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Substituted Benzimidazo[2,1 —*h*]pteridine-2,4-diones

H. K. Gakhar, Punam Sachdev, and **Shashi Bhushan Gupta**

Department of Chemistry, Panjab University, Chandigarh-160014, India

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5-Alkyl-5,6-dihydrobenzimidazo[2,1 —*h*]pteridine-2,4(1*H*,3*H*)-diones (**4a–d**) have been synthesised by the condensation of 2-(alkylaminomethyl)benzimidazole dihydrochloride (**1a–d**) with 5-bromobarbituric acid (**2**). Similarly, 5-alkyl-5,6-dihydro-4a-nitrobenzimidazo[2,1 —*h*]pteridine-2,4(3*H*,4a*H*)-diones (**10a–d**) have also been synthesised by the condensation of **1a–d** with 5-bromo-5-nitrobarbituric acid (**8**) followed by cyclisation of the intermediate 5-[(benzimidazol-2-ylmethyl)alkylamino]-5-nitrobarbituric acid (**9a–d**) with 5% NaOH. Thermal cyclisation of the intermediates **9a–d** have also been studied. Methylation of the compound **10a** has been carried out with CH_3I and K_2CO_3 using *DMF* as solvent to confirm cyclisation. The structures are supported by elemental analyses, IR and PMR spectra.

(Keywords: Heterocycles; Synthesis)

Substituierte Benzimidazo[2,1 —h]pteridin-2,4-dione

Die 5-Alkyl-5,6-dihydrobenzimidazo[2,1 —*h*]pteridin-2,4(1*H*,3*H*)-dione **4a—d** wurden mittels Kondensation von 2-(Alkylaminomethyl)benzimidazoldihydrochloriden **1a—d** mit 5-Brombarbitursäure (**2**) dargestellt. In ähnlicher Weise wurden die 5-Alkyl-5,6-dihydro-4a-nitrobenzimidazo[2,1 —*h*]pteridin-2,4(3*H*,4a*H*)-dione **10a—d** über die Kondensation von **1a—d** mit 5-Brom-5-nitrobarbitursäure (**8**) und nachfolgender Cyclisierung der intermediären 5-[(Benzimidazol-2-ylmethyl)alkylamino]-5-nitrobarbitursäuren **9a—d** mit 5% NaOH dargestellt. Die thermische Cyclisierung der Produkte **9a—d** wurde ebenfalls untersucht. Die Verbindungen wurden mittels Elementaranalyse, IR und PMR charakterisiert.

Introduction

Literature survey reveals that ample studies have been carried out on several benz[g]imidazo[1,2,3 —*ij*]pteridines[1—4] and benzimidazo[5,4 —*g*]pteridines[5,6], but no attempt seems to have been made so far for the syntheses of benzimidazo[2,1 —*h*]pteridine-2,4-diones where biologically active benzimidazole and pteridine rings are fused together in a slightly different fashion.

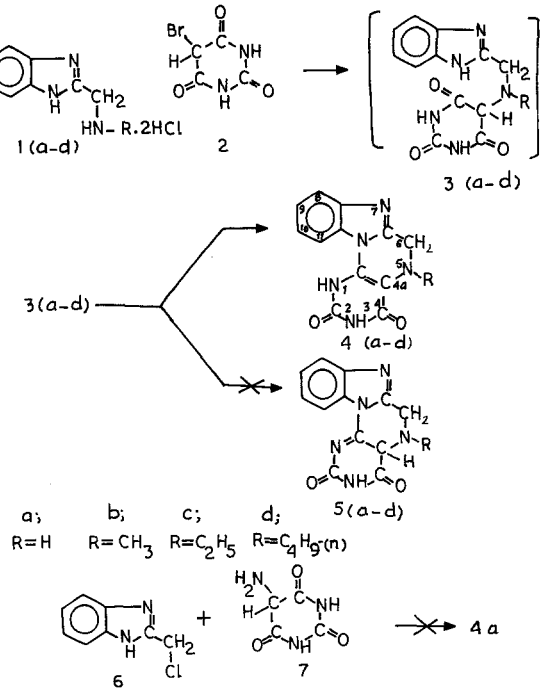
Results and Discussion

5-Alkyl substituted-5,6-dihydrobenzimidazo[2,1 $-h$]pteridine-2,4(1*H*,3*H*)-diones (**4 a–d**) have been synthesised by the condensation of 2-(alkylaminomethyl)benzimidazole dihydrochloride (**1 a–d**) with 5-bromobarbituric acid (**2**) in ethanol. The first step is expected to lead to the formation of 5-[(benzimidazol-2-yl methyl) alkylamino]barbituric acid (**3 a–d**), which can cyclise in two ways to **4 a–d** or **5 a–d**. However, we isolated only one product (tlc evidence). Although imines are more stable than enamines and the preferred structure should have been **5**, we have assigned structure **4** to the condensation product on the basis of PMR which showed the absence of a $-CH-$ proton attached to C-4 a.

The PMR spectrum of **4 a** (*TFA* $+CDCl_3$) showed a multiplet at 7.73–8.03 due to four aromatic protons. Besides, it also showed a singlet of two proton intensity at 5.17 assignable to two methylene protons ($-C-CH_2-N<$). Further, analytical results also support structure **4**.

Efforts to synthesise **4 a** by an alternative route involving the condensation of 2-chloromethylbenzimidazole (**6**) with 5-aminobarbituric acid (**7**) were not successful.

Scheme 1

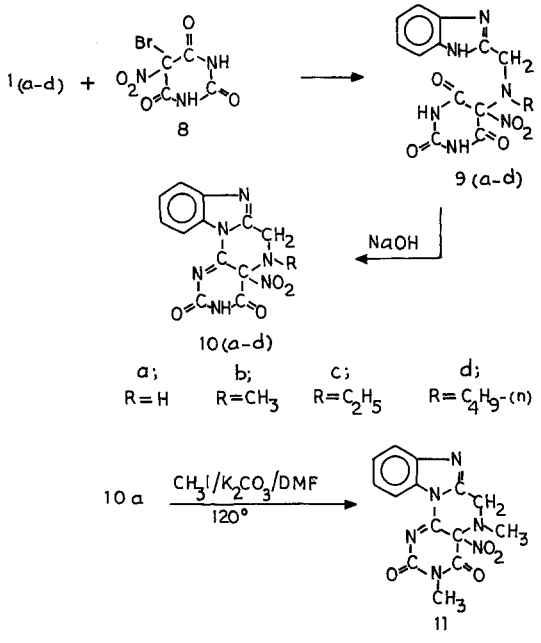


Next, we thought to extend our studies by introducing a nitro group at position **4 a**. So we carried out the condensation of **1 a–d** with 5-bromo-5-nitrobarbituric acid (**8**) which resulted in the formation of intermediate 5-[(benzimidazol-2-ylmethyl)alkylamino]-5- nitrobarbituric acid **9a–d**). **9a–d** could be cyclised to 5-alkyl-5,6-dihydro-4a-nitrobenzimidazo[3,1 −*h*]pteridine-2,4(3*H*,4a*H*)-diones **10a–d** with 5% sodium hydroxide solution.

The PMR spectrum of **10 a** (*TFA* + $CDCl_3$) showed a multiplet at 7.76–7.93 assignable to four aromatic protons and a singlet at 5.25 which could be assigned to two methylene protons (=C−CH_2−N).

10 a (*R*=H), when subjected to methylation with methyl iodide, gave the dimethylated product **11**. The IR spectrum of **11** showed no bands of N−H or O−H indicating the cyclised structure of **10**. Efforts to record the PMR spectrum of **11** failed because of its insolubility.

Scheme 2



While determining the melting points of **9 a–d**, it was observed that these intermediates underwent thermal cyclisation to **10 a–d** before their melting points were reached. Because of this difficulty, melting points of the intermediates **9 a–d** could not be determined. This observation is

supported by the report of *Taylor* et al.[7] who also observed that during heating a dehydrative cyclisation of such intermediates takes place. This was confirmed further by heating **9a** to a temperature of 280° in a dry test tube followed by methylation of the product thus formed. It was found to be identical with the cyclisation product of **9a** after subsequent methylation with methyl iodide in the presence of K_2CO_3/DMF.

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Experimental

Melting points were determined in open glass capillaries using a liquid paraffin bath and are uncorrected. IR spectra were recorded in nujol on Perkin-Elmer 377 and PMR on Varian EM 390 90 MHz spectrometer using *TMS* as the internal reference. The analytical values (C, H, N) agree with the proposed structures (**4a–d**, **9a–d**, **10a–d** and **11**).

5,6-Dihydrobenzimidazo[2,1−h]pteridine-2,4(1H,3H)-dione (**4a**, R=H)

A solution of **1a**[8] (1.10 g, 0.05 mol) in ethanol (40 ml) was added dropwise with continuous stirring at room temperature (30°) to a solution of 5-bromobarbituric acid (**2**)[9] (1.215 g, 0.05 mol) in 125 ml of the same solvent. After keeping it overnight, the contents were refluxed on a steam bath. The progress of reaction was monitored by tlc. The reaction was complete after 1 h. Ethanol was removed under reduced pressure and the solid thus separated was recrystallised from distilled water; m.p. 258–260°; yield 1.045 g (82%). $C_{12}H_9N_5O_2$.

IR (in nujol): 3540–3360 (b), 1655, 1630, 1620, 1460, 1380, 1310 and 1135 cm^{-1}.

PMR ($CDCl_3 + TFA$): 7.73–8.03 (m, 4H, aromatic), 5.17 (s, 2H, $-CH_2-$).

5-Methyl-5,6-dihydrobenzimidazo[2,1−h]pteridine-2,4(1H,3H)-dione (**4b**, R=CH_3)

4b was prepared by the above procedure starting from **1b**[10] and **2**. Crystallisation from ethanol gave the desired product, m.p. 238–240°; yield (65%). $C_{13}H_{11}N_5O_2$.

IR (in nujol): 3500–3340 (b), 1660, 1645, 1625, 1460, 1380, 1310 and 725 cm^{-1}.

PMR ($CDCl_3 + TFA$): 7.66–8.06 (m, 4H, aromatic protons), 5.23 (s, 2H, $-CH_2-$), 3.20 (s, 3H, $N-CH_3$).

5-Ethyl-5,6-dihydrobenzimidazo[2,1−h]pteridine-2,4(1H,3H)-dione (**4c**, R=C_2H_5)

It was prepared as stated above starting from **1c**[10] and **2**. Crystallisation from ethanol gave **4c**, m.p. 273–275°; yield (71%). $C_{14}H_{13}N_5O_2$.

IR (in nujol): 3520–3380 (b), 1650, 1640, 1620, 1460, 1380 and 720 cm^{-1}.

PMR ($CDCl_3 + TFA$): 7.76–7.93 (m, 4H, aromatic protons), 5.17 (s, 2H, $-CH_2-$), 3.60 (q, 2H, $N-CH_2CH_3$), 1.56 (t, 3H, $N-CH_2CH_3$).

5-Butyl-5,6-dihydrobenzimidazo[2,1−h]pteridine-2,4(1H,3H)-dione (**4 d**, $R=C_4H_9$-*n*)

4 d was prepared as above from **1 d**[10] and **2**. Crystallisation from ethanol gave **4 d**, m.p. 218–220°; yield (63%). $C_{16}H_{17}N_5O_2$.

IR (in nujol): 3 520–3 360 (b), 1 668, 1 650, 1 622, 1 460, 1 380 and 725 cm^{-1}.

PMR ($CDCl_3+TFA$): 7.76–7.96 (m, 4 H, aromatic, protons), 5.07 (s, 2 H, $-CH_2-$), 3.40 (t, 2 H, $N-CH_2CH_2CH_2CH_3$), 1.60–1.96 (m, 2 H, $N-CH_2CH_2CH_2CH_3$), 1.23–1.56 (m, 2 H, $N-CH_2CH_2CH_2CH_3$), 0.97 (t, 3 H, $N-CH_2CH_2CH_2CH_3$).

Attempted Condensation of 5-Aminobarbituric Acid (**7**) *with 2-(Chloromethyl)benzimidazole* (**6**)

Method "A": A solution of uramil (**7**)[11] (1.43 g, 0.01 mol) in hot ethanol (125 ml) was mixed with a solution of **6** (1.67 g, 0.01 mol) in the same solvent (25 ml). The reaction mixture was heated under reflux on a steam bath for 12 h. No reaction took place and both the reactants were recovered as such.

Method "B": A mixture of **7** (1.43 g, 0.01 mol) and **6** (1.67 g, 0.01 mol), in a dry test tube, was heated in an oil bath at 120–130° for 5 h. No reaction took place and the reactants were recovered as such.

5-[(Benzimidazol-2-yl methyl)amino]-5-nitrobarbituric acid (**9 a**, $R=H$)

A solution of **1 a** (1.10 g, 0.005 mol) in ethanol (40 ml) was added with constant stirring at room temperature to a solution of **8**[12] (1.44 g, 0.005 mol) in 125 ml of the same solvent. The reaction was exothermic and after keeping it overnight, the yellow product thus separated was filtered under suction and crystallised from dilute alcohol.

Other 2-(alkyl substituted aminomethyl)benzimidazole dihydrochlorides (**1 b–d**) were condensed with **8** in a similar fashion. Data regarding their yields, solvent for crystallisation, molecular formulae, and IR of **9 a–d** are enlisted in Table 1.

Table 1. *5-[(Benzimidazol-2-yl methyl) alkylamino]-5-nitrobarbituric acids* **9 a–d***

Compound No.	*R*	yield %	Molecular formulae	$\nu_{max.}$ N−H's	C=O's
9 a	H	75	$C_{12}H_{10}N_6O_5$	3 480–3 380 (b)	1 660–1 650
9 b	CH_3	92	$C_{13}H_{12}N_6O_5$	3 480–3 360 (b)	1 645–1 630
9 c	C_2H_5	69	$C_{14}H_{14}N_6O_5$	3 500–3 360 (b)	1 660–1 640
9 d	C_4H_9(*n*)	83	$C_{16}H_{18}N_6O_5$	3 540–3 400 (b)	1 650–1 630

* All compounds were crystallised from ethanol; melting points could not be determined due to thermal cyclisation.

5-Alkyl-5,6-dihydro-4a-nitrobenzimidazo[2,1—h]pteridine-2,4(3H,4aH)-diones (**10a–d**)

Intermediate **9a** (500 mg) was added to a solution of 5% NaOH (6 ml). The mixture was warmed for 40–50 min at 45–50°, cooled and filtered. The deep yellow solution was acidified with dil. HCl and the precipitates were collected under suction. The product was washed with water and dried. It was crystallised from dilute ethanol.

Similarly other intermediates **9b–d** were cyclised and data regarding m.p.'s, yields and molecular formulae of all the compounds are enlisted in Table 2.

Table 2. *5-Alkyl-5,6-dihydro-4a-nitrobenzimidazo[2,1—h]pteridine-2,4(3H,4aH)-diones* **10a–d**

Compound No.	*R*	m.p.* (°C)	yield %	Molecular formulae
10a	H	286	84	$C_{12}H_8N_6O_4$
10b	CH_3	284	85	$C_{13}H_{10}N_6O_4$
10c	C_2H_5	271	92	$C_{14}H_{12}N_6O_4$
10d	C_4H_9-(*n*)	261	80	$C_{16}H_{16}N_6O_4$

* All compounds recrystallised from ethanol.

3,5-Dimethyl-5,6-dihydro-4a-nitrobenzimidazo[2,1—h]pteridine-2,4(3H,4aH)-dione (**11**)

A mixture of **10a** (300 mg, 0.001 mol), methyl iodide (2 ml) and potassium carbonate (345 mg, 0.005 mole) in *DMF* (50 ml) was stirred at 120° for 2 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was treated with water and the separated product was filtered off, washed with water and recrystallised from ethanol, m.p. > 300°; yield (85%). $C_{14}H_{12}N_6O_4$.

IR (in nujol): 1720, 1640, 1620, 1450, 1380, 1300, 1150 and 855 cm^{-1}.

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