Synthesis of 2,4-Substituted 6,7-Phenanthreno- and 6,7-Acenaphthenopteridines

Vishnu J. Ram and Hrishi Kesh Pandey

Department of Chemistry, S. C. College, Ballia (U.P.), India

and

Arnold J. Vlietinck

Department of Pharmaceutical Sciences, University of Antwerp, Belgium

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A series of 6,7-phenanthreno- and 6,7-acenaphthenopteridines bearing different substituents at positions 2 and 4 are prepared. The structures of the compounds are confirmed by spectroscopic studies and elemental analyses.

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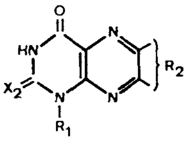
Many pteridine-analogues possessing antifolate activity have been prepared as potential anti-cancer (1,2), antimalarial (3), diuretic (4) and antileprotic (5) agents.

Fusion of alicyclic functions onto the pyrazine ring of the pteridine nucleus resulted in a series of compounds having increased inhibitory activity with the extension of the alicyclic ring (6). Recent studies have revealed that a maximum inhibitory activity was obtained against reductases from rat liver and L-210 mouse leukemia cells when a 12 membered ring was attached to the pyrazine portion of the molecule. Further extension of the ring size to a 15 membered ring resulted in a sharp decrease of the inhibitory activity. 2,4-Diaminoptheridines bearing an alicyclic function fused at positions 6 and 7 of the pyrazine ring were found to strongly inhibit dihydrofolate reductase from a protozoal source, but not from a bacterial source. Fusion of a benzene nucleus to the alicyclic ring did not improve the inhibitory activity of the parent compound against the mammalian and bacterial enzymes (7).

Evaluation of the inhibitory effects of a series of pteridine derivatives with a sulphide linkage at position 6 revealed that such compounds inhibit dihydrofolate reductase to a degree comparable to that observed for folic acid. Elslager (8) recently reported that 2,4-diaminopteridines bearing an arylthio substituent at position 6 were ineffective as inhibitors of dihydrofolate reductase.



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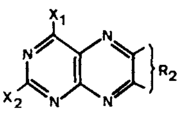

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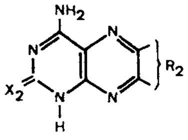

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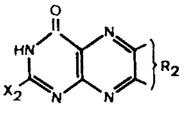

IV

Intensive research efforts on the 4-thio analogue of methotrexate indicated that this compound is inferior to folic acid in inhibiting mammalian, bacterial and protozoal dihydrofolate reductase enzymes.

Since up until now only a few analogues of pteridine, bearing various substituents at positions 2 and 4 and fused with phenanthrene or acenaphthene rings onto the 6 and 7 positions of the pyrazine ring of the molecule have been investigated (9,10), we synthetized a number of such compounds. These derivatives of pteridine represented by formulas I to IV were prepared by condensation of the substituted 5,6-diaminopyrimidines with 9,10-phenanthraquinone and 1,2-acenaphthone. The mercaptopteridines were transformed into their corresponding sulphides by reaction with an alkylhalide. The structures of all molecules were confirmed by spectroscopic data and elemental analyses.

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are uncorrected. The ir spectra were recorded on a Beckman Acculab No. 4 spectrometer. Mass spectra were recorded on a Jeol JMS-01SG apparatus operating at 70 eV ionization energy.

1-Phenyl-6,7-phenanthrenolumazine (1-phenyl-2,4-dihydroxy-6,7-phenanthrenopyrimido[4,5-*b*]pyrazine) (**1**).

A mixture of 1-phenyl-2,4-dioxo-5,6-diaminopyrimidine (1 mmole) and phenanthraquinone (1 mmole) in acetic acid (5 ml.) was refluxed for 2 hours. After cooling the precipitate was filtered and crystallized from dimethylformamide (DMF) (78%), m.p. > 300°; ms: m/e 390; ir (potassium bromide): 3200, 3100 (ν NH), 1718 (ν CO).

Anal. Calcd. for $C_{24}H_{14}N_4O_2$: C, 73.8; H, 3.5; N, 14.3. Found: C, 73.6; H, 3.7; N, 14.6.

1-Phenyl-6,7-acenaphthenolumazine (**2**).

/-Phenyl-;acenaphthenolumazine (**2**).

This compound was prepared as described in the preceding experiment from 1-phenyl-2,4-dioxo-5,6-diaminopyrimidine and acenaphthone and crystallized from DMF (75%), m.p. > 300°; ms: m/e 364; ir (potassium bromide): 3160, 3040 (ν NH), 1700 (ν CO).

Anal. Calcd. for $C_{22}H_{12}N_4O_2$: C, 72.5; H, 3.3; N, 15.3. Found: C, 72.4; H, 3.5; N, 15.1.

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Table I

2,4-Substituted 6,7-Phenanthreno- and Acenaphthenopteridines (a)

Compound No.	Structure	Substituents	Formula	M^+	Solvent for Crystallization	Yield (%)	M.p.
1	I	X_2 = O; R_1 = C_6H_5; R_2 = $C_{12}H_8$	$C_{24}H_{14}N_4O_2$	390	DMF	78	>300°
2	I	X_2 = O; R_1 = C_6H_5; R_2 = $C_{10}H_6$	$C_{22}H_{12}N_4O_2$	364	DMF	75	>300°
3	I	X_2 = O; R_1 = $C_6H_5CH_2$; R_2 = $C_{12}H_8$	$C_{25}H_{16}N_4O_2$	404	DMF	43	>300°
4	I	X_2 = O; R_1 = $C_6H_5CH_2$; R_2 = $C_{10}H_6$	$C_{23}H_{14}N_4O_2$	378	DMF	58	>300°
5	II	X_1 = NH_2; X_2 = C_6H_5; R_2 = $C_{12}H_8$	$C_{24}H_{15}N_5$	373	DMF-water	73	>300°
6	II	X_1 = NH_2; X_2 = C_6H_5; R_2 = $C_{10}H_6$	$C_{22}H_{13}N_5$	347	DMF-water	29	234-235°
7	II	X_1 = S; X_2 = H; R_2 = $C_{12}H_8$	$C_{18}H_{10}N_4S$	314	DMF-water	56	>300°
8	II	X_1 = S; X_2 = H; R_2 = $C_{10}H_6$	$C_{16}H_8N_4S$	288	DMF	62	>300°
9	I	X_2 = S; R_1 = H; R_2 = $C_{12}H_8$	$C_{18}H_{10}N_4OS$	330	DMF-water	48	>300°
10	I	X_2 = S; R_1 = H; R_2 = $C_{10}H_6$	$C_{16}H_8N_4OS$	304	DMF	60	>300°
11	I	X_2 = O; R_1 = CH_3; R_2 = $C_{12}H_8$	$C_{19}H_{12}N_4O_2$	328	DMF-water	69	>300°
12	I	X_2 = O; R_1 = CH_3; R_2 = $C_{10}H_6$	$C_{17}H_{10}N_4O_2$	302	DMF	69	>300°
13	III	X_2 = O; R_2 = $C_{12}H_8$	$C_{18}H_{11}N_5O$	313	DMF-water	78	>300°
14	III	X_2 = O; R_2 = $C_{10}H_6$	$C_{16}H_9N_5O$	287	DMF-water	78	>300°
15	III	X_2 = S; R_2 = $C_{12}H_8$	$C_{18}H_{11}N_5S$	329	DMF-water	55	>300°
16	III	X_2 = S; R_2 = $C_{10}H_6$	$C_{16}H_9N_5S$	303	DMF-water	63	>300°
17	IV	X_2 = SCH_3; R_1 = $C_{10}H_6$	$C_{17}H_{10}N_4OS$	378	acetic acid	74	299-300°
18	IV	X_2 = SC_2H_5; R_1 = $C_{10}H_6$	$C_{18}H_{12}N_4OS$	332	ethanol	68	278-279°
19	IV	X_2 = SCH_3; R_1 = $C_{12}H_8$	$C_{19}H_{12}N_4OS$	344	DMF	70	299-300°
20	IV	X_2 = SC_2H_5; R_1 = $C_{12}H_8$	$C_{20}H_{14}N_4OS$	358	acetic acid	65	257-258°

(a) $C_{10}H_6$ = 1,2-acenaphtheno; $C_{12}H_8$ = 9,10-phenanthreno.

1-Benzyl-6,7-phenanthrenolumazine (**3**).

This compound was prepared as described earlier from 1-benzyl-2,4-dioxo-5,6-diaminopyrimidine hydrochloride and phenanthraquinone and crystallized from DMF (43%), m.p. > 300°; ms: m/e 404 (M^+), 332 (M^+-HNCO and CHO); ir (potassium bromide): 3140, 3040 (ν NH), 1730, 1680 (ν CO).

Anal. Calcd. for $C_{25}H_{16}N_4O_2$: C, 74.2; H, 3.9; N, 13.8. Found: C, 74.3; H, 4.1; N, 13.6.

1-Benzyl-6,7-acenaphthenolumazine (**4**).

This compound was prepared from 1-benzyl-2,4-dioxo-4,5-diaminopyrimidine hydrochloride and acenaphthone as described earlier and crystallized from DMF, (58%), m.p. > 300°; ms: m/e 378 (M^+), 306, (M^+ -HNCO and CHO), 216 (306 - C_6H_5CH); ir (potassium bromide): 3180, 3060 (ν NH), 1710, 1690 (ν CO).

Anal. Calcd. for $C_{23}H_{14}N_4O_2$: C, 73.0; H, 3.7; N, 14.8. Found: C, 73.2; H, 3.9; N, 14.5.

2-Phenyl-4-amino-6,7-phenanthrenopteridine (**5**).

This compound was prepared as described earlier from 2-phenyl-4,5,6-triaminopyrimidine and phenanthraquinone and crystallized from a DMF-water mixture (73%), m.p. > 300°; ms: m/e 373 (M^+), 347 (M^+ -CN), 270 (347 - C_6H_5), 243 (270 - HCN); ir (potassium bromide): 3450, 3280 (ν NH_2), 1640, 1620 (ν NH_2).

Anal. Calcd. for $C_{24}H_{15}N_5$: C, 77.2; H, 4.0; N, 18.7. Found: C, 76.9; H, 3.8; N, 18.9.

2-Phenyl-4-amino-6,7-acenaphthenopteridine (**6**).

This compound was prepared as described earlier from 2-phenyl-4,5,6-triaminopyrimidine and acenaphthone and crystallized from DMF (29%), m.p. 234-235°; ms: m/e 347; ir (potassium bromide): 3430, 3300, (ν NH_2).

Anal. Calcd. for $C_{22}H_{13}N_6$: C, 76.0; H, 3.7; N, 20.3. Found: C, 76.2; H, 3.8; N, 20.5.

6,7-Phenanthreno-4-thiopteridine (**7**).

This compound was prepared in the usual manner from 4-thio-5,6-diaminopyrimidine and phenanthraquinone and crystallized from a DMF-water mixture (56%), m.p. > 300°; ms: m/e 314; ir (potassium bromide): 3440, 3300, 3250, 3200 (ν NH), 1630 (ν NH), 1230, 1160, 1115 (ν C=S).

Anal. Calcd. for $C_{18}H_{10}N_4S$: C, 68.7; H, 3.1; N, 17.8. Found: C, 68.5; H, 3.2; N, 18.1.

6,7-Acenaphtheno-4-thiopteridine (**8**).

This compound was prepared as described earlier from 4-thio-5,6-diaminopyrimidine and acenaphthone and crystallized from DMF (62%), m.p. > 300°; ms: m/e 288; ir (potassium bromide): 3430, 3120, 3060 (ν NH), 1615 (ν NH), 1300, 1175, 1035, (ν C=S).

Anal. Calcd. for $C_{16}H_8N_4S$: C, 66.6; H, 2.7; N, 19.4. Found: C, 66.8; H, 2.5; N, 19.1.

6,7-Phenanthreno-2-thiolumazine (**9**).

This compound was prepared in the usual way from 2-thio-4-oxo-5,6-diaminopyrimidine and phenanthraquinone and crystallized from a DMF-water mixture (48%), m.p. > 300°; ms: m/e 330, (M^+), 302 (M^+ − CO), 243 (302 - HNCS), 217 (243 - CN), 190 (217 - HCN); ir (potassium bromide): 3040 (ν NH), 1690 (ν CO), 1295, 1265, 1150 (ν C=S).

Anal. Calcd. for $C_{18}H_{10}N_4OS$: C, 65.4; H, 3.0; N, 16.9. Found: C, 65.6; H, 3.2; N, 16.7.

6,7-Acenaphtheno-2-thiolumazine (**10**).

This compound was prepared by condensation of 2-thio-4-oxo-5,6-diaminopyrimidine with acenaphthone as described in the previous experiment. It was crystallized from DMF (60%), m.p. > 300°; ms: m/e 304 (M^+), 217 (304 - HNCS and CO); ir (potassium bromide): 3120 (ν NH), 1700, 1645 (ν CO), 1312, 1173, 1140 (ν C=S).

Anal. Calcd. for $C_{16}H_8N_4OS$: C, 63.1; H, 2.6; N, 18.4. Found: C, 63.2; H, 2.5; N, 18.7.

1-Methyl-6,7-phenanthrenolumazine (**11**).

A solution of 1-methyl-2,4-dioxo-5,6-diaminopyrimidine hydrochloride (1 mmole) in water was added to a solution of phenanthraquinone (1 mmole) in acetic acid and refluxed for 6 hours. The precipitate thus obtained was filtered off washed with ethanol and crystallized from a DMF-water mixture (69%), m.p. > 300° ms: m/e 328, (M^+), 257 (328 - HNCO and CO), 229 (257 - N=CH_2), 202 (229 - HCN); ir (potassium bromide): 3170, 3050 (ν NH), 1720, 1675 (ν CO).

Anal. Calcd. for $C_{19}H_{12}N_4O_2$: C, 69.5; H, 3.6; N, 17.0. Found: C, 69.2; H, 3.5; N, 17.2.

1-Methyl-6,7-acenaphthenolumazine (**12**).

This compound was prepared from 1-methyl-2,4-dioxo-5,6-diaminopyrimidine hydrochloride and acenaphthone as described in the preceding experiment. It was crystallized from DMF (69%), m.p. > 300°; ms: m/e 302 (M^+), 231 (302 - HNCO and CO), 216 (231 - CH_3), 203 (231 - CH_2=N); ir (potassium bromide): 3175, 3050 (ν NH), 1720, 1625 (ν CO).

Anal. Calcd. for $C_{17}H_{10}N_4O_2$: C, 67.5; H, 3.3; N, 18.5. Found: C, 67.4; H, 3.1; N, 18.7.

2-Oxo-4-amino-6,7-phenanthrenopteridine (**13**).

This compound was prepared as described earlier from 2-oxo-4,5,6-triaminopyrimidine hyrogen-sulphate and phenanthraquinone. The crude product was washed with ethanol and crystallized from a DMF-water mixture (78%), m.p. > 300°; ms: m/e 313; ir (potassium bromide): 3175, 3060 (ν NH), 1725, 1690 (ν CO), 1610, 1570 (ν NH).

Anal. Calcd. for $C_{18}H_{11}N_5O$: C, 69.1; H, 3.5; N, 22.4. Found: C, 69.2; H, 3.6; N, 22.6.

2-Oxo-4-amino-6,7-acenaphthenopteridine (**14**).

To a hot solution of 2-oxo-4,5,6-triaminopyrimidine hydrogensulphate (1 mmole) in water, a solution of acenaphthone (1 mmole) in acetic acid was added and refluxed for 5 hours. The precipitate was filtered, washed with water and crystallized from a DMF-water mixture (78%), m.p. > 300°; ms: m/e 287; ir (potassium bromide): 3180, 3060 (ν NH), 1700 (ν CO), 1630, 1560 (ν NH).

Anal. Calcd. for $C_{16}H_9N_5O$: C, 66.9; H, 3.1; N, 24.3. Found: C, 66.8; H, 3.3; N, 24.5.

2-Thio-4-amino-6,7-phenanthrenopteridine (**15**).

This compound was prepared from 2-thio-4,5,6-triaminopyrimidine and phenathraquinone as described earlier and crystallized from a DMF-water mixture (55%), m.p. > 300°; ms: m/e 329; ir (potassium bromide): 3430 (ν NH_2), 1630, 1590, 1570 (ν NH), 1310, 1040 (ν C=S).

Anal. Calcd. for $C_{18}H_{11}N_5S$: C, 65.6; H, 3.3; N, 21.2. Found: C, 65.6; H, 3.5; N, 21.5.

2-Thio-4-amino-6,7-acenaphthenopteridine (**16**).

This compound was prepared from 2-thio-4,5,6-triaminopyrimidine and acenaphthone as described earlier (63%), m.p. > 300°; ms: m/e 303; ir (potassium bromide): 3440 (ν NH_2), 1630, 1550 (ν NH), 1340, 1240, 1180 (ν C=S).

Anal. Calcd. for $C_{16}H_9N_5S$: C, 63.3; H, 2.9; N, 23.1. Found: C, 63.4; H, 3.1; N, 23.4.

General Preparation of 2-Alkylmercapto-4-oxo-6,7-phenanthreno/acenaphthenopteridines (**17-20**).

To a solution of 6,7-phenanthreno/acenaphtheno-2-thiolumazine (10 mmoles) in dimethylformamide, solid potassium carbonate (15 mmoles) and an appropriate alkyl halide were added. The resulting mixture was stirred for 2 hours and then the reaction content was poured into an excess of water. The precipitate was filtered off, washed with water and crystallized from a suitable solvent.

2-Methylmercapto-4-oxo-6,7-acenaphthenopteridine (**17**).

Anal. Calcd. for $C_{17}H_{10}N_4OS$: C, 64.1; H, 3.1; N, 17.6. Found: C, 64.5; H, 3.3; N, 18.0.

2-Ethylmercapto-4-oxo-6,7-acenaphthenopteridine (**18**).

Anal. Calcd. for $C_{18}H_{12}N_4OS$: C, 65.1; H, 3.6; N, 16.9. Found: C, 65.2; H, 3.4; N, 17.1.

2-Methylmercapto-4-oxo-9,10-phenanthrenopteridine (**19**).

Anal. Calcd. for $C_{19}H_{12}N_4OS$: C, 66.2; H, 3.5; N, 16.3. Found: C, 66.5; H, 3.3; N, 16.0.

2-Ethylmercapto-4-oxo-9,10-phenanthrenopteridine (**20**).

Anal. Calcd. for $C_{20}H_{14}N_4OS$: C, 67.0; H, 3.9; N, 15.6. Found: C, 67.3; H, 4.2; N, 15.8.

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