Pteridines, CIV.[1] REGIOSELECTIVE ALKOXYLATION OF PTERIDINES AT THE 6-POSITION BY *N*-BROMOSUCCINIMIDE AND ALCOHOL

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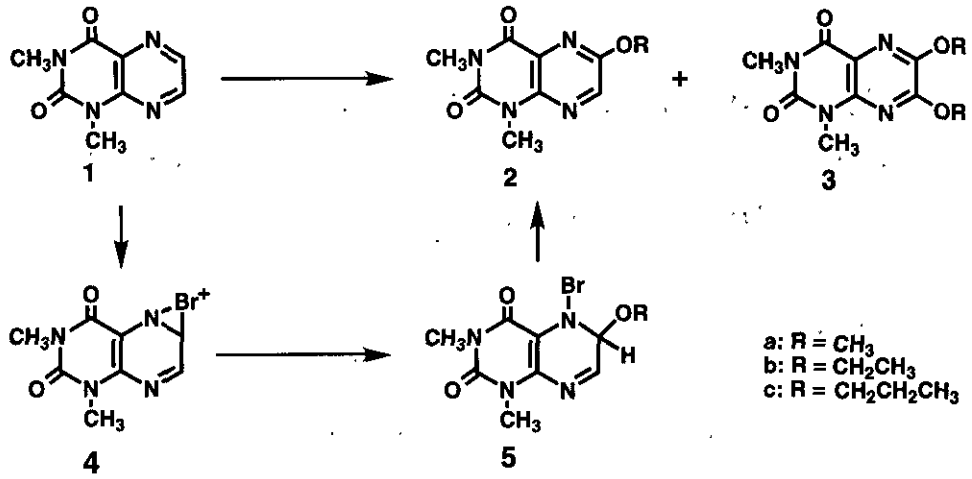
Abstract— Reaction of 1,3-dimethyllumazine with *N*-bromosuccinimide or bromine in an appropriate alcohol afforded 6-alkoxy-1,3-dimethyllumazine. *N*-Iodosuccinimide or iodine also brought about the same reaction. This procedure was applicable to other pteridine compounds, such as 2-dimethylamino-4(3*H*)-oxopteridine. The mechanism of this alkoxylation reaction is discussed.

Substitution of a hydrogen at the pteridine ring by a nucleophilic reagent like alcohols or amines has not been recorded in the literature.[2] This is attributed to the competitive and more avid covalent addition of such reagent to the pteridine nucleus.[2] Indeed, almost all alkoxypteridines were synthesized either from the corresponding chloropteridines by nucleophilic replacement or from appropriate synthons bearing the alkoxy substituent. We describe here a new method to introduce an alkoxy group directly to the pteridine nucleus by the action of *N*-bromosuccinimide or bromine in an appropriate alcohol.

Reaction of 1,3-dimethyllumazine (**1**) with *N*-bromosuccinimide (NBS; 2 eq.) in boiling methanol gave a monomethoxy derivative of **1** in 77% yield. The structure of the product was confirmed to be 6-methoxy-1,3-dimethyllumazine (**2a**) by a direct comparison with the authentic 6-methoxy-[3] and 7-methoxy-1,3-dimethyllumzines[4] by tlc on a silica gel plate and mixture melting point test. When the



Scheme 1. Formation of 6-alkoxy- and 6,7-dialkoxy-1,3-dimethyllmazines (**2** and **3**) from **1** by NBS (or Br_2) in alcohol.

reaction was carried out by employing 6 molar eq. of NBS at room temperature for 7 days, 6,7-dimethoxy-1,3-dimethyllumazine (**3a**)[5] was also formed together with the 6-methoxy compound. No 7-methoxy-1,3-dimethyllumazine could be detected.

When ethanol was used as the reaction medium in place of methanol, the corresponding 6-ethoxy-1,3-dimethyllumazine (**2b**) and 6,7-diethoxy-1,3-dimethyllumazine (**3b**) were obtained. A similar reaction in 1-propanol gave 1,3-dimethyl-6-propoxylumazine (**2c**). However, **1** did not react with NBS in 2-propanol and 2-methyl-2-propanol. In the above reactions, development of a color typical to bromine was observed, indicating that bromine might also bring about the alkoxylation reaction. Indeed, **1** and bromine in methanol produced the 6-methoxy- and 6,7-dimethoxy-1,3-dimethyllumazines.

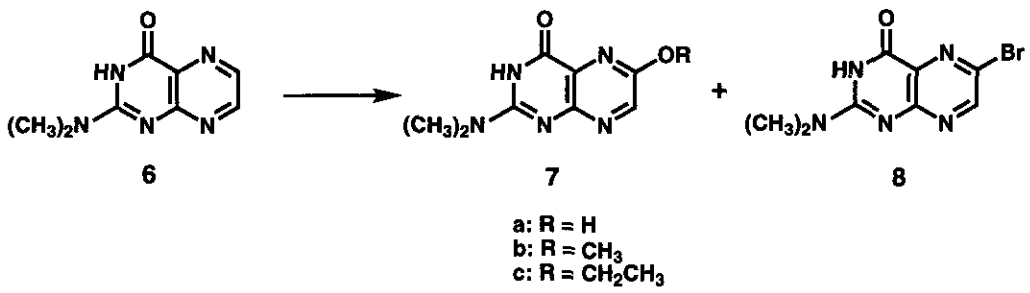
The regioselective formation of the 6-alkoxy-1,3-dimethyllumazine (**2**) is best explained by a mechanism shown in Scheme 1. Namely, interaction of **1** with NBS or bromine at the 5,6-double bond to form the bromonium compound (**4**) seems to be the most probable initial step of the reaction. The cation (**4**) easily reacts with alcohol at the 6-position to give the ring opened product (**5**), which on subsequent elimination of hydrogen bromide forms the 6-alkoxy-1,3-dimethyllumazines (**2**). An AM1 calculation on 1,3-dimethyllumazine (**1**) supports this assumption: among the four possible reaction cites, the carbon at the 6-position has the highest HOMO as shown in Table 1. Electrophilic bromine first attacks this position to form the initial intermediate (**4**). An alternative path from **1** to **2** *via* an

Table 1. The atomic charges and HOMOs of 1,3-dimethyllumazine and 2-dimethylamino-4(3*H*)-oxopteridine obtained by AM1 calculation.

	1,3-Dimethyllumazine		2-Dimethylamino-4(3*H*)-oxopteridine	
position	atomic charge*	HOMO	atomic charge*	HOMO
N-5	-0.059	0.066	-0.069	0.088
C-6	0.050	0.418	0.040	0.385
C-7	0.160	0.208	0.138	0.128
N-8	-0.197	0.198	-0.150	0.205

*Atomic charges with hydrogens summed into heavy atoms.

initial addition of an alcohol across the 5,6-double bond and subsequent oxidation of the adduct by NBS (or bromine) seems not plausible; no reaction of the substrate (**1**) was detected on a prolonged heating with manganese dioxide in methanol. The following three sets of reaction conditions were examined with an expectation to get 6-bromo- or 6-acetoxy-1,3-dimethyllumazine: (A) **1** and bromine in carbon tetrachloride, (B) **1** and NBS in the presence of tetrabutylammonium bromide in chloroform, and (C) **1** and NBS in the presence of sodium acetate in acetic acid. Under these three conditions, no change of **1** was observed. However, addition of methanol to (A), or ethanol to (B) resulted in the production of 6-methoxy- or 6-ethoxy-1,3-dimethyllumazine, respectively. Probably, alcohol contributes to decrease the activation energy leading to **4**. *N*-Iodosuccinimide and iodine also reacted with **1** in methanol, giving the 6-methoxy compound (**2a**), though the reaction proceeded much slower than with NBS and bromine. In an oxidation by peroxyacrboxylic acid or hydrogen peroxide in an appropriate acid, **1** produces the *N*-oxide at the 5- position selectively,[6] even though the atomic charge at the N-5 position is lower than that at the N-8 position. This regioselectivity owes much to steric hindrance by the methyl group at the 1-position, which prevents hydrogen peroxide or peroxycarboxylic acid to approach to the N-8 position.[7] Indeed, those pteridines carring no substituent at the 1-position, such as lumazine and 2-amino-4(3*H*)-oxopteridine, produce the *N*-oxides at the 8-position.[6] If the present alkoxylation reaction proceeds through a mchanism similar to that for *N*-oxidation, 2-dimethylamino-4(3*H*)-oxopteridine (**6**) is expected to produce a 7-alkoxy derivative through an initial bromination on the more electron rich nitrogen atom at the 8-position, addition of aclohol to the 7,8-double bond, and subsequent elimination of hydrogen bromide. In order to prove the reaction mechanism shown in Scheme 1, we examined the



Scheme 2. Formation of 6-alkoxy- and 6-bromo-2-dimethylamino-4(3*H*)-oxopteridine (**7** and **8**) from **6** by NBS and alcohol.

reaction of 2-dimethylamino-4(3*H*)-oxopteridine (**6**) with NBS in alcohol. 2-Dimethylamino-4(3*H*)-oxopteridine (**6**) reacted much faster than 1,3-dimethyllumazine (**1**) with NBS in methanol, giving 6-methoxy-2-dimethylamino-4(3*H*)-oxopteridine (**7b**) and 6-bromo-2-dimethylamino-4(3*H*)-oxopteridine (**8**). The same substrate with NBS in ethanol gave 6-ethoxy-2-dimethylamino-4(3*H*)-oxopteridine (**7c**) and the bromo compound (**8**). The position of the introduced alkoxyl group was confirmed to be the 6-position by a direct comparison of its hydrolysis product with the authentic 2-dimethylamino-4,6(3*H*,5*H*)-dioxopteridine[8] (**7a**) on a cellulose plate. The bromo compound (**8**), on heating with potassium *t*-butoxide in ethanol, gave the 6-ethoxy derivative (**7c**).

Here again, the substituion on **6** took place at the 6-position. It seems that a reaction path analogous to that in Scheme 1 proceeds also with **6**; addition of bromine across the 5,6-double bond to form the bromonium intermediate analogous to **4**, attack by alcohol to open to the three-member ring, and subsequent elimination of hydrogen bromide. Loss of the proton on C-6 of the bromonium intermediate leads to the 6-bromopteridine (**8**). Evidently, the 6-alkoxypteridines (**7**) were not formed *via* the 6-bromopteridine (**8**), because the latter was stable in hot methanol.

EXPERIMENTAL

6-Methoxy- and 6,7-dimethoxy-1,3-dimethyllumazines (2a and 3a)

(a) A solution of 1,3-dimethyllumazine (**1**) (1.92 g, 10 mmol) and NBS (3.6 g, 20 mmol) in methanol (80 ml) was heated under reflux for 24 h. The solution was evaporated to dryness on a rotary evaporator. The residue was mixed with hot water (80 ml) and chilled. Filtration gave practically pure 6-

methoxy-1,3-dimethyllumazine (**2a**) (1.72 g, 77%). Recrystallization from toluene gave colorless needles, mp 216-217 °C (lit.,[3] 224 °C) (Anal. Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.22. Found: C, 48.76; H, 4.58; N, 22.25). ^{1}H Nmr ($CDCl_3$): δ 8.32 (1H, s, 7-H), 4.10 (3H, s, *O*-CH_3), 3.70 (3H, s, *N*-CH_3), and 3.52 (3H, s, *N*-CH_3); λ_{max} nm (log ε) in methanol: 245 (4.20), 337 (sh, 3.69), 354 (3.86), and 364 (sh, 3.81).

(b) A solution of **1** (0.48 g, 2.5 mmol) and NBS (2.5 g, 14 mmol) in methanol (100 ml) was stirred at room temperature for 7 days. The solution, after evaporation, extraction of the residue with chloroform (2 x 30 ml), and chromatography on a silica gel column (2 x 25 cm) eluted with a mixture of toluene and ethyl acetate (1:1, v/v), gave **2a** (0.15 g, 27%) and 6,7-dimethoxy-1,3-dimethyllumazine (**3a**) (0.155 g, 25%) as colourless prisms, mp 217-218 °C (from toluene) (lit.,[5] 226 °C)(Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.54; H, 4.75; N, 21.91). ^{1}H Nmr ($CDCl_3$): δ 4.16(3H, s, *O*-CH_3), 4.15 (3H, s, *O*-CH_3), 3.66 (3H, s, *N*-CH_3), and 3.50 (3H, s, *N*-CH_3); λ_{max} nm (log ε) in methanol: 234 (sh, 4.04), 264 (3.98), 318 (sh, 3.92), 333 (4.05), and 342 (sh, 4.04).

Compound (**1**)(0.19 g, 1 mmol) and *N*-iodosuccinimide (0.45 g, 2 mmol) in methanol (20 ml) at room temperature for 3 weeks gave **2a** (40 mg, 18%).

(c) A solution of bromine (0.64 g, 4 mmol) in methanol (2 ml) was added to a boiling solution of **1** (0.48 g, 2.5 mmol) in methanol (20 ml). After refluxing for 1 h, the same amount of bromine was added and refluxing was continued for an additional 1 h. Then the solution was evaporated to dryness. The residue, on extraction, chromatography, and crystallization as above, gave **2a** (0.26 g, 47%) and **3a** (70 mg, 11%).

Compound (**1**) (0.48 g, 2.5 mmol) and iodine (1.65 g, 6.5 mmol) in methanol (100 ml) under reflux for 24 h gave **2a** (70 mg, 13%).

(d) A solution of **1** (0.48 g, 2.5 mmol) and bromine (3 g, 18 mmol) in tetrachloromethane (250 ml) was stirred at room temperature for 3 days. No reaction of the substrate was observed on tlc analysis. Then, methanol (20 ml) was added to the solution and stirred for 3 days. Evaporation and column chromatography as above, followed by crystallization from toluene, gave **2a** (0.19 g, 34%).

6-Ethoxy- and 6,7-diethoxy-1,3-dimethyllumazines (2b and 3b)

(a) A solution of **1** (0.48 g, 2.5 mmol) and NBS (3 g, 17 mmol) in ethanol (150 ml) was stirred at room temperature for 4 days. Evaporation to dryness, extraction with chloroform, chromatography on a silica gel column, and crystallization from toluene as above gave 6-ethoxy-1,3-dimethyllumazine (**2b**) as

colorless needles (0.27 g, 50%), mp 190-191 °C (Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.71. Found: C, 50.91; H, 5.14; N, 23.52) and 6,7-diethoxy-1,3-dimethyllumazine (**3b**) as colorless needles (0.14 g, 20%), mp 180.5-181.5 °C (Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.35; H, 5.75; N, 19.82). **2b**: ^{1}H Nmr ($CDCl_3$): δ 8.30 (1H, s, 7-H), 4.53 (2H, q, J = 7.1 Hz, CH_2), 3.65 (3H, s, *N*-CH_3), 3.52 (3H, s, *N*-CH_3), and 1.44 (3H, t, J = 7.1 Hz, CH_3); λ_{max} nm (log ε) in methanol: 245 (4.19), 355 (3.84), and 363 (sh, 3.80). **3b**: ^{1}H Nmr ($CDCl_3$): 4.28 (2H, q, J = 7.1 Hz, CH_2), 4.47 (2H, q, J = 7.1 Hz, CH_2), 3.62 (3H, s, *N*-CH_3), 3.47 (3H, s, *N*-CH_3), 1.50 (3H, t, J = 7.1 Hz, CH_3), and 1.45 (3H, t, J = 7.1 Hz, CH_3); λ_{max} nm (log ε) in methanol: 236 (sh, 4.02), 265 (3.97), 320 (sh, 3.92), 334 (4.05), and 346 (sh, 3.96).

(b) A solution of **1** (0.48 g, 2.5 mmol), NBS (1.8 g, 10 mmol), and tetrabutylammonium bromide (1 g, 3 mmol) in chloroform (30 ml) was stirred at room temperature for 4 days. No reaction of the substrate was observed on tlc analysis. Ethanol (20 ml) was added and the solution was allowed to stand at room temperature for 7 days. The Product (**2b**) (0.155 g, 26%) was isolated from the reaction solution in an analogous way including chromatography and crystallization from toluene as above.

Compound (**1**) (0.48 g, 2.5 mmol) and bromine (3.2 g, 10 mmol) in ethanol (30 ml) under refluxing for 1 h gave **2b** (70 mg, 10%).

1,3-Dimethyl-6-propoxylumazine (2c)

A solution of **1** (0.48 g, 2.5 mmol) and NBS (4 g, 22 mmol) in 1-propanol (150 ml) was stirred at room temperature for 2 days. Evaporation to dryness, extraction with chloroform, chromatography on a silica gel column, and crystallization from toluene as above gave 1,3-dimethyl-6-propoxylumazine (**2c**) as colorless needles (0.10 g, 16%), mp 134-135 °C (Anal. Calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.78; H, 5.69; N, 22.32). ^{1}H Nmr ($CDCl_3$): δ 8.29 (1H, s, 7-H),, 4.41 (2H, q, J = 6.7 Hz, *O*-CH_2-), 3.68 (3H, s, *N*-CH_3), 3.50 (3H, s, *N*-CH_3), 1.92-1.77 (2H, m, CH_2), and 1.04 (3H, t, J = 7.4 Hz, CH_3); λ_{max} nm (log ε) in methanol: 245 (4.20), 355 (3.85), and 363 (sh, 3.81).

6-Methoxy- and 6-bromo-2-dimethylamino-4(3H)-oxopteridines (7b and 8)

A solution of 2-dimethylamino-4(3*H*)-oxopteridine (0.48 g, 2.5 mmol) and NBS (0.58 g, 3.2 mmol) in methanol (90 ml) was stirred at room temperature for 2 days. Silica gel (5 g) was added to the solution and the mixture was evaporated to dryness on a rotary evaporator. The solid residue was placed on the top of a silica gel column (2 x 20 cm) and eluted first with a mixture of acetonitrile and toluene (2:1, v/v). Evaporation and crystallization from methanol gave yellow needles (0.125 g, 19%) of 6-bromo-2-

dimethylamino-4(3*H*)-oxopteridine (**8**), mp 270-272 °C (decomp). (Anal. Calcd for $C_8H_8N_5OBr$: C, 35.57; H, 2.98; N, 25.93. Found: C, 35.56; H, 3.00; N, 25.80). ^{1}H Nmr ($CDCl_3$): δ 8.72 (1H, s, 7-H) and 3.33 [6H, s, *N*(CH_3)2]; λ_{max} nm (log ε) in methanol: 222(sh, 4.04), 249 (3.93), 292(4.36), 370 (sh, 3.64), and 386 (3.68). The column was then eluted with a mixture of chloroform and methanol (9:1, v/v). Evaporation of the eluate and crystallization of the residue from methanol gave ivory needles (0.123 g, 22%) of 6-methoxy-2-dimethylamino-4(3*H*)-oxopteridine (**7b**), mp 235-237 °C (Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.85; H, 5.05; N, 31.46). ^{1}H Nmr ($CDCl_3$): δ 8.41 (1H, s, 7-H), 4.05 (3H, s, *O*-CH_3), and 3.27 [6H, s, *N*(CH_3)2]; λ_{max} nm (log ε) in methanol: 229 (4.11), 249 (sh, 4.02), 283 (4.29), 348 (sh, 3.58), 367 (3.68), and 390 (sh, 3.56).

*6-Ethoxy- and 6-bromo-2-dimethylamino-4(3*H*)-oxopteridines (7c and 8)*

A solution of **6** (0.48 g, 2.5 mmol) and NBS (0.50 g, 2.8 mmol) in ethanol (150 ml) was stirred at room temperature for 4 days. Silica gel (5 g) was added to the solution and the mixture was evaporated to dryness on a rotary evaporator. The solid residue was placed on the top of a silica gel column (2 x 20 cm) and eluted with a mixture of chloroform and methanol (9:1, v/v). Evaporation of the first blue fluorescent eluate and crystallization of the residue from methanol gave yellow needles (75 mg, 11%) of **8**. Evaporation of the second blue fluorescent eluate and crystallization of the residue from methanol gave ivory needles (0.21 g, 36%) of 6-ethoxy-2-dimethylamino-4(3*H*)-oxopteridine (**7c**), which decomposed above 270 °C without melting (Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.56; N, 29.77. Found: C, 51.00; H, 5.69; N, 29.58). ^{1}H Nmr (DMSO-d_6): δ 8.41 (1H, s, 7-H), 4.34 (2H, q, *J* = 7.1 Hz, CH_2), 3.09 [6H, s, *N*(CH_3)2], and 1.35 (3H, t, *J* = 7.1 Hz, CH_3); λ_{max} / nm (log ε) in methanol: 230 (4.13), 248 (sh, 4.04), 283 (4.30), 349 (sh, 3.61), 367 (3.69), and 390 (sh, 3.58).

*Hydrolysis of 6-ethoxy-2-dimethylamino-4(3*H*)-oxopteridine*

A solution of 6-ethoxy-2-dimethylamino-4(3*H*)-oxopteridine (40 mg, 0.17 mmol) in 0.5 M hydrochloric acid (10 ml) was heated under gentle reflux for 45 min. The solution was treated with activated charcoal, neutralized with 1.4% ammonia, and evaporated to dryness. The residue was submitted to chromatography twice on a silica gel column (2 x 25 cm) by eluting with a mixture of chloroform and methanol (5:1, v/v). Evaporation of the eluate gave a solid, which was dissolved in hot ethanol and concentrated to about 1 ml to give yellowish brown powder (8 mg, 23%) of 2-dimethylamino-4,6(3*H*,5*H*)-dioxopteridine (**7a**).

*Conversion of 6-bromo- 2-dimethylamino-4(3*H*)-oxopteridineinto 6-ethoxy-2-dimethylamino-4(3*H*)-oxopteridine*

A few milligrams of 6-bromo-2-dimethylamino-4(3*H*)-oxopteridine (**8**) and t-BuOK (about 20 mg) in ethanol (20 ml) were heated under reflux overnight. After neutralization with acetic acid, the product was identified as 6-ethoxy-2-dimethylamino-4(3*H*)-oxopteridine (**7c**) by a direct comparison on silica gel plates.

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