Commun. Fac. Sci. Univ. Ank. Series B
V. 38. pp. 9–14 (1992)

SYNTHESIS OF 5′-SUBSTITUTED DERIVATIVES OF URIDINE

A. F. SAYED AHMED

Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt.

(Received Oct. 15, 1991; Accepted Sept. 11, 1992)

ABSTRACT

Synthesis of 5'–substituted, 2', 3'–O–sulphinyluridine derivatives followed by the conversion of such derivatives into their corresponding 2, 2'-anhydronucleosides subsequent formation of the related 2'–chloro 2'–bromo and 2–hydroxy derivatives of these compounds were accomplished.

INTRODUCTION

One of the most distinctive structural features of tRNAs (transfer ribonucleic acids) is the presence of a significant proportion of post–transcriptional modifications of the common nucleosides U, A, C, G[1,2,3]. The number and structural variety of hypermodified nucleosides is rather large. Many unidentified nucleosides have been found in sequenced tRNAs. Hypermodified derivatives of uridine are located in the first "wobble" position of the anticodon loop. Thus, the importance of a given modification is not necessarily related to the chemical nature of functional groups but rather to the interplay of these groups to produce and define a standard conformation or dynamics existing between limited number of conformers[4,5].

The synthesised nucleosides could be considered as strong centres of a chelation due to the presence of the amino acid residue in their structures as will be shown later and expected to have a biological importance.

RESULTS AND DISCUSSION

Considering general aspects of the mechanism of S_N2 displacement, one can assume that bulky 5′–chloro 5′–deoxy, 2′, 3′–O–sulphinyluridine should be a good reagent for the preparation of N–monosubstituted derivatives of amines.

Commercially available uridine was utilized as starting material for the synthesis of 5′–chloro–5′–deoxy, 2′, 3′–O–sulphinyluridine[6] in a suitable yield. The latter compound was subsequently used for a series of condensations with tert–butyl glycine ester, L–proline and phenylalanine. It is important to mention, that the tert–butyl group is often used for the protection of the amino acid carboxyl function and can be easily removed by the action of 1N HCl at the room temperature[2]. Such conditions do not lead to degradation of N–glycosidic bond of the pyrimidine nucleosides[8]. 5′–chloro–5′–deoxy–2′,3′–O–sulphinyluridine was condensed with tert–butyl glycinate, L–proline and phenylalanine. The mixture of products were separated on silica gel column, using chloroform–acetone gradient for elution. Consequently, compounds I, II, III afforded the 2′,2′ anhydro nucleosides[9] IV, V, VI when heated with imidazole in dimethylformamide. The anhydronuclosides IV, V, VI could be converted into the corresponding 2′–chloro derivatives VII, X, XIII on heating with hydrogen chloride in dimethylformamide at 90°C.

Similarly the corresponding 2′–bromo derivatives VIII, XI, XIV were obtained on heating of such cyclonucleosides with hydrogen bromide in dimethylformamide at 90°C. It is important that the reactions of these anhydronucleosides IV, V, VI with one equivalent sodium hdyroxide solution yielded the corresponding 5′–substituted ribofuranosyl derivatives IX, XII, XV.

EXPERIMENTAL

Melting points: uncorrected.

Mass spectra were recorded using the apparatus GCMS LKB 2091 (at 15 eV).

^{1}HNMR spectra: varian GEM–200 MHz TMS as internal reference (chemical shift in δ scale), DMSO as a solvent.

IR spectra (KBr): Unicam SP 1200.

5′–chloro–5′deoxy–2′,3′–O–sulphinyluridine[6] and tert–butyl glycinate[10] were prepared as in literature.

Synthesis of Compounds I, II, III:

Three portions of 5′–chloro–5′–deoxy–2′,3′–O– sulphinyluridine (878 mg, each 3 mmol) were reacted successively with tert–butyl glycinate

(393 mg, 3 mmol), L–proline (348 mg, 3 mmol) and phenylalanine (495 mg, 3 mmol) in 10 ml dimethylformamide at 60°C for 4 hours. Chromatography of mother liquors on a silica gel column, system chloroform–acetone (9:1 v / v) yielded the compounds I, II, III.

Compound I m.p. 154°C (yield 42 %, 487 mg) $C_{15}H_{21}O_8N_3S$ calculated 44.66 % C, 5.21 % H, 10.42 % N, 7.94 % S. Found 44.82 % C, 5.21 % H, 11.16 % N, 8.14 % S. Mass spectrum: m / e 403 (M^+). ^{1}HNMR spectrum: 7.96 (s, 1H, H_5), 7.48 (s, 1H, H_6), 6.18 (d, J = 2Hz, 1H, H1,), 4.61 (s, 2H, CH_2N–), 4.42 (s, 2H, NCH_2), 1.42 (s, 9H,–$C(CH_3)_3$). IR spectrum (KBr): 3210 cm^{-1} (NH), 1695 cm^{-1} (C = O) 1620 cm^{-1} (C = C).

Compound II m.p. 143°C (yield 35 %, 355 mg), $C_{14}H_{17}O_8N_3S$ calculated, 43.41 % C, 4.39 %H, 10.89 %N, 8.29 %S found 44.86 %C, 4.62 %H, 10.26 %N, 8.51 %S. Mass spectrum: m /e 387 (M^+). ^{1}HNMR spectrum 7.84 (s, 1H, H_5), 7.36 (s, 1H, H_6), 5.95 (br.s 1H, $H_{1,}$), 5.21 (s, 2H, –CH_2N–). IR spectrum (KBr): 3420 cm^{-1} (OH), 3185 cm^{-1} (NH), 1680 cm^{-1} (C = O).

Compound III. m.p. 148°C (yield 38 %, 480 mg), $C_{18}H_{19}O_8N_3S$ calculated 49.42 % C, B4.34 %H, 9.61 %N, 7.32 %S, found 50.1 %C, 4.8 %H, 9.86 %N, 7.78 %S. Mass spectrum: m /e 437 (M^+) ^{2}HNMR spectrum. 7.87 (s, 1H, H_5), 7.42 (s, 1H, H_6), 7.21 (m, 5H, aromatic), 5.78 (br.s 1H, H1,), 4.81 (s, 2H, –CH_2N–). IR spectrum (KBr): 3480 cm^{-1} (OH), 3192 cm^{-1} (NH), 1690 cm^{-1} (C = O).

Synthesis of the Anhydronucleosides IV, V, VI:

Solutions from compounds (I), (774 mg, 2 mmol), (II) (742 mg, 2 mmol), (III), (842 mg, 2 mmol) were individually reacted with imidazole (140 mg) in dimethylformamide (10 ml) at 150°C for 2h. Dimethylformamide was evaporated in vacuo. The residues were chromatographed on silica gel column, system chloroform–acetone (9:1 v / v) to give the following compounds IV, V, VI.

Compound IV m.p. 191°C (yield 74 %, 478 mg), $C_{15}H_{21}O_6N_3$ calculated 53.09 % C, 6.19 %H, 12.39 %N, found 52.68 %C, 6.8 %H, 13.2 %N. Mass spectum: m /e 339 (M^+). ^{1}HNMR spectrum: 8.02 (s, 1H, H_5), 7.72 (s, 1H, H_6), 5.95 (d, J = 2Hz, 1H, H1,), 4.65 (s, 2H, –CH_2N–), 4.38 (s, 2H, –NCH_2–), 1.32 (s, 9H, –$C(CH_3)_3$). IR spectrum (KBr), 3190 cm^{-1} (NH), 1690 cm^{-1} (C = O), 1625 cm^{-1} (C = C).

Compound V m.p. 174°C (yield 62 %, 380 mg), $C_{14}H_{17}O_6N_3$ calculated 52.0 %C, 5.26 %H, 13.0 %N, found 52.12 %C, 5.68 %H, 12.98 %N. Mass spectrum: m/e 323 (M^+). ^{1}HNMR spectrum 7.91 (s, 1H, H_5), 7.81 (s, 1H, H_6), 5.87 (br.s, 1H, H1,), 4.85 (s, 2H, $-CH_2N-$). IR spectrum (KBr): 3420 cm^{-1} (OH) 3180 cm^{-1} (NH). 1685 cm^{-1} (C = O).

Compound VI m.p. 181°C, (yield 76 %, 542 mg), $C_{18}H_{19}O_6N_3$ calculated 57.93 %C, 5.09 %H, 11.26 %N, found 58.28 %C, 5.46 %H, 11.21 %N. Mass spectrum: m/e 373 (M^+). ^{1}HNMR spectrum: 7.98 (s, 1H, H_5), 7.52 (s. 1H, H_6), 7.16 (m, 5H, aromatic) 5.75 (br.s, 1H, H1,), 4.72 (s, 2H, $-CH_2N-$). IR spectrum (KBr): 3450 cm^{-1} (OH), 3190 cm^1 (NH), 1690 cm^{-1} (C = O).

Synthesis of Nucleosides VII, X, VIII:

Solutions from the anhydronucleosides (IV) (646 mg, 2 mmol), (V) (614 mg, 2 mmol), (VI) (714 mg, 2 mmol) in 7 ml of 10 % hydrogen chloride in dimethylformamide were heated at 90°C for 20 min. Dimethylformamide was evaporated under vacuum. The residues were coevaporated with a mixture of methanol and toluene. Chromatography of the residues on silica gel columns yielded compounds VII, X, XIII.

Compound VII m.p. 163°C, (yield 82 % 589 mg), $C_{15}H_{22}O_6N_3Cl$, calculated 48.38 % C, 5.10 %H, 11.29 %N, 9.42 %Cl, found 48.68 % C, 5.16 %H, 11.29 %N, 9.95 %Cl. Mass spectrum: m/e 372 (M^+). ^{2}HNMR spectrum: 7.98 (s, 1H, H_5), 7.45 (s, 1H, H_6), 5.79 (br.s, 1H, H1,), 4.68 (s, 2H, $-C\underline{H}_2N$), 4.45 (s, 2H, $-N-C\underline{H}_2$), 1.42 (s, 9H, $-C(CH_3)_3$. IRspectrum (KBr): 3385 cm^{-1} (+wH), 3192 cm^{-1} (NH), 1690 cm^{-1} (C = O), 716 cm^{-1} (C–Cl).

Compound X m.p. 156°C (yield 76 %, 522 mg), $C_{14}H_{18}O_6N_3Cl$ calculated 46.79 %C, 5.01 %H, 11.69 %N, 9.75 %Cl, found 46.2 %C, 5.14 % H, 12.33 % N, 10.42 % Cl. Mass spectrum: m/e 359 (M^+). ^{1}HNMR spectrum 7.82 (s, 1H, H_5), 7.26 (s, 1H, H_6), 5.92 (d, J = 2Hz, 1H, H1,), 4.52 (s, 2H, $-C\underline{H}_2-N$).

Compound XIII m.p. 151°C (yield 84 %, 690 mg), $C_{18}H_{20}O_6N_3Cl$ calculated 52.83 %C, 4.89 %H, 10.26 %N, 8.53 %Cl, found 52.72 %C, 5.22 % H, 10.74 %N, 9.14 % Cl. Mass spectrum: m/e 409 (M^+). ^{1}HNMR spectrum: 8.01 (s, 1H, H_5), 7.81 (s, 1H, H_6), 7.22 (m, 5H, aromatic), 5.72 (br.s, 1H, H1,), 4.53 (s, 2H, $-CH_2N-$). IR spectrum: 3350 cm^{-1} (OH), 3198 cm^{-1} (NH), 1690 cm^{-1} (C = O), 715, cm^{-1} (C–Cl).

Synthesis of Nucleosides VIII, XI, XIV:

Solutions from the 2',2' anhydro derivatives (IV) (646 mg, 2 mmol), (V), (614 mg, 2 mmol), (VII), (714 mg, 2 mmol) in 5 ml of 1M hydrogen bromide in dimethylformamide were heated at 90°C for 15 min. The residues were chromatographed on columns of silica gel in chloroform–acetone to yield compounds VIII, XI, XIV.

Compound VIII, m.p. 182°C. (yield 78 %, 530 mg), $C_{15}H_{22}O_5N_3Br$ calculated 44.55 %C, 5.44 %H, 10.39 %N, 19.8 %Br, found 45.12 % C, 5.23 %H, 10.45 %N, 20.1 %Br. Mass spectrum: m/e 404 (M^+). ^{2}HNMR spectrum 4.54 (s, 2H, $-C\underline{H}_2N$), 4.21 (s, 2H, $-NC\underline{H}_2$), 1.32 (s, 9H, $-C(CH_3)_3$). IR spectrum (KBr): 3475 cm^{-1} (OH), 3195 cm^{-1} (NH), 1690 cm^{-2} (C = O).

Compound XI, m.p. 157°C (yield 65 %, 505 mg), $C_{14}H_{18}O_5N_3Br$ calculated 43.29 %C, 4.63 %H, 10.82 %N, 20.06 %Br, found 43.63 %C, 4.82 %H, 10.64 %N, 20.25 %Br. Mass spectrum: m/e 388 (M^+). ^{1}HNMR spectrum 7.87 (s, 1H, H_5), 7.36 (s. 1H, H_6), 5.82 (br.s, 1H, H1,), 4.58 (s, 2H, $-CH_2N-$). IR spectrum (KBr): 3395 cm^{-1} (OH), 1670 cm^{-1} (C = O), 1630 cm^{-1} (C = C).

Compound XIV, m.p. 164°C, (yield 67 %, 587 mg), $C_{18}H_{20}O_5N_3Br$ calculated 49.31 %C, 4.56 %H, 9.58 %N, 18.26 %Br, found 50.1 %C, 4.38 %H, 9.29 %N, 18.52 %Br. Mass spectrum: m/e 438 (M^+). ^{1}HNMR spectrum: 7.24 (m, 5H, aromatic), 7.48 (s, 1H, H_6), 4.62 (s, 2H, $-C\underline{H}_2N-$). IR spectrum (KBr): 3250 cm^{-1} (OH), 1680 cm^{-1} (C = O), 1665 cm^{-1} (C = C).

Synthesis of Compounds IX, XII, XV:

Solutions from the anhydronucleosides IV (969 mg, 3 mmol), (V), (921 mg, 3 mmol), (VI) (1.07 gm, 3 mmol) in 0.1M sodium hydroxide (35 ml) were stirred at room temperature for 3 hr and then neutralized with Dowex 50 H^+. The resins were filtered off and washed with water. The combined filtrates were evaporated under vacuo. Crystallization of the residues from ethanol yielded compounds IX, XII, XV.

Compound IX, m.p. 189°C (yield 62 %, 687 mg), $C_{15}H_{23}O_6N_3$ calculated 52.78 %C, 6.74 %H, 12.31 %N. Found 52.36 %C, 6.86 %H, 12.54 %N. Mass spectrum: m/e 341 (M^+). ^{1}HNMR spectrum: 7.85 (s, 1H, H_5), 7.48 (s, 1H, H_6), 6.18 (d, J = 2Hz, 1H, H1'), 4.62 (s, 2H, $-C\underline{H}_2-N$), 4.32 (s, 2H, $-N-C\underline{H}_2$), 1.28 (s, 9H, $-C(CH_3)_3$. IR spectrum (KBr): 3420 cm^{-1} (OH), 3230 cm^{-1} (NH), 1680 cm^{-1} (C = O).

Compound XII, m.p. 171°C (yield 64 %, 624 mg), $C_{14}H_{19}O_6N_3$ calculated 51.69 %C, 5.84 %H, 12.92 %N. Found 51.42 %C, 5.79 %H, 13.18 %N. Mass spectrum: m/e 325 (M^+). ^{1}HNMR spectrum: 8.06 (s, 1H, H_5), 7.26 (s, 1H, H_5), 6.08 (br.s, 1H, H1,), 4.68 (s, 2H, $-C\underline{H}_2N$). IR spectrum (KBr): 3390 cm^{-1} (OH), 3220 cm^{-1} (–NH), 1670 cm^{-1} (C = O).

Compound XV, m.p. 182°C, (yield 56 %, 573 mg), $C_{18}H_{21}O_6N_3$ calculated 57.6 %C, 5.6 %H, 11.2 %N. Found 57.8 %C, 5.42 %H, 11.38 %N. Mass specytrum: m/e 375 (M^+). ^{1}HNMR spectrum: 7.92 (s, 1H, H_5), 7.48 (s, 1H, H_6), 7.21 (p, 5H, aromatic), 5.82 (br.s, 1H, H1,), 4.45 (s, 2H, $-C\underline{H}_2N-$). IR spectrum (KBr): 3420 cm^{-1} (OH), 318 cm^{-1} (NH), 1690 cm^{-1} (C = O).

REFERENCES

1. McCLOSKEY, J.A., NISHIMURA, S., Acc. Chem. Res., 10, 403 (1977).

2. NISHIMURA, S., Modified Nucleosides in tRNA (TRANSFER RNA): Structural properties and recognition, eds., Schimmel P.R., SOLL D., Abelson J.N., Cold Spring Harber Laboraratory, P. 59 (1979).

3. BARCISZEWSKI, J., RAFALSKI, J., Atlas of tRNA and modified nucleosides, Polish Scientific Publishers, Warsaw–Paznan', (1981).

4. ADAMIAK, R., GORNICKI, R., Prog. Nucl. Ac. Res. Mol. Biol., 32, 27 (1985).

5. GROSJEAN, H., HAUSSIER, C., CEDERGREN, R., Three dimensional structure and dynamics of ribonucleic acids, NATO Advances Research Workshop, Renesse, The Netherlands (1985).

6. HREBABECKY', H., BERANEK., Nucleic Acids Res., 5, 1029 (1978).

7. BODANSZKY, M., BODANSKY, A., "The practice of peptide synthesis", Academic–Verlag, Berlin (1985).

8. MATKIEWICZ, A., SOCHACKA, E., Tetrahedron Lett., 48, 5387 (1983).

9. HREBABECKY', H. and BERANEK, J., Collection Czechoslov. Chem. Commun, 43, 3268 (1978).

10. CHIMIAK, A., KOLASA, T., BIERNAT, J.F., Z. Chem., 12, 264 (1972). Taschner E. Wasielewski C., Biernat J.F., Ann., 646, 119 (1961).