A Simple and Convenient Method for the Synthesis of 1-Methyl-7-arylfuro[3,2-g]pteridine-2,4(1H,3H)-diones and Their Substituted Derivatives

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Abstract

A simple and effective method for the synthesis of unknown 1-methyl-7-arylfuro[3,2-g]pteridine-2,4(1H,3H)-diones by dehydration of the corresponding 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7(1H,3H,8H)-triones is reported in the article. It was shown that their alkylation by butyl chloroacetate in basic medium proceeded by the N3-atom of the heterocycle. The structure and purity of the synthesized compounds were confirmed by IR, 1H, 13C NMR spectroscopy, gas chromatography-mass spectrometry, mass spectrometry, as well as X-ray diffraction analysis. The proposed mechanism of the dehydration reaction was discussed.

Keywords: 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7(1H,3H,8H)-triones; dehydration; 1-methyl-7-arylfuro[3,2-g]pteridine-2,4(1H,3H)-diones; alkylation; X-ray diffraction analysis

1. Introduction

Condensed heterocyclic derivatives of pteridines belong to the important, but insufficiently studied group of organic substances. Although, the methods for the synthesis of annelated pteridines were systematized in few monographs1,2 and reviews,3-5 research devoted to the synthesis of condensed pteridines continues due to their high biological activity. Antimicrobial,6,7 anticancer,8-10 anti-inflammatory and analgesic activities11,12 of condensed pteridines as well as their ability to inhibit PLK1 kinase13,14 have been described. Besides, these substances could be used as functional materials as shown in previous reports.15-17 The furo[3,2-g]pteridine system was not mentioned in the scientific literature, however methods for the isomeric furo[2,3-g]pteridines synthesis are known.3

Based on the above, the purpose of this work consists in developing a simple and convenient method for the synthesis of 1-methyl-7-arylfuro[3,2-g]pteridine-2,4(1H,3H)-diones by dehydration of 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7(1H,3H,8H)-triones.

2. Experimental Part

2.1. Chemistry

Melting points were determined in open capillary tubes in a Mettler Toledo MP 50 apparatus and are uncorrected. The elemental analyses (C, H, N) were performed using the ELEMENTAR vario EL cube analyzer (USA) and are within ±0.3% of the theoretical values. IR spectra (4000-600 cm⁻¹) were recorded on a Bruker ALPHA FT-IR spectrometer (Bruker Bioscience, Germany) using a module for measuring attenuated total reflection (ATR). 1H NMR spectra (400 MHz) were recorded on a Varian-Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometers with TMS as internal standard in DMSO-d6 solution. 13C NMR spectra of compounds (3b-e, 3g-j, 100 MHz) were recorded in TFA-d1 solution. LC-MS were re-
corded using chromatography/mass spectrometric system which consists of high performance liquid chromatography Agilent 1100 Series (Agilent, Palo Alto, CA, USA) equipped with diode-matrix and mass-selective detector Agilent LC/MSD SL (atmospheric pressure chemical ionization – APCI). Electron impact mass spectra (EI-MS) were recorded on a Varian 1200 L instrument at 70 eV (Varian, USA).

Compounds 1a–k (1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7(1H,3H,8H)-triones) were obtained according to the previously described method. For the experiment commercially available reagents from Merck (Darmstadt, Germany), Sigma-Aldrich (Missouri, USA) and Enamine (Kyiv, Ukraine) were used.

**General Method for the Synthesis of 1-Methyl-7-arylufro[3,2-g]pteridine-2,4(1H,3H)-diones 2a–k.** A suspension of 10 mmol of the corresponding 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7(1H,3H,8H)-trione 1a–k in 20 mL of polyphosphoric acid was heated to 130 °C and stirred for 1 hour. Afterwards, the reaction mixture was cooled, poured into 100 mL of water and stirred. The precipitate formed was filtered off, washed with water and dried.

**1-Methyl-7-phenylfuro[3,2-g]pteridine-2,4(1H,3H)-dione (2a).** Yield: 2.35 g (75%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 1698, 1504, 1340, 1274, 1178, 1058, 1010, 895, 831, 781, 761, 694, 670; ¹H NMR δ (ppm): 11.75 (s, 1H, 3-NH), 8.01 (d, J = 7.3 Hz, 2H, Ar-H-2,6), 7.67 (s, 1H, H-6), 7.56–7.12 (m, 3H, Ar-H-3,5, 4), 3.60 (s, 3H, 1-N-CH3); LC-MS m/z = 336 [M+H]+. Anal. Calcd. for C₁₅H₁₆N₄O₃: C, 62.33; H, 3.48; N, 19.09.

**1-Methyl-7-(2-fluorophenyl)furo[3,2-g]pteridine-2,4(1H,3H)-dione (2b).** Yield: 2.41 g (77%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 1696, 1488, 1338, 1263, 1175, 1056, 1088, 895, 808, 777, 762, 745, 652; ¹H NMR δ (ppm): 11.96 (s, 1H, 3-NH), 8.24–8.02 (m, 1H, Ar-H-6), 7.70–7.50 (m, 2H, H-6, Ar-H-4), 7.47–7.28 (m, 2H, Ar-H-3,5), 3.60 (s, 3H, 1-N-CH3); LC-MS m/z = 312 [M+H]+. Anal. Calcd. for C₁₅H₁₆N₄O₃: C, 64.28; H, 4.79; N, 16.66; found: C, 64.33; H, 4.84; N, 16.71.

**7-(2,4-Difluorophenyl)-1-methylfuro[3,2-g]pteridine-2,4(1H,3H)-dione (2f).** Yield: 2.59 g (79%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 3047, 1716, 1689, 1504, 1433, 1342, 1288, 1177, 1090, 1059, 1003, 893, 841, 826, 805, 751; ¹H NMR δ (ppm): 11.83 (s, 1H, 3-NH), 8.18–7.96 (m, 2H, Ar-H-6, 7.49 (s, 1H, H-6), 7.33–7.08 (m, 2H, Ar-H-3, 5), 3.57 (s, 3H, 1-N-CH3); LC-MS m/z = 330 [M+H]+. Anal. Calcd. for C₁₅H₁₆F₂N₄O₃: C, 54.55; H, 2.44; N, 16.97; found: C, 54.61; H, 2.50; N, 17.02.

**1-Methyl-7-(4-chlorophenyl)furo[3,2-g]pteridine-2,4(1H,3H)-dione (2g).** Yield: 2.59 g (79%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 3054, 1716, 1689, 1503, 1433, 1342, 1288, 1177, 1090, 1059, 1003, 893, 841, 826, 805, 751; ¹H NMR δ (ppm): 11.86 (s, 1H, 3-NH), 8.03 (d, J = 8.9 Hz, 2H, Ar-H-2,6), 7.78 (s, 1H, H-6), 7.54 (d, J = 9.3 Hz, 2H, Ar-H-3, 5), 3.58 (s, 3H, 1-N-CH3); LC-MS m/z = 328 [M+H]+. Anal. Calcd. for C₁₅H₁₄ClN₄O₃: C, 54.81; H, 2.76; N, 17.04; found: C, 54.88; H, 2.81; N, 17.09.

**7-(4-Bromophenyl)-1-methylfuro[3,2-g]pteridine-2,4(1H,3H)-dione (2h).** Yield: 3.09 g (83%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 3054, 1691, 1503, 1340, 1286, 1059, 1001, 893, 837, 822, 803, 749; ¹H NMR δ (ppm): 11.44 (s, 1H, 3-NH), 7.98 (d, J = 7.3 Hz, 2H, Ar-H-2,6), 7.84 (s, 1H, H-6), 7.71 (d, J = 7.4 Hz, 2H, Ar-H-3, 5), 3.59 (s, 3H, 1-N-CH3); LC-MS m/z = 373 [M+H]+. Anal. Calcd. for C₁₅H₁₃BrN₄O₃: C, 48.28; H, 2.43; N, 15.01; found: C, 48.32; H, 2.49; N, 15.08.

**1-Methyl-7-(3-nitrophenyl)furo[3,2-g]pteridine-2,4(1H,3H)-dione (2i).** Yield: 2.74 g (81%), light brown comp-

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1-Methyl-7-(naphthalen-2-yl)-furo[3,2-g]pteridine-2,4-(1H,3H)-dione (2j). Yield: 2.85 g (83%), light orange substance, mp > 300 °C; IR (cm⁻¹): 3019, 2958, 1738, 1613, 1450, 1433, 1377, 1330, 1232, 1151, 1045, 998, 948, 879, 805, 775, 750; 1H NMR δ (ppm): 10.42 (s, 1H, 6H), 7.96 (d, J = 7.6 Hz, 2H, CH(CH₃)₂), 2.28 (t, J = 7.2 Hz, 4H, OCH₂CH₂CH₂CH₃), 0.97 (t, J = 7.2 Hz, 3H, OCH₂CH₂CH₂CH₃); 13C NMR δ (ppm): 167.1 (COO, C-8a), 161.3 (C-4), 158.9 (C-7), 155.4 (C-2), 155.0 (C-1), 147.7 (C-5), 130.8 (C-6a), 129.4 (C-5a), 121.3 (C-4a), 111.1 (C-3a), 108.9 (C-6), 108.4 (C-7a), 106.8 (C-7), 101.7 (C-3), 100.3 (C-2), 99.1 (C-5), 18.9 (OCH₂CH₂CH₂CH₃), 13.9 (OCH₂CH₂CH₂CH₃); LC-MS m/z = 422 [M+H]+. Anal. Calcd. for C₂₅H₂₃NO₅: C, 69.26; H, 4.97; N, 16.23; found: C, 69.29; H, 4.95; N, 16.27.

Butyl 2-(2,4-Dioxo-1-methyl-7-(p-tolyl)-1,4-dihydrofuro[3,2-g]pteridine-3(2H)-yl)acetate (3b). Yield: 3.21 g (76%), light yellow compound, mp: 295–297 °C; IR (cm⁻¹): 1754, 1714, 1674, 1505, 1453, 1360, 1279, 1195, 1000, 932, 892, 818, 801, 756; 1H NMR δ (ppm): 7.93 (d, J = 7.5 Hz, 2H, Ar H-2,6), 7.69 (s, 1H, H-6), 7.36 (d, J = 6.9 Hz, 2H, Ar H-3,5), 4.74 (s, 2H, NCH₂), 4.17 (t, J = 6.4 Hz, 2H, OCH₂CH₂CH₂CH₃), 3.70 (s, 3H, 1-N-CH₃), 2.46 (s, 3H, ArCH₂), 1.86–1.55 (m, 5H, 2H, OCH₂CH₂CH₂CH₃) 13C NMR δ (ppm): 172.7 (COO), 170.1 (C-8a), 157.5 (C-4), 150.3 (C-7), 148.3 (C-2), 145.7 (C-9a), 135.5 (C-5a), 130.4 (Ar C-2,6), 127.8 (Ar C-3,5), 122.5 (Ar C-1), 117.6 (C-4a), 113.8 (Ar C-4), 95.1 (C-6), 68.2 (OCH₂CH₂CH₂CH₃), 43.5 (NCH₂CO), 30.0 (N-CH₃), 29.7 (OCH₂CH₂CH₂CH₃), 20.2 (Ar-CH₂), 18.2 (OCH₂CH₂CH₂CH₃), 11.7 (OCH₂CH₂CH₂CH₃); LC-MS m/z = 422 [M+H]+. Anal. Calcd. for C₂₈H₂₇NO₇: C, 72.85; H, 6.52; N, 12.34; found: C, 72.95; H, 6.56; N, 12.37.

Butyl 2-(2,4-Dioxo-7-(4-isopropylphenyl)-1-methyl-1,4-dihydrofuro[3,2-g]pteridine-3(2H)-yl)acetate (3c). Yield: 3.46 g (77%), light yellow compound, mp: 288–291 °C; IR (cm⁻¹): 2975, 1761, 1724, 1667, 1512, 1455, 1362, 1282, 1157, 1006, 894, 843, 805, 755; 1H NMR δ (ppm): 7.95 (d, J = 8.1 Hz, 2H, Ar H-2,6), 7.69 (s, 1H, H-6), 7.40 (d, J = 8.1 Hz, 2H, Ar H-3,5), 4.74 (s, 2H, NCH₂), 4.16 (t, J = 6.6 Hz, 2H, OCH₂CH₂CH₂CH₃), 3.70 (s, 3H, 1-N-CH₃), 3.16–2.62 (m, 1H, CH(CH₃)₂), 1.66 (m, 2H, OCH₂CH₂CH₂CH₃), 1.41 (m, 2H, OCH₂CH₂CH₂CH₃), 1.31 (d, J = 6.8 Hz, 6H, CH(CH₃)₂), 0.97 (t, J = 7.3 Hz, 3H, OCH₂CH₂CH₂CH₃); 13C NMR δ (ppm): 161.8 (COO, C-8a), 161.4 (C-4), 159.1 (C-7), 155.7 (Ar C-4), 152.2 (C-2), 150.1 (C-9a), 145.6 (C-5a), 139.0 (C-4a), 127.7 (Ar C-2,6), 125.9 (Ar C-3,5), 125.0 (Ar C-1), 116.0 (C-4a), 101.4 (C-6), 65.3 (OCH₂CH₂CH₂CH₃), 43.2 (NCH₂CO), 33.9 (CH(CH₃)₂), 30.5 (OCH₂CH₂CH₂CH₃), 30.0 (N-CH₃), 23.9 (CH(CH₃)₂), 18.9 (OCH₂CH₂CH₂CH₃), 13.9 (OCH₂CH₂CH₂CH₃); LC-MS m/z = 450 [M+H]+. Anal. Calcd. for C₂₇H₂₆N₂O₇: C, 63.99; H, 5.82; N, 12.44; found: C, 64.04; H, 5.87; N, 12.49.

Butyl 2-(2,4-Dioxo-1-methyl-7-(2-fluorophenyl)-1,4-dihydrofuro[3,2-g]pteridine-3(2H)-yl)acetate (3d). Yield: 3.24 g (76%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 1752, 1720, 1676, 1504, 1456, 1361, 1276, 1199, 894, 772, 752; 1H NMR δ (ppm): 8.22–7.84 (m, 1H, Ar H-6), 7.63–7.49 (m, 2H, H-6, Ar H-4), 7.46–7.23 (m, 2H, Ar H-3,5), 4.74 (s, 2H, NCH₂), 4.17 (t, J = 6.6 Hz, 2H, OCH₂CH₂CH₂CH₃), 3.69 (s, 3H, 1-N-CH₃), 1.67 (quintet, J = 6.9 Hz, 2H, OCH₂CH₂CH₂CH₃), 1.42 (sextet, J = 7.3 Hz, 2H, OCH₂CH₂CH₂CH₃).
Butyl 2-(2,4-Dioxo-1-methyl-7-(naphthalen-2-yl)-1,4-dihydrofuro[3,2-g]pteridine-3(2H)-yl)acetate (3f). Yield: 3.55 g (80%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 1709, 1679, 1603, 1505, 1453, 1361, 1275, 1203, 1058, 1005, 929, 894, 817, 801, 756; ¹H NMR δ (ppm): 8.01 (d, J = 9.0 Hz, 2H, Ar H-2,6), 7.89 (s, 1H, H-6), 7.73 (d, J = 7.9 Hz, 2H, Ar H-3,5), 4.75 (s, 2H, NCH₂), 4.21–4.07 (m, 2H, OCH₂CH₂CH₂CH₃), 3.71 (s, 3H, 1-N-CH₃), 1.75–1.55 (m, 2H, OCH₂CH₂CH₂CH₃), 1.52–1.36 (m, 3H, 2H, OCH₂CH₂CH₂CH₃), 1.02–0.92 (m, 3H, OCH₂CH₂CH₂CH₃); LC-MS m/z = 487 [M+H]⁺. Anal. Calcd. for C₂₁H₁⁹ClN₄O₅: C, 55.07; H, 4.30; N, 12.67; found: C, 55.05; H, 4.30; N, 12.70.

Butyl 2-(2,4-Dioxo-1-methyl-7-(3-nitrophenyl)-1,4-dihydrofuro[3,2-g]pteridine-3(2H)-yl)acetate (3i). Yield: 3.53 g (78%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 1719, 1679, 1603, 1522, 1454, 1359, 1279, 1194, 1157, 1007, 895, 833, 800, 755; ¹H NMR δ (ppm): 8.12 (d, J = 7.6 Hz, 2H, Ar H-2,6), 7.79 (s, 1H, H-6), 7.33 (t, J = 7.9 Hz, 2H, Ar H-3,5), 4.75 (s, 2H, NCH₂), 4.17 (t, J = 6.5 Hz, 2H, OCH₂CH₂CH₂CH₃), 3.71 (s, 3H, 1-N-CH₃), 1.66 (quintet, J = 7.2 Hz, 2H, OCH₂CH₂CH₂CH₃), 0.97 (t, J = 7.2 Hz, 3H, OCH₂CH₂CH₂CH₃); ¹³C NMR δ (ppm): 170.4 (COO), 159.7 (C-8a), 151.2 (C-4), 148.8 (C-7), 135.1 (C-5), 132.7 (Ar C-6), 128.3 (C-3,5), 127.6 (Ar C-1), 125.1 (C-4), 119.4 (C-4a), 98.3 (C-6), 68.2 (OCH₂CH₂CH₂CH₃), 43.6 (NCH₂CO), 29.9 (N-CH₃), 29.7 (OCH₂CH₂CH₂CH₃), 18.2 (OCH₂CH₂CH₂CH₃), 151.4 (OCH₂CH₂CH₂CH₃); LC-MS m/z = 426 [M+H]⁺. Anal. Calcd. for C₂₁H₁⁹N₅O₇: C, 55.69; H, 4.28; N, 15.48; found: C, 55.69; H, 4.28; N, 15.48.

Butyl 2-(2,4-Dioxo-1-methyl-7-(4-fluorophenyl)-1,4-dihydrofuro[3,2-g]pteridine-3(2H)-yl)acetate (3e). Yield: 3.79 g (78%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 1748, 1718, 1678, 1503, 1453, 1361, 1275, 1203, 1058, 1005, 929, 894, 817, 801, 756; ¹H NMR δ (ppm): 7.98 (s, 1H, H-6), 7.73 (t, J = 7.9 Hz, 2H, Ar H-3,5), 4.75 (s, 2H, NCH₂), 4.21–4.07 (m, 2H, OCH₂CH₂CH₂CH₃), 3.71 (s, 3H, 1-N-CH₃), 1.75–1.55 (m, 2H, OCH₂CH₂CH₂CH₃), 1.52–1.36 (m, 3H, OCH₂CH₂CH₂CH₃), 1.02–0.92 (m, 3H, OCH₂CH₂CH₂CH₃); LC-MS m/z = 442 [M+H]⁺. Anal. Calcd. for C₂₁H₁⁹F₂N₅O₇: C, 51.76; H, 3.93; N, 11.50; found: C, 51.82; H, 3.98; N, 11.57.

Butyl 2-(2,4-Dioxo-1-methyl-7-(4-chlorophenyl)-1,4-dihydrofuro[3,2-g]pteridine-3(2H)-yl)acetate (3g). Yield: 3.86 g (78%), light yellow compound, mp > 300 °C; IR (cm⁻¹): 1748, 1718, 1678, 1503, 1453, 1361, 1275, 1203, 1058, 1005, 929, 894, 817, 801, 756; ¹H NMR δ (ppm): 7.98 (s, 1H, H-6), 7.73 (t, J = 7.9 Hz, 2H, Ar H-3,5), 4.75 (s, 2H, NCH₂), 4.21–4.07 (m, 2H, OCH₂CH₂CH₂CH₃), 3.71 (s, 3H, 1-N-CH₃), 1.75–1.55 (m, 2H, OCH₂CH₂CH₂CH₃), 1.52–1.36 (m, 3H, OCH₂CH₂CH₂CH₃), 1.02–0.92 (m, 3H, OCH₂CH₂CH₂CH₃); LC-MS m/z = 442 [M+H]⁺. Anal. Calcd. for C₂₁H₁⁹BrN₅O₇: C, 51.76; H, 3.93; N, 11.50; found: C, 51.82; H, 3.98; N, 11.57.
945, 906, 748; $^1$H NMR δ (ppm): 8.59 (s, 1H, naphthalene H-1), 8.11 (d, $J$ = 8.7 Hz, 1H, naphthalene H-4), 8.06–8.00 (m, 2H, naphthalene H-3,8), 7.95–7.83 (m, 2H, H-6, naphthalene H-5), 7.59 (d, $J$ = 5.2 Hz, 2H, naphthalene H-6,7), 4.76 (s, 2H, NCH$_2$), 4.18 (t, $J$ = 7.4 Hz, 2H, OCH$_2$CH$_2$CH$_2$CH$_3$), 3.71 (s, 3H, 1-N-CH$_3$), 1.52–1.34 (m, 2H, OCH$_2$CH$_2$CH$_2$CH$_3$), 1.52–1.34 (m, 2H, OCH$_2$CH$_2$CH$_2$CH$_3$); $^{13}$C NMR δ (ppm): 170.2 (COO), 166.6 (C-8a), 158.8 (C-4), 158.3 (C-7), 150.4 (C-2), 145.0 (C-9a), 137.2 (naphthalene C-5a), 134.8 (C-5a), 132.2 (naphthalene C-4a), 129.2 (naphthalene C-4), 128.9 (naphthalene C-8), 128.8 (naphthalene C-5), 127.4 (naphthalene C-6), 127.3 (naphthalene C-3), 127.1 (naphthalene C-7), 123.1 (naphthalene C-2), 121.7 (naphthalene C-1), 118.4 (C-4a, 98.3 (C-6), 68.1 (OCH$_2$CH$_2$CH$_2$CH$_3$), 43.5 (NCH$_2$CO), 29.8 (N-CH$_3$), 29.7 (OCH$_2$CH$_2$CH$_2$CH$_3$), 18.3 (OCH$_2$CH$_2$CH$_2$CH$_3$), 11.8 (OCH$_2$CH$_2$CH$_2$CH$_3$); LC-MS m/z = 458 [M+H]$^+$.

Anal. Calcd. for C$_{25}$H$_{22}$N$_4$O$_5$: C, 65.49; H, 4.84; N, 12.22; found: C, 65.52; H, 4.87; N, 12.25.

2. 2. X-Ray Diffraction Analysis

Crystals of compound 2a were monoclinic, C$_{15}$H$_{10}$N$_4$O$_3$, at 20 °C, $a$ = 7.7443(6) Å, $b$ = 6.4905(4) Å, $c$ = 12.7022(8) Å, β = 105.371(7), V = 615.63(7) Å$^3$, $M_r$ = 294.27, Z = 2, space group P21, $d_{calc}$. = 1.587 g/cm$^3$, μ (MoKα) = 0.115 mm$^{-1}$, F(000) = 304. Unit cell parameters and intensities of 5928 reflections (3081 independent, $R_{int}$ = 0.022) were measured on a Xcalibur-3 diffractometer (MoKα) radiation, a CCD detector, a graphite monochromator, $ω$-scanning, $2θ_{max}$ = 60°). The structure was deciphered by the direct method using the SHELXTL software package. The positions of the hydrogen atoms were revealed from the difference synthesis of electron density and refined using the rider model with $U_{iso}$ = n$U_{eq}$ non-hydrogen atom associated with this hydrogen atom (n = 1.5 for the methyl group and n = 1.2 for the remaining hydrogen atoms). The hydrogen atom of the amino group was refined in the isotropic approximation. The structure was refined by F2 by full-matrix least squares in the anisotropic approximation for non-hydrogen atoms up to $wR_2 = 0.090$ by 3021 reflections ($R_1 = 0.035$ by 2646 reflections with $F > 4σ (F)$, $S$ = 0.998). The atomic coordinates, as well as the complete tables of bond lengths and bond angles, were deposited with the Cambridge Structural Data Bank (e-mail: deposit@ccdc.cam.ac.uk) under the number CCDC 1940140.

3. Results and Discussion

The Paal–Knorr synthesis, despite more than a century of experience in use, remains to be one of the most efficient methods for the construction of benzopyrano[2,3-f]quinoline or naphthalene frameworks. The dehydration of 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7/(1H,3H,8H)-triones and the alkylation of 1-methyl-7-arylfuro[3,2-g]pteridine-2,4/(1H,3H)-diones

Scheme 1. The dehydration of 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7/(1H,3H,8H)-triones and the alkylation of 1-methyl-7-arylfuro[3,2-g] pteridine-2,4/(1H,3H)-diones

Scheme 2. The supposed mechanism of 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7/(1H,3H,8H)-triones dehydration

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effective methods for the formation of five-membered heterocycles with one heteroatom. Considering the structural similarity of 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4,7(1H,3H,8H)-triones 1a–k with 1,4-dicarbonyl compounds and in the continuation of modification studies of pteridines their dehydrogenation was investigated. It was found that dehydrogenation of compounds 1a–k in concentrated sulfuric acid both at room temperature and during heating proceeded doubtfully. In this case, either a mixture of substances difficult to identify was formed, or its tarring occurred. The dehydration reaction was carried out by heating the starting materials in polyphosphoric acid (Scheme 1). Pure 1-methyl-7-arylfuro[3,2-g]pteridine-2,4(1H,3H)-diones 2a–k were formed with high yields.

It should be noted that dehydrogenation of compounds 1a–k (A in Scheme 2) in the solution of polyphosphoric acid proceeded according to the Paal–Knorr synthesis. The mechanism of this reaction assumes the nucleophilic attack of the amide fragment oxygen atom of the molecule at the carbon atom of the protonated carbonyl group (B). The oxonium cation C became aromatic in the result of deprotonation and dehydration with the formation of the final product E.

To increase the solubility of 1-methyl-7-arylfuro[3,2-g]pteridine-2,4(1H,3H)-diones 2a–k in organic solvents (DMSO, DMF), the next step was to study their alkylation. It was found that alkylation of compounds 2a–k by butyl chloroacetate in DMF in the presence of K2CO3 proceeded by butyl chloroacetate in DMF in the presence of K2CO3 by K2CO3 and KNO3. An additional analysis of the mass spectra (EI) of compounds 2a and 3a showed the fragmentation of the furo[3,2-g]pteridine system. Thus, the high stability of the molecular ion of compound 2a ([M]+, m/z = 294, Irel = 66.8%), determined its fragmentation along the less aromatic dihydropyrimidine cycle with a step-by-step release of HNCO molecules (F1, m/z = 251, Irel = 12.6%), CO (F2, m/z = 223, Irel = 100%) and the NCH3+ ion (F3, m/z = 194, Irel = 10.5%). Formed 6-phenylfuro[2,3-b]pyrazine ion (F4) eliminated two HCN molecules with formation of ions with F4 (m/z = 167, Irel = 5.9%) and F5 (m/z = 140, Irel = 24.8%), while for F5 formation of two alternative fragmentation ions [C6H5N4]+ (m/z = 77, Irel = 25.3%) and [C6H5O]+ (m/z = 67, Irel = 16.8%) was characteristic. Whereas, the molecular ion of ether 3a was less stable ([M]+, m/z = 408, Irel = 46.6%). The main ways of its fragmentation were associated with the initial elimination of C6H5N+ (F1, m/z = 352, Irel = 10.6%) and CO2 (F2, m/z = 308, Irel = 31.9%). Further degradation of the fragmented ion (F3) proceeded similarly to the path described for compound 2a, which led to the appearance of signals with m/z = 251 (Irel = 9.5%), m/z = 223 (Irel = 23.9%) and m/z = 140 (Irel = 10.2%).

The final structure of compound 2a was confirmed by X-ray diffraction study (Fig. 1). It was found that it...
crystallized in the non-centrosymmetric space group P21, despite the absence of chiral centers in the molecule (Fig. 1).

All non-hydrogen atoms in the molecule lie in the plane with an accuracy of 0.05 Å, despite the presence of slight steric repulsion between the atoms of the tricyclic fragment and the phenyl substituent (shortened intramolecular contacts H(11)⋯C(5) 2.79 Å with the sum of the van der Waals radii 24. 2.87 Å and H(15)⋯O(3) 2.43 Å (2.46 Å). In the crystal of molecule 2a double chains in the crystallographic direction [0 1 0] were formed due to the intermolecular hydrogen bond N(2)⋯H⋯O(2)' (−x, −0.5 + y, −z), H⋯O 1.94 Å, N–H⋯O 175° and stacking interactions, the distance between the π-systems of neighboring molecules was 3.37 Å).

4. Conclusion

Using spectral methods and X-ray diffraction studies, it was found that the dehydration of 1-methyl-6-(2-oxo-2-arylethyl)pteridine-2,4(1H,3H,8H)-triones proceeded according to the Paal–Knorr synthesis with the formation of the original 1-methyl-7-aryluraco[3,2-g]pteridine-2,4(1H,3H)-diones. For these molecules, the alkylation reaction was studied.

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5. References

1. W. Pfleiderer, Compr. Heterocycl. Chem. II, Bicyclic 6-6 Systems: Pteridines; A. R. Katritzky, C. W. Rees, E. F. V. Scriven, (Eds.): Pergamon Press, 1996, pp. 679–736. DOI: 10.1016/B978-008096518-5.00162-3
2. C. Suckling, C. Gibson, J. Huggan, Compr. Heterocycl. Chem. III, Bicyclic 6-6 Systems: Pteridines; Katritzky, A. R.; Ramsden, C. A.; Taylor, R. J. K. Eds.; Elsevier, 2008, pp. 915–975. DOI: 10.1016/B978-008044992-0.00918-4
3. A. V. Gulevskaya, A. F. Pozharskii, Russ. Chem. Rev. 2011, 80(6), 495–529. DOI: 10.1070/RC2011v080n06ABEH004168
4. A. A. Sayed, A. H. Elghandour, H. S. Elgendy, Pharma Chem. 2014, 6(3), 194–219
5. C. Suckling, IUBMB Life 2013, 65(4), 283–299. DOI: 10.1002/iub.1148
6. A. Fadda, N. Bayoumy, I. El-Sherbiny, Drug Dev. Ind. Pharm. 2015, 42(7), 1–16. DOI: 10.3109/03639045.2015.1108331
7. I. H. El Azab, M. E. Khalifa, A. A. Gobouri, T. A. Altalhi, J. Heterocycl. Chem. 2019, 56, 1352–1361. DOI: 10.1002/jhet.3509
8. M. Mokaber-Esfahani, H. Esghii, A. Shiri, M. Akbarzadeh, M. Mirzaei, J. Chem. Res. 2015, 39, 216–219. DOI: 10.3184/174751915X1427134610550
9. S. El Kalyoubi, E. Fayad, J. Chem. Res. 2016, 40, 771–777. DOI: 10.3184/174751916X14798125870610
10. X. Bi, J. Li, J. Li, W. Shi, Y. Dai, Q. Li, W. Zhang, W. Huang, H. Qian, C. Jiang, Bioorg. Med. Chem. 2019, 27, 2813–2821. DOI: 10.1016/j.bmc.2019.05.006
11. A. Abu-Hashem, M. El-Shazly, Med. Chem. 2018, 14, 356–371. DOI: 10.2174/1573406414666180112110947
12. A. A. Ghoneim, N. Ali, A. Elkanzi, R. B. Bakr, J. Taibah. Univ. Sci. 2018, 12(6), 774–782. DOI: 10.1080/16583655.2018.1510163
13. A. K. Kiryanov, S. Natala, B. Jones, C. McBride, V. Feher, B. Lam, Y. Liu, K. Honda, N. Uchiyama, T. Kawamoto, Y. Hikichi, L. Zhang, D. Hosfield, R. Skene, H. Zou, J. Stafford, X. Cao, T. Ichikawa, Bioorg. Med. Chem. Lett. 2017, 27, 1311–1315. DOI: 10.1016/j.bmcl.2016.10.009
14. K. Ishimoto, K. Nakaoka, O. Yabe, A. Nishiguchi, T. Ikemoto, Tetrahedron 2018, 74, 5779–5790. DOI: 10.1016/j.tet.2018.08.020
15. A. A. Wiles, B. Fitzpatrick, N. A. McDonald, M. M. Westwater, De-L. B. Long, E. V. Karpenko, B. O. Priimenko, S. I. Kovalenko, J. Heterocycl. Chem. 2018, 55, 65–76. DOI: 10.1002/jhet.2978
16. V. A. Mamedov, N. A. Zhukova, A. T. Gubaidullin, V. V. Prokhorov, I. Kh. Rizvanov, S. K. Latypov, Acta Cryst. B 2016, 14942–14964. DOI: 10.1021/acscn10392k
17. M. S. Kazunin, O. Yu. Voskoboynik, I. S. Nosulenko, G. G. Berest, T. Sergeieva, S. Okovytyy, O. V. Karpenko, B. O. Priimenko, S. I. Kovalenko, J. Heterocycl. Chem. 2018, 4, 1033–1041. DOI: 10.1002/jhet.3135
18. G. M. Sheldrick Acta Cryst. B 2008, A64, 112–122. DOI: 10.1107/S0108767708034930
19. A. R. Katritzky, C. W. Rees, Comprehensive Heterocyclic Chemistry; (Eds.): Pergamon Press, Oxford, 1984, 4, p. 705.
20. A. Venkateraman, A. Kalyani, J. Org. Chem. 1995, 60, 301–307. DOI: 10.1021/jo00107a006
21. O. I. El-Sabbagh, M. E. El-Sadek, S. El-Kalyoubi, I. Ismail, Arch. Pharm. Chem. Life Sci. 2007, 340, 26–31. DOI: 10.1002/ardp.200600149
22. N. E. Jacobsen, NMR spectroscopy explained: simplified theory, applications and examples for organic chemistry and structural biology; John Wiley & Sons, Inc., 2007, p. 688.
23. Yu. V. Zefirov, Crystallography 1997, 42(5), 936–958.
Povzetek

V članku predstavljamo enostavno in učinkovito metodo sinteze doslej neopisanih 1-metil-7-arilfuro[3,2-g]pteridin-2,4(1H,3H)-dionov s pomočjo dehidratacije ustreznih 1-metil-6-fenacilpteridin-2,4,7(1H,3H,8H)-trionov. Pokazali smo, da njihovo alkiliranje z butil kloroacetatom v bazičnem poteka na N3-atomu heterocikla. Strukturo in čistočo pripravljenih produktov smo dokazali z IR, 1H in 13C NMR spektroskopijo, plinsko kromatografijo-masno spektrometrijo, masno spektrometrijo in tudi z rentgensko difrakcijsko analizo. Opisujemo tudi predlagani mehanizem dehidratacije.