Novel Derivatives of 1,3-Dimethyl-5-methylenebarbituric Acid

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Abstract: The ability of the pyridinium adduct of 1,3-dimethyl-5-methylenebarbituric acid (**2**) to undergo nucleophilic substitution reaction has been examined. Various types of nucleophiles, including cyanide, barbiturate, sulfide anions and 1,2-bis(diphenylphosphino)ethane substitute the pyridinium fragment in **2** leading to synthesis of new organic derivatives.

Keywords: 1,3-dimethyl-2,4,6(*1H,3H,5H*)-pyrimidinetrione (1,3-dimethylbarbituric acid), zwitterionic pyridinium adduct, nucleophilic substitution reaction.

INTRODUCTION

Derivatives of 1,3-dimethylbarbituric acid (**1**) play an important role in the pharmaceutical chemistry [1,2]. The condensation of **1** with aqueous formaldehyde solution in pyridine afforded the zwitterionic pyridinium adduct **2**, which was first prepared and characterized by our group [3]. Compound **2** may be considered as an important precursor in organic synthesis since the exocyclic methylene carbon atom exhibits electrophilic properties, which enhance the substitution of a pyridinium fragment with various types of nucleophiles. For example, novel zwitterionic compounds were prepared by reactions of **2** with triphenylphosphine and 2,3-dihydro-1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene to produce 1,3-dimethyl-2,4,6-trioxo-5-triphenylphosphoniomethyl-1,3-perhydrodiazin-5-yl-phosphonium and 1,3-dimethyl-2,4,6-trioxo-5-(1,3-diisopropyl-4,5-dimethylimidazoliomethyl)-1,3-perhydrodiazin-5-yl-imidazoliumylides, respectively, in good yields [3].

Introduction of sulfur atom in the exomethylene fragment of uracil (pyrimidine derivative) was achieved by the reaction of 1-(5-uraciylmethylene)pyridinium chloride or iodide with (4-nitrophenyl)methanethiol in the light to process the resulted formation of the thymine *via* exocyclic methylene intermediate [4]. The concurring displacement of sulfur with cyano group took place by free radical alkylation of 1,3-dimethyluracil with benzoyl peroxide in acetonitrile [5].

Continuing our previous study, this work investigates the ability of pyridinium fragment substitution in **2** using different nucleophiles.

RESULTS AND DISCUSSION

We extended our previous work [3] concerning the synthesis of novel derivatives of 1,3-dimethyl-5-methylene barbituric acid by applying the nucleophilic substitution reaction at the pyridinium fragment in **2**. We examined the reactions of **2** with different types of nucleophiles, including cyanide and sulfide anions, sodium barbiturate and 1,2-bis(diphenylphosphino)ethane. The synthesis of 5,5'-methylene bis-derivatives of uracils by acidic hydrolysis of bis-[4-methylamino-2,6-dioxo-1,3-dimethyltetrahydropyrimidinyl]methane was reported in the literature [6]. In addition, the reduction of 5-arylidene barbiturates by thiols in the presence of triethylamine followed by oxidation process led to the formation of 5-benzyl-5-hydroxy-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrion [7].

Zoorob *et al.* [8] reported a procedure for monoacylation at C5 of 1,3-dimethylbarbituric acid by the reaction of sodium derivatives of barbiturate (act as nucleophiles) with acyl chlorides. This procedure is limited only for sensitive acyl chlorides compounds (act as electrophiles). In addition, the conversion of carbonyl functionality at C5 into a methylene group requires a further reduction step. In contrast, the advantage of the proposed procedure is that a wide range of nucleophiles can react at the electrophilic center of the exo-methylene group under mild conditions in a single step.

Reaction of **2** with sodium cyanide and sodium 1,3-dimethylbarbiturate produced **3** and **4,** respectively, (Scheme **1**). In spite of the localization of negative charge at the cyanide carbon atom or its delocalization at the barbiturate ring, the substitution of the pyridinium occurred readily. The reaction of barbituric acid derivatives and bis(dialkylamino)malononitrile afforded a mixture of salts in which the cyano group is attached directly at the exo-methylene carbon atom of the 5-methylenebarbituric acid [9].

The ^{1}H-NMR spectrum of **4** reveals that the barbiturate ring is connected to the methylene carbon atom of **2** through carbon atom (C5) rather than its oxygen atoms at C4 or C6. Changing the solvent from water to chloroform led to the same result. The neutral barbituric ring in **4** adopted a keto form which was confirmed by DEPT-NMR analysis. It was reported that two symmetrical 1,3-dimethylbarbituric rings

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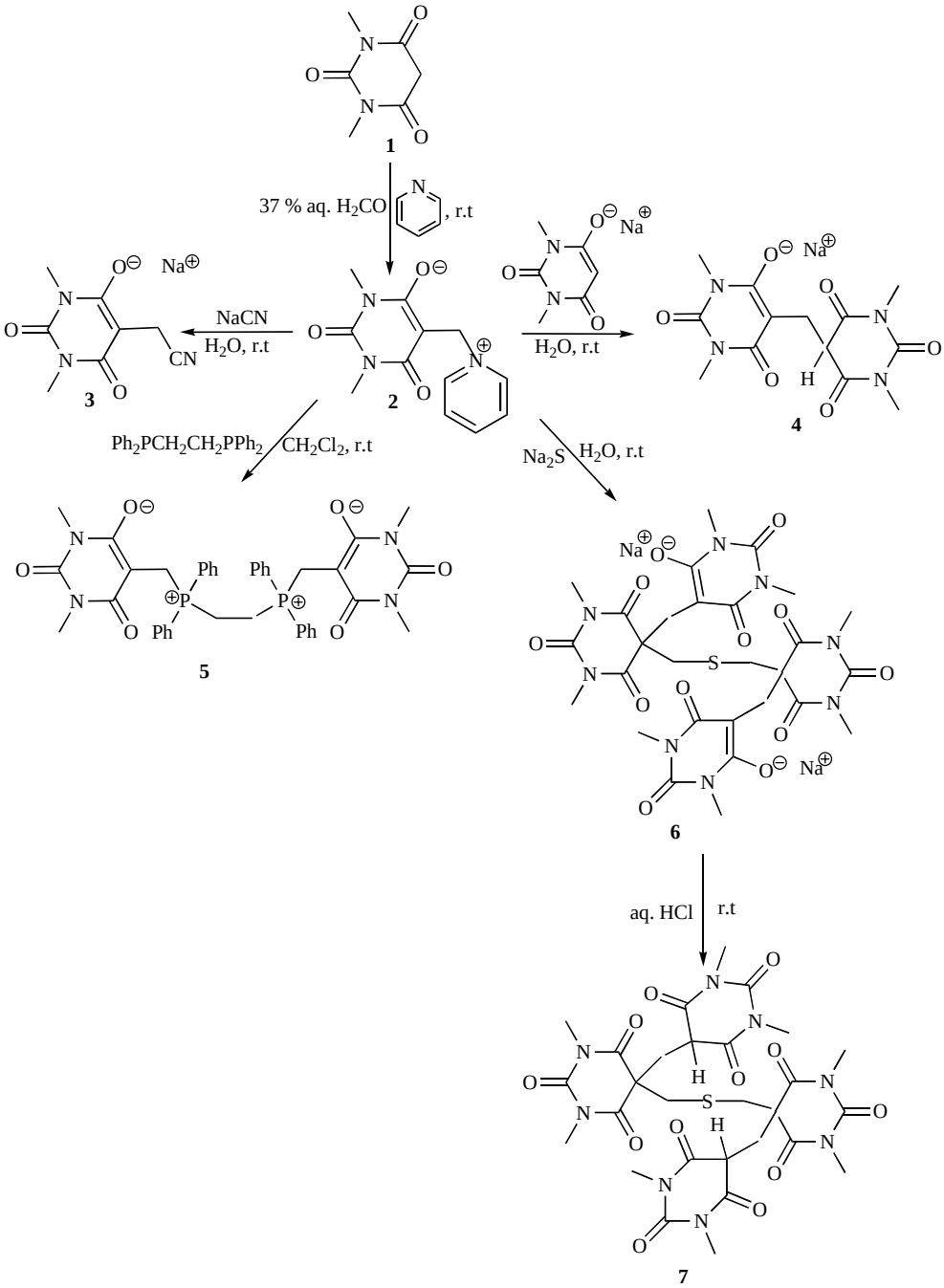
were connected through methylene fragment by synthesis of 6-amino-1,3-dimethyluracil followed by a reaction with formaldehyde under neutral or basic conditions. Acidic hydrolysis of the resulted compounds gave the desired product [10]. On the other hand, unsymmetrical barbituric rings may be prepared by the reaction of N-methyl-o-nitroaniline hydrochloride, diethoxymethane and 1,3-dimethylbarbituric acid [11].

1,2-Bis(diphenylphosphino)ethane reacts readily with two equivalents of **2** forming **5** which was the expected product according to the formation of the stable zwitterionic phosphonium compound from the reaction of **2** with triphenylphosphine [3]. On the other hand, reaction of **2** and 1,2-bis(diphenylphosphino)ethane in a stoichiometric ratio led to a mixture of unidentified products.

Bis[1,3-dimethylbarbituryl(5)]sulfide, in which a sulfur atom is connected directly with two barbiturate rings was prepared and characterized by using X-ray diffraction analysis [12]. Similarly, the reaction of **2** with sulfide anion produced **6** in which a sulfur atom is attached with two 5-methylenebarbituric acid rings. Apparently, **6** consists of two additional methylenebarbituric fragments attached at C5 atoms of the di-anion salt which formed initially. To verify this result, the protonation of **6** with aqueous hydrochloride



Scheme 1.

solution produces **7** which was characterized by NMR, MS and elemental analysis. The DEPT-NMR analysis of **7** showed that protonation occurred at each C5 atom of the barbiturate rings rather than at oxygen atoms (Scheme **1**) leading to a keto-form tautomer which was reported formerly [13]. Other nucleophiles including iodide anion, phenol and thioanisol failed to substitute the pyridinium fragment in **2** even under reflux.

EXPERIMENTAL

Materials and Instruments

All experiments have been performed in purified solvents under argon. 1,3-Dimethylbarbituric acid (B), formaldehyde solution (37%), sodium cyanide, sodium hydroxide, 1,2-bis(diphenylphosphino)ethane, and sodium sulfide were purchased from Aldrich and used without further purification. Nuclear magnetic resonance (NMR) spectra were acquired by a Bruker DRX 400 NMR spectrometer with tetramethylsilane (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P) as external standards. The FAB-mass spectra were obtained on a Finnigan TQS 70 by 70 eV in 3-nitrobenzylalcohol (NBA)-matrix at 30°C. Elemental analyses were determined by Carlo Erba Company, model 1106. Melting points were obtained by the device from Büchi, model 510.

Sodium 5-(cyanomethyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinolate (3)

2.5 mmol (0.62 g) of **2** was dissolved in 20.0 mL of H_2O, and then 2.3 mmol (0.11 g) of NaCN was added in one portion to the aqueous solution which was stirred at r.t overnight. The solvent was removed under vacuum; the residue was then washed with $CHCl_3$, filtered and dried under vacuum.

Yield: 85%; m.p. 307-309 °C (decomp.); ^{1}H NMR (400.13 MHz, D_2O): 3.14 (s, 6H, $1,3_B$-Me); 3.35 (s, 2H, CH_2) ppm. ^{13}C NMR (100.62 MHz, D_2O): 12.7 (CH_2); 27.8 ($1,3_B$-Me); 80.6 ($C^5{}_B$); 121.0 (CN); 153.9 ($C^2{}_B$); 164.1 ($C^{4,6}{}_B$) ppm. MS (FAB): *m/z* (%) = 168 (21) [M^+ - CN], 194 (100) [M^+]. Anal. Calcd. for $C_8H_8N_3O_3Na$: C, 44.3; H, 3.7; N, 19.4. Found: C, 43.9; H, 4.1; N, 19.1%.

Sodium 5-[(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinolate (4)

3.2 mmol (0.79 g) of **2** was dissolved in 15.0 mL of H_2O, and then 2.8 mmol (0.50 g) of sodium 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinolate was added in one portion to the aqueous solution which was stirred at r.t overnight. The solvent was removed under vacuum; the residue was washed with $CHCl_3$, filtered and dried under vacuum.

Yield: 80%; m.p. 237-240 °C (decomp.); ^{1}H NMR (400.13 MHz, D_2O): 2.90 (t, 1H, $C^5{}_B$, J= 6.5 Hz); 2.98 (s, 6H, $1,3_B$-Me); 3.09 (s, 6H, $1,3_{B(-ve)}$-Me); 3.26 (d, 2H, CH_2, J= 6.5 Hz) ppm. ^{13}C NMR (100.62 MHz, D_2O): 27.8 ($1,3_{B(-ve)}$-Me); 28.8 ($1,3_B$-Me); 40.0 (CH_2); 55.2 ($C^5{}_B$); 82.7 ($C^5{}_{B(-ve)}$); 154.0 ($C^2{}_B$); 164.4 ($C^{4,6}{}_B$); 173.2 ($C^{4,6}{}_{B(-ve)}$) ppm. MS (FAB): *m/z* (%) = 153 (100) [NBA matrix], 169 (9) [M^+-($C_6H_6N_2O_3$)], 323 (9) [M^+]. Anal. Calcd. for $C_{13}H_{15}N_4O_6Na$: C, 45.1; H, 4.4; N, 16.2. Found: C, 44.7; H, 4.8; N, 16.0%.

1,3-dimethyl-5-{[{2-[[(1-methyl-6-oxido-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl) methyl](diphenyl)phosphonio] ethyl}(diphenyl)phosphonio]methyl}-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinolate (5)

3.0 mmol (0.74 g) of **2** was dissolved in 15.0 mL of CH_2Cl_2, and then 1.5 mmol (0.59 g) of 1,2-bis(diphenylphosphino)ethane was added in one portion to the solution which was stirred at r.t overnight. The precipitate was filtered off, washed with CH_2Cl_2 and dried under vacuum.

Yield: 80%; m.p. 253-256 °C (decomp.); ^{1}H NMR (400.13 MHz, $CDCl_3$): 3.01 (m, 4H, P-$(CH_2)_2$-P), 3.09 (s, 12H, $1,3_B$-Me); 3.99 (d, 4H, B-CH_2-P, J= 7.5 Hz); 7.58-7.77 (m, 20 H, Ph) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): 15.9 (d, B-CH_2-P, J_{pc} = 47.9 Hz); 20.7 (d, CH_2-P, J_{pc} = 47.7 Hz); 27.6 ($1,3_B$-Me); 72.7 ($C^5{}_B$); 119.5 (d, C_{arom}, J_{pc} = 79.8 Hz), 130.0 (C_m), 132.9 (C_o), 134.6 (C_p); 153.1 ($C^2{}_B$); 163.8 ($C^{4,6}{}_B$) ppm. ^{31}P NMR (161.98 MHz, $CDCl_3$): 23.9 ppm. MS (FAB): *m/z* (%) = 399 (100) [$Ph_4P_2C_2H_4$], 567 (49) [M^+-($C_7H_8N_2O_3$)], 734 (3) [M^+]. Anal. Calcd. for $C_{40}H_{40}N_4O_6P_2$: C, 65.4; H, 5.5; N, 7.6. Found: C, 65.0; H, 5.9; N, 7.8%.

Disodium 5-[(5-{[({5-[(1,3-dimethyl-6-oxido-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl) methyl]-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl}methyl) sulfanyl]methyl}-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinolate (6)

To a suspended solution of 3.0 mmol (0.74 g) of **2** in 25.0 mL of THF, 12.0 mmol (0.94 g) of sodium sulfide was added in one portion to the solution which was stirred at r.t for 72 h. The solvent was removed under vacuum; the residue was washed with CH_2Cl_2, filtered and dried under vacuum.

Yield: 70%; m.p. 223-226 °C (decomp.); ^{1}H NMR (400.13 MHz, D_2O): 2.85 (s, 4H, B-CH_2-S); 3.04 (s, 12H, $1,3_B$-Me); 3.08 (s, 12H, $1,3_{B(-ve)}$-Me); 3.29 (s, 4H, B-CH_2-B) ppm. ^{13}C NMR (100.62 MHz, D_2O): 27.8 ($1,3_{B(-ve)}$-Me); 28.8 ($1,3_B$-Me); 36.1 (CH_2); 37.9 (CH_2); 60.3 ($C^5{}_B$); 83.1 ($C^5{}_{B(-ve)}$); 153.2 ($C^2{}_B$); 154.4 ($C^2{}_{B(-ve)}$); 164.2 ($C^{4,6}{}_B$); 171.6 ($C^{4,6}{}_{B(-ve)}$) ppm. MS (FAB): *m/z* (%) = 391 (63) [(M^++Na)-$C_7H_8N_2O_3$], 599 (100) [(M^++Na)-$C_7H_8N_2O_3$], 727 (13) [M^++Na]. Anal. Calcd. for $C_{28}H_{32}N_8O_{12}SNa_2$: C, 44.8; H, 4.3; N, 14.9. Found: C, 44.4; H, 4.1; N, 15.1%.

5-[(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-5-{[({5-[(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl} methyl)sulfanyl]methyl}-1,3-dimethyl-2,4,6(1H,3H, 5H)-pyrimidinetrione (7)

To a clear aqueous solution of 1.8 mmol (1.35 g) of **6**, 3.6 mmol (0.36 ml of 10 M HCl) was added in one portion followed by stirring at r.t for 30 min. The resulting precipitate was filtered off, washed with distilled H_2O and dried under vacuum.

Yield: 83%; m.p. 129-132 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$): 2.80 (s, 4H, B-CH_2-S); 3.23 (s, 12H, $1,3_B$-Me); 3.27 (s, 12H, $1,3_B$-Me); 3.59 (d, 4H, B-CH_2-B, J= 6.7 Hz); 4.10 (t, 2H, $C_B{}^5$H, J= 6.7 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$):

28.5 ($1,3_B$-Me); 28.8 ($1,3_B$-Me); 35.2 (B-CH_2-S); 42.9 (B-CH_2-B); 44.5 ($C^5{}_BH$); 55.6 ($C^5{}_B$); 150.8 ($C^2{}_B$); 170.4 ($C^{4,6}{}_B$) ppm. MS (FAB): *m/z* (%) = 154 (100) [NBA-matrix], 371 (28) [(M^+- $C_{14}H_{16}N_4O_6$)], 707 (16) [M^+]. Anal. Calcd. for $C_{28}H_{34}N_8O_{12}S$: C, 47.6; H, 4.9; N, 15.9. Found: C, 47.3; H, 4.9; N, 15.5%.

CONCLUSION

In summary, 1,3-dimethylbarbituric acid pyridinium adduct is considered an excellent organic precursor for synthesis of new organic derivatives of 1,3-dimethylbarbituric acid; based on the readily substitution of its pyridinium fragment different types of nucleophiles may applied under mild experimental conditions.

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