Imidazopteridines. II.[1] Synthesis of Imidazo[1,2-*c*]pteridines with a Functional Group at the 6-Position

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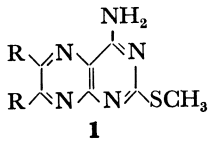
Several imidazo[1,2-*c*]pteridines with a functional group such as amino, alkylamino, alkoxyl, or hydroxyl group at the 6-position were synthesized by a nucleophilic replacement of 6-methylthioimidazo[1,2-*c*]pteridine with an appropriate nucleophile. The key intermediate methylthio compound was synthesized by condensation of 4-amino-2-methylthiopteridine with chloroacetaldehyde. Similarly, 4-amino-6,7-dimethyl-2-methylthiopteridine and chloroacetaldehyde gave 2,3-dimethyl-6-methylthioimidazo[1,2-*c*]pteridine, which was also used as a precursor to synthesize several imidazopteridines analogous to above.

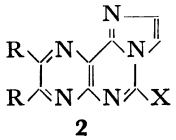
In the course of our research programs on tricyclic imidazoazines,[1-4] we previously reported the synthesis of the parent imidazo[1,2-*c*]pteridine and its *C*-alkyl derivatives.[1] These compounds were found to be susceptible to ring-opening reaction into an 2-amino-3-(2-imidazolyl)pyrazine *via* a nucleophilic addition of water at the 6-position. This ring-opening reaction proceeded easily even in the presence of a blocking methyl group[5] at the site of addition. All these results indicated a high reactivity of the ring system toward various nucleophiles at the 6-position. This paper reports the synthesis of some 6-methylthio derivatives of the ring system and their easy derivation into a variety of imidazo[1,2-*c*]pteridines with a functional group at the 6-position.

Condensation of 4-amino-2-methylthiopteridine(**1a**) with chloroacetaldehyde at pH 6—7 gave intensive blue fluorescent 6-methylthioimidazo[1,2-*c*]pteridine-(**2a**) in about 45% yield. When the reaction was carried out at the pH values out of the above range, either higher or lower, the yield of **2a** lowered significantly, probably due to instability of **2a** under such conditions. The structure of the product was confirmed from the elemental analyses, pK_a values, and UV spectra (Table 1) which showed a characteristic bathochromic shift when the molecule was doubly protonated. The ^1H NMR spectrum of **2a** showed two singlets at δ 2.68 for the methyl group and at δ 7.86 for the imidazole ring protons and a pair of doublets at δ 8.82 and 8.92 (J=2 Hz) representing the pyrazine ring protons. Analogous treatments of 4-amino-6,7-dimethyl-2-methylthiopteridine(**1b**) with chloroacetaldehyde furnished 2,3-dimethyl-6-methylthioimidazo[1,2-*c*]-pteridine(**2b**).



1

a: R=H
b: R=CH_3



2

a: R=H, X=SCH_3
b: R=CH_3, X=SCH_3
c: R=H, X=NH_2
d: R=CH_3, X=NH_2
e: R=H, X=$NHCH_3$
f: R=CH_3, X=$NHCH_3$
g: R=H, X=$NHCH_2CH_3$
h: R=CH_3, X=$NHCH_2CH_3$
i: R=H, X=$NHCH_2CH_2OH$
j: R=CH_3, X=$NHCH_2CH_2OH$
k: R=H, X=OH
l: R=CH_3, X=OH
m: R=H, X=OCH_2CH_3
n: R=CH_3, X=OCH_2CH_3
o: R=H, X=OCH_3
p: R=CH_3, X=OCH_3

These methylthioimidazopteridines(**2a** and **2b**) were found to be highly reactive toward various nucleophiles and proved to be useful precursors for the synthesis of many other imidazo[1,2-*c*]pteridines with a functional group such as amino, alkylamino, hydroxyl, or alkoxyl group at the 6-position. Aminolysis of **2a**, carried out by heating with ethanolic ammonia, gave 6-aminoimidazo[1,2-*c*]pteridine(**2c**) in a high yield. A similar aminolysis of the methylthio compound (**2a**) with methylamine, ethylamine, or 2-aminoethanol gave 6-methylamino-(**2e**), 6-ethylamino-(**2g**), and 6-(2-hydroxyethylamino)imidazo[1,2-*c*]pteridines (**2i**), respectively. The basic characters of these amino compounds were fairly strenghened compared to that of the precursor (see Table 1) on replacement of the methylthio group by an amino group. All of these aminoimidazopteridines (**2e**, **2g**, and **2i**) were of very similar UV spectra, which also showed a large bathochromic shift on double protonation. Similarly, 2,3-dimethyl-6-methylthioimidazo[1,2-*c*]pteridine (**2b**) gave the 6-amino and 6-alkylamino analogues (**2d**, **2f**, **2h**, and **2j**) on aminolysis with the corresponding amine. Conversion of the methylthio compounds (**2a** and **2b**) into 6-hydroxyimidazo[1,2-*c*]pteridines (**2k** and **2l**) was achieved by heating either in dilute aqueous sodium hydroxide or in dilute hydrochloric acid. On the other hand, 6-ethoxyimidazo[1,2-*c*]pteridine (**2m**) and its 2,3-dimethyl derivative (**2n**) were obtained in a rather unusual way from the corresponding methylthio precursors (**2a** and **2b**) by heating in ethanol with silver oxide, a reagent recently reported useful for an exchange of alkoxyl groups in several heterocyclic systems.[6] Treatment of **2a** with sodium ethoxide or hydrogen chloride in ethanol gave no ethoxy compound (**2m**); the sole product was 6-hydroxyimidazopteridine(**2k**). Similar treatments of **2a** and **2b** with silver oxide in methanol gave the corresponding 6-methoxyimidazo[1,2-*c*]pteridines (**2o** and **2p**).

Experimental

The elemental analyses were carried out at the Analytical Section, Meijo University and at the Analytical Section,

TABLE 1. THE pK_a VALUES AND UV SPECTRA OF IMIDAZO[1,2-*c*]PTERIDINES

Compound	pK_a	Ionic species[a]	λ_{max} (log ε)[b]	pH of buffer[c]
2a	2.20±0.02	○	232(4.29), 255(4.30), *292(3.76)*, 303(3.78), 350(4.09)	4.5
	−2.62±0.02	+	225(4.21), 253(4.23), *287(4.03)*, 294(4.04), 343(4.06), *355(4.00)*	0.0
		++	241(4.19), *270(4.03)*, 290(4.00), 386(4.09)	−4.0
2b	2.60±0.02	○	232(4.38), 252(4.24), *294(3.81)*, 304(3.82), 351(4.19)	5.0
	−1.50±0.02	+	226(4.25), 248(4.24), *288(4.05)*, 296(4.07), 342(4.17) 353(4.14)	0.5
		++	242(4.28), *265(3.97)*, *297(3.98)*, 310(4.03), 384(4.20)	−3.5
2c	2.71±0.02	○	228(4.43), 255(3.96), *280(3.58)*, 357(4.13)	5.0
	−0.96±0.04	+	214(4.32), 251(4.11), 273(3.91), 354(4.01)	1.0
		++	224(4.37), 270(4.01), *337(3.68)*, 354(3.82), 392(4.08)	−3.0
2d	3.19±0.03	○	227(4.54), 255(4.00), 282(3.73), 358(4.22)	5.5
	−0.18±0.04	+	219(4.41), 251(4.17), 275(3.99), *285(3.96)*, 356(4.12)	1.5
		++	224(4.46), 270(4.06), *290(3.91)*, 396(4.25)	−2.5
2e	2.71±0.02	○	228(4.44), *260(3.97)*, *290(3.72)*, 361(4.14)	5.0
	−0.81±0.03	+	217(4.32), *230(4.20)*, 259(4.12), 277(4.07), 364(4.01)	0.5
		++	228(4.37), 278(4.07), *295(3.92)*, 402(4.15)	−3.0
2f	3.38±0.02	○	227(4.55), 257(4.01), 284(3.88), 362(4.23)	5.5
	0.03±0.05	+	220(4.40), 254(4.16), 279(4.15), 286(4.15), 365(4.11)	1.5
		++	227(4.44), *280(4.10)*, 296(4.12), 406(4.28)	−2.5
2g	2.91±0.02	○	228(4.42), *260(4.01)*, *285(3.76)*, 362(4.13)	5.0
	−0.72±0.03	+	217(4.30), *230(4.17)*, 260(4.13), 279(4.09), *282(4.08)*, 367(4.00)	1.0
		++	228(4.35), 279(4.08), *293(3.97)*, 403(4.15)	−3.0
2h	3.42±0.02	○	227(4.51), 257(3.99), 283(3.87), *290(3.86)*, 363(4.20)	5.5
	0.31±0.05	+	219(4.39), 255(4.14), 279(4.14), 286(4.15), 367(4.07)	1.5
		++	226(4.37), 280(4.06), 296(4.08), 407(4.22)	−3.0
2i	2.76±0.02	○	228(4.43), *260(4.00)*, *285(3.75)*, 361(4.14)	5.0
	−0.86±0.03	+	217(4.31), 258(4.14), 278(4.08), *283(4.06)*, 363(4.01)	1.0
		++	228(4.37), 277(4.09), *293(3.94)*, 399(4.17)	−3.0
2j	3.32±0.02	○	228(4.53), 257(4.01), 284(3.89), *290(3.87)*, 362(4.21)	5.5
	0.00±0.05	+	220(4.38), 255(4.16), 279(4.15), 286(4.14), 364(4.10)	1.5
		++	228(4.43), 279(4.10), 297(4.11), 404(4.27)	−2.5
2k	7.39±0.02	−	223(4.42), 256(3.99), *283(3.58)*, 363(4.16)	9.5
	2.08±0.05	○	218(4.16), 240(3.89), 278(3.38), 343(4.21)	5.0
		+	230(4.02), 262(3.60), 337(4.19), 350(4.15)	−0.5
2l	7.79±0.02	−	222(4.48), 254(3.99), *280(3.71)*, 365(4.20)	10.0
	2.34±0.02	○	217(4.29), 241(3.93), *270(3.51)*, 346(4.26)	4.5
		+	209(4.22), 232(4.11), 262(3.75), *270(3.67)*, 341(4.25), 354(4.22)	−0.5
2m	2.28±0.02	○	220(4.34), *250(3.82)*, 278(3.37), 342(4.01)	4.5
	−2.60±0.02	+	215(4.14), *235(3.97)*, 263(3.56), 330(4.00), *345(3.90)*	0.0
		++	218(4.31), *255(3.82)*, 354(4.05)	−4.0
2n	2.85±0.02	○	223(4.37), *245(3.87)*, 279(3.51), 287(3.51), 344(4.12)	5.0
	−1.29±0.03	+	213(4.42), *235(4.03)*, 265(3.74), *273(3.66)*, 333(4.12) 347(4.08)	0.5
		++	220(4.36), 258(3.86), *277(3.57)*, *360(4.16)*, 369(4.17)	−3.4
2o	2.20±0.04	○	220(4.19), *247(3.75)*, 289(3.27), 343(3.93)	4.5
	−2.54±0.03	+	215(4.19), *235(3.90)*, 263(3.46), 329(3.93), *342(3.83)*	0.0
		++	215(4.22), *255(3.71)*, 352(3.97), *365(3.92)*	−4.0
2p	2.83±0.02	○	223(4.24), *243(3.74)*, 286(3.38), 343(3.98)	5.0
	−1.42±0.04	+	213(4.28), *235(3.89)*, 265(3.60), *273(3.51)*, 332(3.98) 346(3.95)	0.5
		++	218(4.24), 255(3.74), *277(3.44)*, 360(4.05), *365(4.04)*	−3.5

a) Ionic species in an aqueous buffer of the indicated pH are shown by −(anion), ○(neutral molecule), +(monocation), and ++(dication). b) Wavelength in nm and inflexions or shoulders in italics. c) Negatives figures are H_0 values.

Faculty of Agriculture, Nagoya University. The pK_a values were determined by a spectroscopic method. The UV spectra were measured on a Shimadzu UV-300 spectrophotometer and NMR spectra on a JEOL JNM-NH-100 spectrometer in TFA-*d* with TMS as an internal standard.

*6-Methylthioimidazo[1,2-c]pteridine(**2a**) and Its 2,3-Dimethyl Derivative(**2b**).* 4-Amino-2-mercaptopteridine[7] was methylated with dimethyl sulfate in an alkaline solution to give 4-amino-2-methylthiopteridine(**1a**) in 80% yield, mp 210.5—211.5 °C (from water) (Found: C, 43.69; H, 3.56%. Calcd for $C_7H_7N_5S$: C, 43.50; H, 3.66%). A solution of **1a** (10 g) and chloroacetaldehyde (40 g) in 50% aqueous methanol (1500 ml) was heated at 65 °C for 20 h, during which time the pH of the solution was maintained at pH 6—7 by addition of sodium acetate. The solution was evaporated to dryness under reduced pressure and the residue was extracted with hot acetone (500 ml). The extract, after evaporation to dryness, was chromatographed on a silica gel column (Wako Gel C-100, 4×40 cm) eluted first by a mixture of ethyl acetate and benzene (1 : 4) to remove a small amount of fluorescent impurities. The column was then eluted by a 1 : 1 mixture of the two solvents. The eluate was evaporated to dryness and the residue was crystallized from ethyl acetate to give ivory needles (4.9 g) of **2a**, mp 195—196 °C (Found: C, 49.81; H, 3.11; N, 32.00%. Calcd for $C_9H_7N_5S$: C, 49.75; H, 3.25; N, 32.24%).

By using 4-amino-6,7-dimethyl-2-methylthiopteridine (**1b**)[8] in stead of **1a** in the above reaction, **2b** was obtained in 36% yield as ivory needles, mp 216—216.5 °C (from ethyl acetate)(Found : C, 53.69; H, 4.40; N, 28.46%. Calcd for $C_{11}H_{11}N_5S$: C, 53.85; H, 4.53; N, 28.55%); NMR: three singlets at δ 2.50(3H), 2.56(6H), and 7.70 (2H).

*6-Aminoimidazo[1,2-c]pteridine(**2c**) and Its 2,3-Dimethyl Derivative(**2d**).* A suspension of **2a** (300 mg) in a saturated ethanolic ammonia (50 ml) was heated in a sealed tube at 100 °C for 5 h. After cooling, the solid was collected and crystallized from methanol to give colorless needles (200 mg) of **2c**, mp>300 °C (Found: C, 50.68; H, 2.92; N, 43.93%. Calcd for $C_8H_6N_6 \cdot 0.2\,H_2O$: C, 50.84; H, 3.40; N, 44.29%).

Its 2,3-dimethyl derivative(**2d**) was synthesized from **2b** in a similar way in 70% yield, mp>300 °C (Found: C, 55.78; H, 4.76; N, 39.23%. Calcd for $C_{10}H_{10}N_6$: C, 56.07; H, 4.71; N, 39.23%).

*6-Methylamino- and 6-Ethylaminoimidazo[1,2-c]pteridines (**2e** and **2g**) and Their 2,3-Dimethyl Derivatives(**2f** and **2h**).* A solution of **1a** (500 mg) and methylamine (40% aqueous solution, 10 ml) in ethanol (100 ml) was heated under reflux for 5 h. The solution was evaporated to dryness in vacuo and the residue was fractionated on a Florisil column (3.5×40 cm) eluted gradiently by 0—3% ammonia (2 l). The eluate, after evaporation and crystallization from water, gave ivory needles (280 mg) of **2e**, mp 296—297 °C (Found: C, 53.62; H, 3.96; N, 41.53%. Calcd for $C_9H_8N_6$: C, 53.98; H, 4.04; N, 41.98%).

Heating of **2a** with ethylamine as above, followed by chromatographic separation on a silica gel column eluted by ethanol-ethyl acetate (1 : 9) gave **2g** as colorless needles (75% yield), mp 211—211.5 °C (from acetone)(Found: C, 55.90; H, 4.56; N, 38.84%. Calcd for $C_{10}H_{10}N_6$: C, 56.07; H, 4.71; N, 39.23%).

Similarly, **2b** was treated with methylamine or ethylamine to give, without using chromatography, **2f** (50% yield), mp>300 °C (from ethanol)(Found : C, 57.93; H, 5.29; N, 36.63%. Calcd for $C_{11}H_{12}N_6$: C, 57.87; H, 5.31; N, 36.82%) and **2h** (65% yiled), mp 295—296 °C (from ethanol)(Found: C, 59.69; H, 5.97; N, 34.59%. Calcd for $C_{12}H_{14}N_6$: C, 59.48; H, 5.84; N, 34.69%), respectively.

*6-(2-Hydroxyethylamino)imidazo[1,2-c]pteridine (**2i**) and Its 2,3-Dimethyl Derivative(**2j**).* A solution of **2a** (500 mg) and 2-aminoethanol (2 g) in water (20 ml) was heated under reflux for 5 h. The solution was adjusted at pH 2—3 with hydrochloric acid and chromatographed on a Florisil column in a similar way to that used for **2e**. Evaporation of the eluate to dryness and crystallization of the residue from water gave colorless needles (200 mg) of **2i**, mp 244—244.5 °C(Found: C, 51.62; H, 4.33; N, 36.02%. Calcd for $C_{10}H_{10}N_6O \cdot 0.1H_2O$: C, 51.75; H, 4.44; N, 36.22%). In a similar way, **2b** and 2-aminoethanol gave **2j** (60% yield), mp 266—267 °C (from ethanol)(Found: C, 55.98; H, 5.60; N, 32.43%. Calcd for $C_{12}H_{14}N_6O$: C, 55.80; H, 5.47; N, 32.54%).

*6-Hydroxyimidazo[1,2-c]pteridine(**2k**) and Its 2,3-Dimethyl Derivative(**21**).* A solution of **2a** (1.0 g) in 0.1 M sodium hydroxide (20 ml) was heated at 60 °C for 1.5 h. The solution was adjusted at pH 2—3 with formic acid and chilled. The solid was collected and crystallized from water to give colorless needles (0.35 g) of **2k**; the compound darkened above 205 °C without melting (Found: C, 51.03; H, 2.47; N, 37.39%. Calcd for $C_8H_7N_5O$: C, 51.33; H, 2.70; N, 37.42%). The same compound(**2k**) was obtained from **2a** by heating in 0.1 M hydrochloric acid at 60 °C, by treatment with sodium ethoxide or hydrogen chloride in ethanol at 25 °C, or by heating in 50% aqueous methanol with silver oxide.

Heating of **2b** (280 mg) in 0.2 M hydrochloric acid at 70 °C for 20 h and evaporation to dryness in vacuo gave a solid, which was dissolved in water (10 ml). The solution was adjusted at pH 3—4 with ammonia and chilled to give colorless needles (200 mg) of **2l**, mp 294—295.5 °C (from water)(Found: C, 54.30; H, 4.60; N, 31.73%). Calcd for $C_{10}H_9N_5O \cdot 0.3H_2O$: C, 54.43; H, 4.39; N, 31.75%).

*6-Ethoxy- and 6-Methoxyimidazo[1,2-c]pteridines(**2m** and **2o**) and Their 2,3-Dimethyl Derivatives(**2n** and **2p**).* A mixture of **2a** (400 mg) and silver oxide (2 g) in ethanol (150 ml) was heated under reflux for 7 h. After filtration, the filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column eluted by ethanol–ethyl acetate(1 : 9). Evaporation of the eluate and crystallization from ethyl acetate gave colorless needles (200 mg) of **2m**, mp 143—143.5 °C (Found: C, 56.00; H, 4.18; N, 32.61%. Calcd for $C_{10}H_9N_5O$: C, 55.81; H, 4.22; N, 32.54%).

By using methanol in place of ethanol in the above reaction, the 6-methoxy compound(**2o**) was obtained in 30% yield, mp 238—239 °C (from ethyl acetate)(Found: C, 53.53; H, 3.33; N, 34.39%. Calcd for $C_9H_7N_5O$: C, 53.72; H, 3.51; N, 34.81%).

Similar treatments of **2b** with silver oxide in ethanol or methanol gave the ethoxy compound(**2n**) in 50% yield, mp 184—185 °C (from benzene)(Found: C, 59.22; H, 5.39; N, 28.51%. Calcd for $C_{12}H_{13}N_5O$: C, 59.24; H, 5.40; N, 28.79%), and the methoxy compound (**2p**) in 55% yield, mp 216—216.5 °C (from toluene)(Found: C, 56.13; H, 4.78; N, 29.64%. Calcd for $C_{11}H_{11}N_5O \cdot 0.3H_2O$: C, 56.29; H, 4.86; N, 29.85%), respectively.

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