept at room temperature overnight. After concentration to a small volume, the mixture was chromatographed over a column of Silica gel G (Ø 2.7 X 30 cm) with a gradient of 5 - 20% EtOH in $CHCl_3$ (1 l) to give white needles (663 mg, 43 %). mp 143 - 147°. Anal. Calcd. for $C_{14}H_{21}N_4O_8P$: C, 41.59, H, 5.23, N, 13.86. Found: C, 41.15, H, 5.07, N, 13.60. UV: $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 262 (14400), $\lambda_{max}^{H_2O}$nm (ε): 262 (14400), $\lambda_{max}^{0.1N\ NaOH}$nm ($\varepsilon$): 260.5 (12600), 275 (sh, 11000). ^{1}H NMR (DMSO-d_6) δ: 12.70 (1H, br s, N^1-H), 8.21 (1H, s, H-2), 6.33 (1H, d, $J_{1',2'}$= 5.86 Hz, H-1'), 5.36 (1H, d, $J_{2'OH,2'}$= 6.23 Hz, H-2'OH), 5.18 (1H, d, $J_{3'OH,3'}$= 4.39 Hz, H-3'OH), 4.97 (2H, m, H-2, H-5'OH), 4.12 - 4.22 (5H, m, $POCH_2CH_3$, H-3'), 3.92 (1H, m, H-4'), 3.69 (1H, m, H-5'a), 3.55 (1H, m, H-5'b), 1.31 and 1.28 (each 3H, t, $POCH_2CH_3$).

Diethyl 2',3',5'-Tri-O-acetylguanosine-8-phosphonate (11). — Triethyl phosphite (20 ml) was added to a suspension of 8-bromo-2',3',5'-tri-O-acetylguanosine (10) (4.00 g, 8.20 mmol) in acetonitrile (250 ml). The mixture was irradiated with stirring at 15° for 7 days. After evapo-

Downloaded At: 09:16 27 January 2011

ration of the solvent, the residue was taken up in a small amount of AcOEt and applied over a column of Silica gel G (⌀4.5 X 20 cm) with a gradient of 0 - 5% MeOH in AcOEt (2 l) to obtain a foam (1.67 g, 37 %). UV $\lambda_{max}^{0.05N\ HCl}$ nm: 268, λ_{max}^{MeOH}nm: 268.5, $\lambda_{max}^{0.05N\ NaOH}$nm: 290. ^{1}H NMR ($CDCl_3$) δ: 6.73 (2H, br s, NH_2), 6.55 (1H, d, H-1'), 5.8 - 6.2 (2H, m, H-2', H-3'), 4.33 (2H, br s, H-5'), 3.9 - 4.5 (5H, m, H-4', $POCH_2CH_3$), 2.10 (6H, 2'- and 3'-Ac), 2.00 (3H, s, 5'-Ac), 1.35 (6H, t-like, $POCH_2CH_3$).

Diethyl Guanosine-8-phosphonate (12). —— A solution of 11 (1.67 g, 3.06 mmol) in methanolic ammonia (30 ml, saturated at 0°) was kept at room temperature overnight. After evaporation of the solvent, the residue was triturated with a small amount of water to give a white solid, which was recrystallized from water to yield white needles (770 mg, 60 %). mp 264 - 266°. Anal. Calcd. for $C_{14}H_{22}N_5O_8P$: C, 40.10, H, 5.29, N, 16.70. Found: C, 40.15, H, 5.14, N, 16.61. UV: $\lambda_{max}^{0.1N\ HCl}$nm ($\varepsilon$): 270 (18500), $\lambda_{max}^{H_2O}$nm (ε): 270 (18900), $\lambda_{max}^{0.1N\ NaOH}$nm ($\varepsilon$): 280 (14100), ^{1}H NMR (DMSO-d_6) δ: 10.91 (1H, s, N^1-H), 6.58 (2H, br s, NH_2), 6.14 (1H, d, $J_{1',2'}$= 5.86 Hz, H-1'), 5.28 (1H, d, $J_{2'OH,2'}$= 6.22 Hz, H-2'OH), 4.93 - 4.98 (3H, m, H-3'OH, H-5'OH, H-2'), 4.19 (1H, m, H-3'), 4.12 (4H, sestet, $POCH_2CH_3$), 3.85 (1H, q-like, H-4'), 3.68 (1H, m, H-5'a), 3.54 (1H, m, H-5'b), 1.29 and 1.25 (each 3H, each t, $POCH_2CH_3$).

Acknowledgments

The authors are grateful to Emeritus Professor Y. Mizuno of Hokkaido University for his helpful suggestions. Thanks are also due to the staff of the Central Analysis Room of our university for elemental analyses.

REFERENCES

1. M. Honjo, T. Maruyama, M. Horikawa, J. Balzarini and E. De Clercq, Chem. Pharm. Bull., 35, 3227 (1987).
2. J. B. Plumb, R. Obrycki, and C. E. Griffin, J. Org. Chem., 31, 2455 (1966).

Downloaded At: 09:16 27 January 2011

3. a. I. Saito, S. Ito and T. Matsuura, J. Am. Chem. Soc., 100, 2901 (1978). b. I. Saito, S. Ito, T. Shinmura and T. Matsuura, Tetrahedron Lett., 21, 2813 (1980).
4. H. Tanaka, Y. Uchida, M. Shinozaki, H. Hayakawa, A. Matsuda and T. Miyasaka, Chem. Pharm. Bull., 31, 787 (1983).
5. N. Công-Danh, J.-P. Beaucourt and L. Pichat, Tetrahedron Lett., 2385 (1979).
6. A. Hampton, J. Amer. Chem. Soc., 83, 3640 (1961).
7. Ratio of the migration distance of the sample to that of adenosine 5'-monophosphate (5'-AMP).

Received September 10, 1987.

Downloaded At: 09:16 27 January 2011