Vol. 1, No.3
Spring, 1990

J.Sci.I.R.Iran

THE ROLE OF CHLOROMETHYL ETHERS IN THE FORMATION OF N(7) – AND N(9)-ALKYLATED ISOMERS OF ADENINE SYNTHESIS OF 2-[9-(ETHOXYMETHYL) ADENYL] PHOSPHONATE

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Abstract

The structural features of chloromethyl ethers are shown to have a significant effect on the formation of N(7)- or N(9)- alkylated isomers of purine acyclo-nucleosides. The chemical synthesis of 2-[9-(ethoxymethyl) adenyl] phosphonate is described. This compound is active against herpesviruses.

Introduction

Coupling condensation of chloromethyl ethers with purines are known to afford the corresponding nucleosides or nucleoside analogues as a mixture of N(7)- and N(9)-alkylated products [1]. However, the exclusive preparation of one isomer has been reported from time to time [2-4].

As a general rule the N(7)-alkylated isomer of purines absorbs in the UV at a higher wavelength than its corresponding N(9)-alkylated product [1-6]. But, sometimes the existing contradiction makes their differentiation difficult [7-8]. Although, it is reasonable to assume that the nucleobases are responsible for the formation of the isomeric mixtures of acyclonucleosides, in this paper we wish to clarify that the structural features of chloromethyl ethers have a marked effect on the formation of N(7)- or N(9)-alkylated isomers of purines.

Results and Discussion

Treatment of compounds **1a–e** with para-formaldehyde gave the corresponding chloromethyl ethers **2a–e** by means of HCl in CH_2Cl_2. Condensation of **2a–b** with 6-chloropurine (11a) in the presence of NEt_3 in DMF gave the corresponding N(9)-alkylated products **3a–b** (~95%). Similarly **2c** was condensed with **11a** to afford the respective N(9)-alkylated isomer **3c** (35%) and N(7)-alkylated product **4c** (62%). Finally, when **2d–e** was reacted with **11a** in the same manner, the N(7)-alkylated isomer **4d–e** (~90%) were the exclusively formed products.

The chemical structure of the above purine acyclonucleosides were unambiguously determined by the following transformations. The first approach in the structural determination of **3a–b** was their conversion to 3,9-(ethanoxymethano) adenin-3-ium halide (**7a–b**) via intermediates **3a′–b′**. Reaction of **3a** with NH_3/MeOH in a pressure bottle at 100°gave **5a** (98%) after 48h. Similar treatment at 25° resulted in adenine compounds **5a** (3%), **7a** (10%) and 6-methoxypurine derivative **6a** (60%). It should be noted that compound **6a** was also converted to **5a** at 100° in a pressure bottle containing NH_3/MeOH. Since the high yield transformation of 3a→[3a^1]→7a failed in MeOH, it was decided to carry out the reaction in CH_3CN. Thus, treatment of **3a** with NH_3/CH_3CN at 25° gave **5a** (40%), 7a (10%), and **8a** (5%) after 48h. When the above reaction was repeated in NH_3/CH_3CN, HOH (15:15), compounds **5a** (16%) and **7a** (60%) were obtained. Having considered that the displacement of the bromine atom in **3a** occurs by an solvent polarity independent SN_2 reaction and the replacement of the chlorine atom in 6-chloropurine moiety of **3a** occurs via a solvent dependent polar

Key words: Chloromethyl Ethers, Nucleosides

transition state, it occured to us that the reaction of **3a** in NH_4OH might result in exclusive production of **7a**. Therefore **3a** was suspended in NH_4OH (1g/40ml) at 25°. After 48h compound **7a** was the exclusively formed product. Compound **3b** was similarly transformed to**7b** (96%). An alternative route to the preparation of **7a** is the following. Compound **3a** was transformed to **9a** by means of NaN_3 in DMF at 25°. Aminolysis of the azide function results in the formation of **7a** (60%). Reaction of **7a–b** with NaN_3 in refluxing DMF gave **10a** in about 70% yield.

At this point we turned our attention to the structural confirmation of compounds **3c** and **4c–e**. Compound **3c** was converted to **5c** (99%) by means of NH_3/MeOH at 25°. As described above **4c–d** were also transformed to **6c** (~95%). Catalytic hydrogenation of **4e** also afforded **6c** (85%). Independent reaction of **5c** and **6c** with p-toluenesulfonyl chloride in CH_3CN and the subsequent displacements of the tosylate functions with NaN_3 in DMF at 80° gave the corresponding acyclo-nucleosides **10a** and **10b** in about 75% yield.

Having established the importance of chloromethyl ethers in governing the formation of N(7)- and N(9)-alkylated isomers of acyclo-nucleosides, we next attempted to examine the role of purines in preparation of the aforementioned isomers.

Treatment of 6-chloropurine (11a) with NaN_3 in DMF at 25° gave 11b (90%) after 20h. Reaction of **11a** with NaOMe in MeOH at reflux temperature afforded **11c** (98%) after 4h. Separated reactions of **11b-c** with **2d** in DMF using NEt_3 gave the corresponding N(7)-alkylated products **13b–c** (~62%), which in turn were converted to **6c** (~80%) by NH_3/MeOH at 100° after 44h. Since compounds **11b–c**, like **11a**, were reacted with **2d** to afford N(7)-alkylated product **6c**, it was decided to react **11b–c** with **2a** in order to see the stereochemistry of the resulting products. Treatment of **11b–c** with chloromethyl ether **2a** in the presence of NEt_3 in DMF gave the respective N(9)-alkylated products **9a** and **6a** (~85%), which in turn were transformed to the corresponding products **12b–c** by means of KOH/18-crown-6 in DMF at 68°. Compounds **12b–c** were transformed to **5c** using NH_3/MeOH at 100° after 50h.

The above results clearly indicate the lack of significance of purines in preparation of isomers. However, the structural features of chloromethyl ethers are shown to be responsible for the formation of N(7)- and N(9)-alkylated isomers of purine acyclo-nucleosides. It should be noted that a novel procedure, independent of the nature of the chloromethyl ethers, for the exclusive preparation of N(9)-alkylated isomer of purines and N(1)-alkylated product of pyrimidines are recently reported [3,7]. We next decided to prepare 2-[9-(ethoxymethyl) adenyl] phosphonate (15) from **6a** and to study its behavior toward herpesviruses. 5′-deoxynucleoside - 5′ - phosphonate **15** which contain a 5′-C-P in place of the 5′–C–O–P bond of the naturally occuring nucleotides may be of some biochemical interest because of their structural resemblance to nucleotides on the one hand and their possible resistance to the action of the nucleolytic enzymes on the other.

Arbuzov reaction [9] of **6a** with triethyl phosphite yielded the phosphonic acid diester **14** (20%). Treatment of **14** with NH_3/MeOH in a pressure bottle at 100° afforded **15** (15%) after 58h. It should be noted that the reactions of **3a–b**, **7a–b**, and **9a** with $P(OMe)_3$, $P(OEt)_3$ and $HPO(OEt)_2/k^+O^-$ + failed and resulted in destruction of the starting materials.

Compound **15** exhibits an excellent antiviral activity *in vivo* against herpes-virus-type-1 (HSV-1), herpes-virus-type-2(HSV-2), and herpes-zoster.

Experimental Section

General Remarks. See [13].

General Procedure for the Preparation of Chloromethyl Ethers: Compounds 2a–e. Representative procedure: Bromoethanol (12.5 g,0.1 mol) was added to CH_2Cl_2 (50 ml) followed by para-formaldehyde (5 g).The reaction mixture was cooled in an ice bath and HCl gas was bubbled through the stirred solution for 8h. Anhydrous $CaCl_2$ was then added and after stirring for 30 min. the solution was collected by filtration. The filtrate was evaporated at reduced pressure and **2a** (95%) was distilled at 95°/5 Torr. ^1H–NMR (CCl_4): 3.50 (t,2H,CH_2Br); 3.99 (t,2H,CH_2O); 5.50 (s,2H,OCH_2Cl).

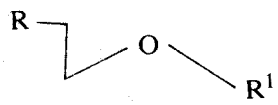
2b: Distilled at 95°/8 Torr (96%). ^1H–NMR (CCl_4): 3.50–4.1 (m, 4H, OCH_2CH_2Cl); 5.50 (s, 2H, OCH_2Cl).

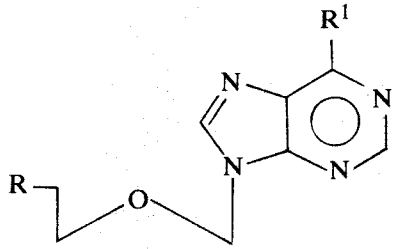
2c: Distilled at 95°/10 Torr (90%). ^1H–NMR (CCl_4): 2.01(s,3H,CH_3); 3.70-3.91 (m,2H,CH_2O); 4.06-4.31 (m,2H,CH_2OAc); 5.49 (s,2H,OCH_2Cl). IR (neat): 1720 (ester).

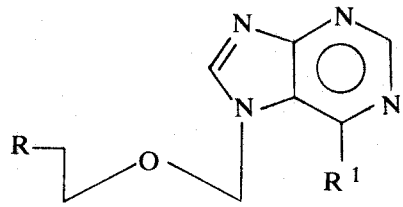
2d: Silica gel/CCl_4 (50%). ^1H–NMR (CCl_4): 3.50-3.90 (m,2H,CH_2O); 4.41-4.75 (m,2H,CH_2OBz); 5.50 (s,2H,OCH_2Cl) 7.31-8.18 (m,5H,Ph). IR (neat): 1725 (ester).

2e: Silica gel/CCl_4 (31%). ^1H–NMR (CCl_4): 3.60-4.01 (m,4H,OCH_2CH_2O); 4.56 (s,2H,CH_2Ph); 5.51 (s,2H,OCH_2Cl); 6.81-7.80 (m,5H,Ph).

General Procedure for the Condensation of Chloromethyl Ethers with Purines: Compounds 3a–c, 4c–e, 6a, 9a, and 13b–c. Representative Procedure:







1a R=Br ,R^1=H

1b R=Cl ,R^1=H

1c R=OAc ,R^1=H

1d R=OBz ,R^1=H

1e R=OBzl ,R^1=H

2a R=Br ,R^1=CH_2Cl

2b R=Cl ,R^1=CH_2Cl

2c R=OAc ,R^1=CH_2Cl

2d R=OBz ,R^1=CH_2Cl

2e R=OBzl ,R^1=CH_2Cl

3a R=Br ,R^1=Cl

3b R=Cl ,R^1=Cl

3c R=OAc ,R^1=Cl

3a^1 R=Br ,R^1=NH_2

3b^1 R=Cl ,R^1=NH_2

5a R =NH_2 R^1=NH_2

6a R=Br, R^1=OMe

8a R=NH_2, ,R^1=Cl

9a R=Br R^1=N_3

5c R=OH, R^1=NH_2

10a R=N_3, R^1=NH_2

12b R=OH, R^1=N_3

12c R=OH, R^1=OMe

4c R=OAc, R^1=Cl

4d R=OBz, R^1=Cl

4e R=OBz^1, R^1=Cl

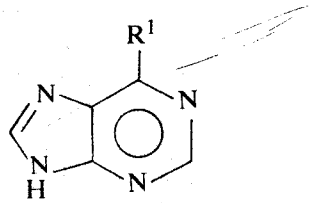
5b R=OBz^1, R^1=NH_2

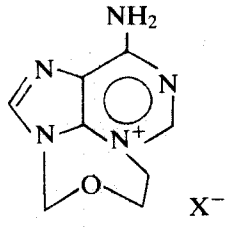
6c R=OH, R^1=NH_2

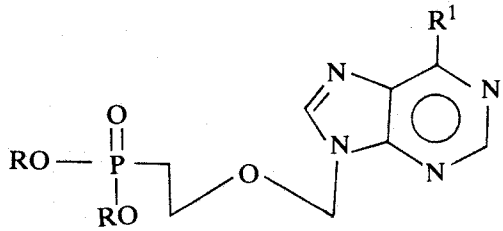
10b R=N_3, R^1=NH_2

13b R=OBz, R^1=N_3

13c R=OBz, R^1=OMe







11a R^1=Cl

11b R^1=N_3

11c R^1=OMe

7a X=Br

7b X=Cl

14 R=Et, R^1=OMe

15 R=H, R^1=NH_2

6-chloropurine (4.5 g, 0.03 mol) was dissolved in DMF (50 ml) and NEt_3 (3.5 g) was added. The solution was cooled in an ice bath and **2a** (0.03 mol) was added. After 1 h the mixture was removed from the ice bath and stirred at 25° for 13 h. The solution was partitioned between AcOEt/H_2O 1:1 (500 ml). The organic layer was then washed with H_2O (5×100 ml), dried (Na_2SO_4), and evaporated to yield 13 g of syrup. Crystallization from MeOH afforded **3a** (75%), m.p. 104-106°. R_f (ether/MeOH 9:1) 0.64. ^{1}H-NMR ($CDCl_3$/DMSO-d_6): 3.39-3.71 (m,2H,CH_2Br); 3.71-3.41 (m,2H,CH_2O); 5.80 (s,2H,OCH_2N); 8.60, 8.70 (2s,2H,H-C(2) and H-C(8)). UV (EtOH): 264 nm.

3b: (96%), foam. R_f (ether/MeOH 9:1) 0.70 ^{1}H-NMR ($CDCl_3$): 3.50-4.01 (m,4H,OCH_2CH_2Cl); 5.75 (s,2H,OCH_2N): 8.40, 8.80 (2s,2H,H-C(2) and H-C(8)). UV (EtOH): 264 nm.

3c: (35%), foam. R_f (ether/MeOH 9:1) 0.48. ^{1}H-NMR ($CDCl_3$): 2.10 (s,3H,CH_3); 3.61-3.95 (m,2H,CH_2O); 4.05-4.31 (m,2H,CH_2OA_3); 5.29 (s,2H,OCH_2N); 8.40, 8.71 (2s,2H,H-C(2) and H-C(8)). IR (neat): 1730 (ester). UV (EtOH): 264 nm.

4c: (62%), foam. R_f (ether/MeOH 9:1) 0.40. ^{1}H-NMR ($CDCl_3$): 1.98 (s,3H,CH_3); 3.61-3.95 (m,2H,CH_2O); 4.05-4.31 (m,2H,CH_2OAc); 5.29 (s,2H,OCH_2N); 8.40, 8.71 (2s,2H,H-C(2) and H-C(8)). IR (neat): 1735 (ester). UV (EtOH): 267 nm.

4d: (90%), oil. R_f (ether/MeOH 9:1) 0.56. ^{1}H-NMR ($CDCl_3$): 3.80-4.10 (m,2H,CH_2O); 4.25-4.60 (m,2H,CH_2OBz); 5.79 (s,2H,OCH_2N); 7.30-8.05 (m,5H,Ph); 8.40, 8.73 (2s,2H,H-C(2) and H-C(8)). UV (EtOH): 267.5 nm.

4e: (93%), oil. R_f (ether/MeOH 9:1) 0.79. ^{1}H-NMR ($CDCl_3$): 3.58-4.00 (m,4H,OCH_2CH_2O); 4.61 (s,2H,CH_2Ph); 5.68 (s,2H,OCH_2N); 7.00-8.10 (m,5H,Ph); 8.40, 8.71 (2s,2H,H-C(2) and H-C(8)). UV (EtOH); 267 nm.

6a: 6-Methoxypurine (11c) was similarly reacted with **2a** to afford **6a** (85%), m.p. 94-95°. R_f (AcOEt) 0.60. ^{1}H-NMR ($CDCl_3$): 3.23-3.65 (m,2H,CH_2Br); 3.65-3.95 (m,2H,CH_2O); 4.00 (s,3H,OCH_3); 5.66 (s,2H,OCH_2N); 8.20, 8.31 (2s,2H,H-C(2) and H-C(8)). UV (EtOH): 249.5 nm.

Treatment of **6a** with KOH/18-crown-6 (1 eq.) in DMF at 68° gave **12c** (40%) after 5h. R_f (AcOEt) 0.37. ^{1}H-NMR spectrum of **12c** is similar to that of **6a** except for OCH_2CH_2O group which shows an A_2B_2 pattern in place of an A_2X_2 pattern for $BrCH_2CH_2O$ in **6a**.

9a: 6-Azidopurine (11b) was treated with **2a** in the same manner to give **9a** (87%), m.p. 196-200° (dec.). R_f (Ether/MeOH 9:1) 0.50. Compound **9a** was also prepared by the reaction of **3a** with NaN_3 using the same method which is decribed for the preparation of **11b** from **11a**. ^{1}H-NMR ($CDCl_3$): 3.30-3.70 (m, 2H, CH_2Br); 3.71-4.01 (m, 2H, CH_2O), 5.70 (s, 2H, OCH_2N); 8.40, 9.20 (2s, 2H, H-C(2) and H-C(8)). UV (EtOH): 274 nm.

Treatment of **9a** with KOH/18-crown-6 in DMF at 68° gave **12b** (30%) after 5h. R_f (AcOEt) 0.26. ^{1}H-NMR spectrum of **12b** is similar to that of **9a** except for variations due to substitutions; OCH_2CH_2O group in **12b** exhibits an A_2B_2 pattern while $BrCH_2CH_2O$ group in **9a** shows an A_2X_2 pattern.

13b: Compound **11b** reacted with **2d** to afford **13b** (62%), foam. R_f (AcOEt) 0.39. ^{1}H-NMR (DMSO-d6): 3.69-3.70 (m,2H,CH_2N_3); 3.72-3.43 (m,2H,CH_2O); 5.80 (s, 2H, OCH_2N); 8.60, 8.80 (2s, 2H, H-C(2) and H-C(8)). UV (EtOH): 278 nm.

13c: Compound **11c** reacted with **2d** to give **13c** (65%), foam. R_f (AcOEt): 0.44. ^{1}H-NMR (Acetone-d6): 3.61-3.90 (m, 2H, CH_2O); 3.91-4.26 (m, 2H, CH_2OBz); 4.10 (s, 3H, OCH_{23}); 5.70 (s,2H,OCH_2N); 7.30-8.11 (m,5H,Ph); 8.12, 8.35 (2s,2H,H-C(2) and H-C(8)). UV (EtOH): 249 nm.

Preparation of Acyclo-nucleosides 5a-8a and 5c-6c. Representative procedure: To a solution of **3a** (0.01 mol) in MeOH (30 ml), 100 ml of saturated NH_3/MeOH was added. The solution was sealed and maintained at 100° for 48 h. The mixture was evaporated and the residue was crystallized from CH_2Cl_2/$CHCl_3$ (1:1) to afford **5a** (98%), m.p. 192-193° (dec.). R_f (MeOH) O.15. ^{1}H-NMR (DMSO-d6): 2.89-3.31 (m, 2H, CH_2N); 3.62-4.01 (m, 2H, CH_2O); 5.70 (s,2H,OCH_2N); 7.10-8.20 (2br. 4h, $2NH_2$, exchanged with D_2O); 8.30, 8.50 (2s,2H,H-C(2) and H-C(8)). UV (EtOH): 260 nm.

When the reaction was carried out at 25° gave **5a** (3%), **7a** (10%), and **6a** (60%).

The above reaction at 25° in CH_3CN gave **5a** (40%), **7a** (10%), and **8a** (5%); spectral data of **8a** was similar to those of **3a** except for variation due to substitution.

5c: Treatment of **3c**, similarly, with NH_3/MeOH at 100° gave **5c** (99%) after 30h, m.p.150°. Lit. [7] m.p. 150°. **12b-c** were converted to **5c** (70%) in the same manner after 50 h.

6c: Compounds **4c-d** were similarly treated with NH_3/MeOH to afford **6c** (95%), m.p. 198.4°. Lit. [2,3] m.p. 198-199°. **13b-c** were transformed to **6c** (80%) in the same manner after 44 h.

5b: Treatment of **4e** with NH_3/MeOH at 100° gave **5b** (90%). Catalytic hydrogenation of **5b** using the described literature procedure [10] afforded **6c**.

Preparation of 6-Methoxypurine (11c). 6-Chloropurine (0.01 mol) was dissolved in MeOH (500 ml) containing (0.015 mol) NaOMe. The mixture was refluxed for 4 h. Conc. HCl solution was added dropwise to have pH 4.5-5. Filtration and evaporation of the filtrate gave **11c** (98%), m.p. 195-196°. Lit. [11] m.p. 195°. R_f (AcOEt) 0.28. ^{1}H-NMR (DMSO-d6/D_2O): 3.98 (s,3H,OCH_3); 8.19, 8.29 (2s,2H,H-C(2) and H-C(8)). UV (EtOH): 249 nm.

Preparation of 6-Azidopurine (11b). 6-Chloropurine (0.01 mol) was dissolved in DMF (50 ml). NaN_3 (0.05 mol) was added and the reaction mixture was stirred at 25° for 20 h. AcOEt (200 ml) and H_2O (330 ml) were added. The organic layer was washed with water (2×100 ml), dried (Na_2SO_4) and evaporated to afford **11b** (90%), m.p. 220°. IR (KBr): 2100 (N_3). Lit. [12] m.p. 223°.

Preparation of 3,9-(Ethanoxymethano) adenin-3-ium Halid (7a-b). Both compounds were obtained by an identical method (~96%). Representative procedure: Compound **3a** (10 g) was suspended in NH_4OH (400 ml). The reaction mixture was stirred for 48 hr at 25°. Filtration gave **7a** as a white precipitate, m.p. 215°. R_f (AcOEt) 0.06. ^{1}H−NMR (DMSO − d6): 3.79 (s,4H,NCH_2CH_2O); 5.67 (s,2H,OCH_2N); 7.68 (br.s, 2H, NH_2 exchanged with D_2O); 8.30 (s,1H,H−C(2)); 8.40 (s,1H,H−C (8)). UV (EtOH): 257.5 nm.

7b: M.P. 225°; identical with the authentic sample [13]. R_f (AcOEt) 0.04. IR (nujol): 3290 (NH_2), 1105 (ether), ^{1}H−NMR (DMSO − d6): 3.75 (s, 4H, NCH_2 CH_2O); 5.61 (s, 2H, OCH_2N); 7.81 (br.s, 2H, NH_2, exchanged with D_2O); 8.32 (s, 1H, H−C(2)); 8.42 (s, 1H, H−C(8)). UV (EtOH): 257nm.

Preparation of 9-[(2-Azidoethoxy) methyl] adenine (10a). To a solution of **7b** (2.27 g, 0.01 mol) in DMF (50 ml), NaN_3 (3.25 g, 0.05 mol) was added. The solution was refluxed for 24 h and then poured into H_2O (200 ml). Filtration of the precipitate and crystallization from H_2O afforded **10a** (70%), m.p. 190-192°. R_f (AcOEt/MeOH 9:1) 0.32. IR (nujol): 3100-3260 (NH_2), 2100 (N_3), 1110 (ether). ^{1}H-NMR (DMSO-d6): 3.59 (m,2H,CH_2N_3); 3.88 (m,2H,CH_2O); 5.79 (s,2H,OCH_2N); 6.81 (br.s, 2H, NH_2, exchanged with D_2O); 7.88 (s,1H,H−C(2); 8.16 (s,1H,H−C(8). UV (EtOH): 260 nm.

Compound **7a** was similarly transformed to **10a** (~70%). Compound **10a** was also prepared by tosylation of the OH function in **5c** [14], followed by replacement of the tosylate with NaN_3 in DMF at 80° after 20 h (see the following procedure).

Preparation of 7-[2-Azidoethoxy) methyl] adenine 10b. Compound **6c** (0.01 mol) was dissolved in DMF/CH_3CN (1:9). P-Toluenesulfonyl chloride (0.01 mol) was added and the reaction mixture was refluxed for 4 h.TLC shows the disappearance of the starting material. The solvents were evaporated and the residue was dissolved in DMF (50 ml) containing (0.05 mol) NaN_3. The reaction mixture was stirred at 80° for 20 h and then poured into H_2O (300 ml). Filtration of the precipitate and crystallization from MeOH gave **10b** (75%), m.p. 250-254°. R_f (AcOEt/MeOH 9:1) 0.15. IR (nujol): 3000-3280 (NH_2), 2100 (N_3), 1115 (ether). ^{1}H-NMR (DMSO−d6): 3.40 (m, 2H, CH_2N_3); 3.70 (m,2H,CH_2O); 5.61 (s,2H,OCH_2N); 7.30 (br.s, 2H, NH_2, exchanged with D_2O); 8.18 (s,1H,H−C(2)); 8.26 (s,1H,H−C(8)). UV (EtOH): 267 nm.

Preparation of 2-Diethyl [9-(ethoxymethyl) 6-methoxypurine] phosphonate (14) and 2-[9-(Ethoxymethyl) adenyl] phosphonate (15). Compound **6a** (5 mmol) and triethyl phosphite (25 mmol) were heated together at 150° for 24 h. After cooling, ether (300 ml) was added and the resulting precipitate was filtered to afford **14** (20%), m.p. 140°. R_f (AcOEt/MeOH 8:2) 0.11. ^{1}H-NMR ($CDCl_3$): 1.10-1.52 (m,8H,2CH_3 and CH_2P); 3.39-4.30 (m,6H,2CH_2OP and CH_2O); 4.15 (s,3H,CH_3); 5.61 (s,2H,OCH_2N); 8.12, 8.41 (2s,2H,H−C(2) and H−C(8)). UV (EtOH): 249 nm.

As described for the preparation of **5a** from **3a**, **14** was converted to **15** (15%), m.p. 296 (dec.). R_f (MeOH): 0.12. ^{1}H-NMR (DMSO-d_6/D_2O): 1.41 (m, 2H, CH_2P); 3.80 (m, 2H, CH_2O); 5.55 (s,2H,OCH_2N); 7.90, 8.19 (2s,2H,H−C(2) and H−C(8)). UV (HOH): 261 nm.

Acknowledgement

This work was supported by the Shiraz University Research Council. We gratefully acknowledge financial support from Radja Chemical and Pharmaceutical Company.

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