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NEW SYNTHETIC POTENTIAL OF PTERIDINE DERIVATIVES: DIRECT SUBSTITUTION OF H IN 1,3-DIMETHYLLUMAZINE DURING REACTION WITH C-NUCLEOPHILES

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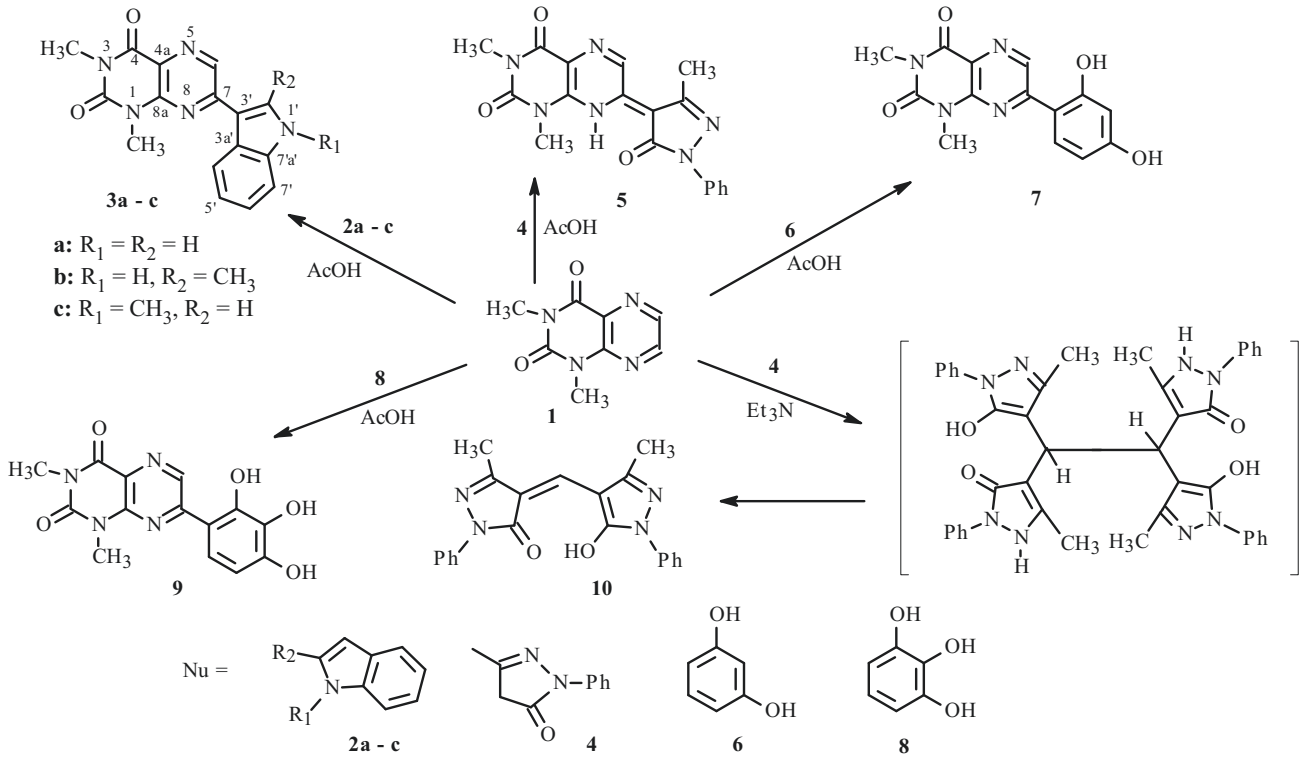
The pteridine core is a heterocyclic scaffold for a large series of significant natural and synthetic biologically active compounds. Many natural pteridines are involved in cellular metabolism. Therefore, the regioselective synthesis of new pteridine derivatives with potential biological activity is exceedingly crucial [1]. Use of S_N^H-functionalization of C–H bonds via direct substitution of H by C-nucleophiles and production of products with C–C bonds was promising during development of effective synthetic methods for natural and synthetic biologically active heterocyclic compounds [2, 3].

Chichibabin substitution of H in unsubstituted 1,3-dimethyllumazine was reported for the reaction with alkylamines in the presence of oxidizers to give 7-substituted 1,3-dimethyl-2,4-dioxopyrimido-[4,5-*b*]pyrazine derivatives [4]. The C-6 atom of 1,3-dimethyllumazine was alkoxylated regioselectively during the reaction with *N*-bromosuccinimide in alcohols [5]. Examples of direct functionalization of C–H bonds using C-nucleophiles are unknown for 1,3-dimethyllumazine.

The goals of the present work were to investigate the specifics and features of direct H substitution in reactions of 1,3-dimethyllumazine with C-nucleophiles, to study ways of activating the substrate and reagents, and to determine the points of nucleophilic attack.



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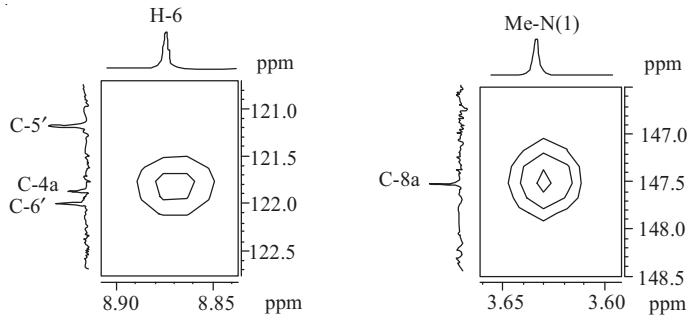

Fig. 1. Portions of 2D $^{1}H–^{13}C$ HMBC spectra (500 MHz, DMSO-d_6) of **3b**.

We found that unsubstituted 1,3-dimethylumazine (**1**) reacted with heating with C-nucleophiles [indoles **2a**–**c**, 3-methyl-1-phenylpyrazolone-5 (**4**), polyphenols **6** and **8**] in the presence of acids to give products of nucleophilic substitution of the C-7 H (**3a**–**c**, **5**, **7**, and **9**).

The reaction of lumazine **1** with indoles **2** was carried out with heating in AcOH for 35–40 h at 110°C. The yield of substitution products was 20–25% (**3a**), 30–35% (**3b**), and 15–20% (**3c**). Lumazine **1** reacted with pyrazolone **4** under analogous conditions to give **5** in 25–30% yields.

Substitution products of **1** with polyphenols formed under these conditions only in trace amounts. However, performing the reaction of **1** with polyphenols in trifluoroacetic acid afforded substitution products **7** and **9** in 45–50% yields.

2D $^{1}H–^{13}C$ HSQC and HMBC experiments proved that H-7 in **1** was substituted during the reactions with C-nucleophiles. Thus, the HMBC spectrum of **3b** showed a cross peak corresponding to spin–spin coupling of H-6 and quaternary C-4a (Fig. 1).

Another analogous coupling between H-7 and C-8a would have been observed if an alternative reaction course (substitution of H-6) had occurred. However, a cross peak corresponding to this was missing in the spectrum. In turn, bridging C atoms C-4a and C-8a had readily differentiated chemical shifts (the C-4a resonance appeared at stronger field than that of C-8a). Furthermore, C-8a was identified unambiguously from a cross peak with the N-1 methyl protons in the HMBC spectrum.

Acid catalysis was found during the course of the work to play a decisive role in the nucleophilic substitution of H in the pyrazine portion of **1**. Moreover, such transformations were not observed without an acid.

Substitution product **5** was not produced during the reaction of **1** with pyrazolone **4** in DMSO in the presence of Et_3N. The known dipyrazolylmethane **10** was identified in the reaction mixture using TLC and GC-MS [6].

We found earlier that the reaction of quinoxaline (or 3-phenyl-1,2,4-triazine) with 3-methyl-1-phenylpyrazolone-5 in the presence of Et_3N led to elimination of a C–C moiety from the pyrazine (or triazine) core and formed the tetrapyrazolylethane derivative, which was readily converted to dipyrazolylmethane [6, 7].

It could be assumed that base catalysis caused the analogous elimination of a C–C moiety from the pyrazine core of **1** to give the tetrapyrazolylethane derivative, which transformed into dipyrazolylmethane **10** during the course of the reaction.

1,3-Dimethyl-7-(1′*H*-indol-3′-yl)pteridine-2,4(1*H*,3*H*)-dione (3a). Yield 20–25%, mp > 300°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.33, 3.70 (3H each, s, NMe), 7.23–7.29 (2H, m, H-5′, 6′), 7.53 (1H, m, H-7′), 8.48 (1H, m, H-4′), 8.68 (1H, d, J = 3.2, H-2′), 9.10 (1H, s, H-6), 12.16 (1H, br.s, NH). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 307 ([M^+], 100), 195 (23), 140 (30). $C_{16}H_{13}N_5O_2$.

1,3-Dimethyl-7-(2′-methyl-1′*H*-indol-3′-yl)pteridine-2,4(1*H*,3*H*)-dione (3b). Yield 30–35%, mp > 300°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.80 (3H, s, CH_3-2′), 3.33 (3H, s, CH_3-N3), 3.64 (3H, s, CH_3-N1), 7.16–7.21 (2H, m, H-5′, 6′), 7.43 (1H, m, H-7′), 8.20 (1H, m, H-4′), 8.88 (1H, s, H-6), 11.98 (1H, s, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6, δ, ppm): 15.03 (CH_3-2′), 28.22 (CH_3-N3), 29.05 (CH_3-N1), 108.35 (C-3′), 111.44 (C-7′), 119.85 (C-4′), 121.18 (C-5′), 121.88 (C-4a), 122.02 (C-6′), 126.29 (C-3′a), 135.49 (C-7′a), 137.39 (C-6), 141.51 (C-2′), 147.56 (C-8a), 150.72 (C-2), 153.79 (C-7), 159.64 (C-4). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 321 ([M^+], 100). $C_{17}H_{15}N_5O_2$.

1,3-Dimethyl-7-(1′-methyl-1′*H*-indol-3′-yl)pteridine-2,4(1*H*,3*H*)-dione (3c). Yield 15–20%, mp > 300°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.34, 3.71 (3H each, s, NCH_3), 3.94 (3H, s, CH_3-N1′), 7.30–7.37 (2H, m, H-5′, 6′), 7.63 (1H, m, H-7′), 8.50 (1H, m, H-4′), 8.70 (1H, s, H-2′), 9.03 (1H, s, H-6). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 321 ([M^+], 100), 209 (20), 140 (17). $C_{17}H_{15}N_5O_2$.

1,3-Dimethyl-7-(3′-methyl-5′-oxo-1′-phenyl-1′,5′-dihydropyrazol-4′-ylidene)-7,8-dihydropteridine-2,4(1*H*,3*H*)-dione (5). Yield 25–30%, mp > 300°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.65 (3H, s, CH_3-3′), 3.25 (1H, br.s, NH + H_2O), 3.31, 3.56 (3H each, s, NCH_3), 7.28 (1H, t, J = 7.3, H_p), 7.48 (2H, t, J = 7.5, H_m), 7.74 (2H, d, J = 7.7, H_o), 9.40 (1H, s, H-6). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 364 ([M^+], 100). $C_{18}H_{16}N_6O_3$.

1,3-Dimethyl-7-(2′,4′-dihydroxyphenyl)pteridine-2,4(1*H*,3*H*)-dione (7). Yield 45–50%, mp > 300°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.37, 3.62 (3H each, s, NCH_3), 6.38–6.40 (2H, m, H-3′, 5′), 7.95 (1H, d, J = 9.2, H-6′), 9.23 (1H, s, H-6), 9.92 (1H, s, OH), 11.06 (1H, s, OH). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 300 ([M^+], 100). $C_{14}H_{12}N_4O_4$.

1,3-Dimethyl-7-(2′,3′,4′-trihydroxyphenyl)pteridine-2,4(1*H*,3*H*)-dione (9). Yield 40–45%, mp > 300°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.38, 3.63 (3H each, s, NCH_3), 6.48 (1H, d, J = 8.8, H-5′), 7.50 (1H, d, J = 8.8, H-6′), 8.5 (1H, br.s, OH), 9.20 (1H, s, H-6), 9.5, 10.7 (1H each, br.s, OH). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 316 ([M^+], 100). $C_{14}H_{12}N_4O_5$.

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