# 60. Pteridines

Part LXXXV[1])

## Chemical Synthesis of Deoxysepiapterin and 6-Acylpteridines by Acyl Radical Substitution Reactions

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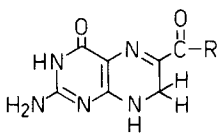
A new synthesis of deoxysepiapterin (**2**), one of the two yellow eye pigments of the *Drosophila* mutant *sepia*, is described. The synthetic approach makes use of a homolytic nucleophilic acylation of 7-(alkylthio)pteridine derivatives (**11**, **13**, **15**, **18**, **20**) leading to the corresponding 6-acyl derivatives (**21–27**). Desulfurizations have been achieved for the first time in the pteridine series using *Raney*-Co, *Raney*-Cu, or Cu-Al alloy in alkaline medium. Besides cleavage of the C(7)–S bond, further reductions of the C=O group at C(6) and the C(7)=N(8) bond are detected as side reactions leading to 6-(1-hydroxyalkyl) (**34**, **35**, **42**, **43**) and 6-acyl-7,8-dihydro derivatives (**2**, **36**, **37**), respectively. The newly synthesized compounds have been characterized by elemental analysis, p*K* determination, UV and $^1$H-NMR spectra.

**1. Introduction.** – The eyes of the wild-type flies of *Drosophila melanogaster* are rich in pteridines which function as red and yellow eye pigments [2–6]. The mutant *sepia* owes only yellow components which have been characterized as sepiapterin (**1**) [7] [8], deoxysepiapterin (**2**) [9] (formerly called isosepiapterin), and sepiapterin C (**3**) [10]. Their chemical structures are very similar and have been elucidated as 6-(L-lactoyl)-(**1**), 6-propionyl-(**2**), and 6-acetyl-7,8-dihydropterin (**3**). Another natural source of **2** has been found in the blue-green alga *Anacystus nidulans* [11], and its formation is also observed on



| | R |
|---|---|
| 1 | CHOH-$CH_3$ |
| 2 | $CH_2CH_3$ |
| 3 | $CH_3$ |

oxidation of 5,6,7,8-tetrahydrobiopterin glucoside [12]. Chemical syntheses of substantial amounts of these pigments have so far not been reported although reaction of 7,8-dihydropterin with 2-oxobutyric acid and thiamine led to deoxysepiapterin [13], and a doubtful approach to sepiapterin [14] is claimed with 3-hydroxy-2-oxobutyric acid in presence of $ZnCl_2$. Furthermore, sepiapterin and deoxysepiapterin are also formed on air oxidation from the hardly accessible 5,6,7,8-tetrahydrobiopterin in phosphate buffer at pH 4 [15] [16] or by an acid-catalyzed dehydration of 7,8-dihydrobiopterin [17].

[1]) Part LXXXIV, see [1].

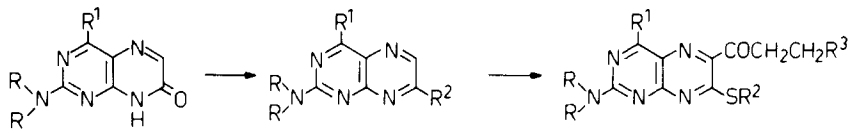
A direct chemical approach to 6- and 7-acylpteridines [18–20] is based on the homolytic nucleophilic substitution [21] [22] of the pteridine nucleus by acyl radicals. We have shown in the pteridine series [19] [20] that the 6,7-unsubstituted derivatives react under these conditions preferentially at the most electron-deficient C(7), whereas radical attack at the adjacent C(6) can only be achieved with 7-substituted pteridine derivatives.

**2. Synthesis.** – In order to develop a general method for the synthesis of 6-acylpteridines and their corresponding 7,8-dihydro derivatives such as deoxysepiapterin (**2**) [23], a useful protecting group for the 7-position with the potential of easy removal is crucial. Obviously, the thioxo or alkylthio function is recommended in the N-heterocyclic series for this purpose, but no thiopteridine derivative has so far been desulfurized successfully on *Raney*-Ni treatment [24]. Despite these facts, we decided to put our synthetic efforts on various 7-(alkylthio)pteridines as starting materials for the acylation at the 6-position. The commonly observed low solubility of pterins [5] [25] in organic solvents was the reason to start the various series of reactions from 2-amino-4-(pentyloxy)-(**4**) [26], 2-(dimethylamino)-4-methoxy-(**5**) [27], 2-(dimethylamino)-4-(benzyloxy)-(**6**) [28], 2,4-diamino-(**7**) [29], and 4-amino-2-(dimethylamino)pteridin-7(8*H*)-one (**8**) [29].

Conversion of **4** into 2-amino-4-(pentyloxy)-7-(propylthio)pteridine (**11**) in an overall yield of 71% was achieved by $POCl_3$ treatment [30] and reaction of the 7-chloro derivative **10** with sodium propanethiolate. The corresponding pteridine-7(8*H*)-ones **5** and **6** were subjected to direct thiation by $P_4S_{10}$, due to their higher solubility in organic solvents, to give **12** and **14**. The former was methylated directly (→**13**) and the latter after purification in the usual manner with dimethylsulfate/alkali. Interestingly enough, from **14** not only the expected 7-(methylthio) derivative **15** but also the corresponding 4-(benzyloxy)-2-(dimethylamino)-8-methylpteridine-7(8*H*)-thione (**9**) was formed in 26% yield under these conditions. Starting from 2,4-diaminopteridin-7(8*H*)-one (**7**), the 2,4-diamino-7-chloropteridine (**16**) was prepared by $POCl_3$ tratment, then nucleophilic displacement by NaSH took place to give **17**, which led, on methylation, to 2,4-diamino-7-(methylthio)pteridine (**18**). On the other hand, the structural analogs **19** and **20** resulted from thiation of **8** with $P_4S_{10}$ and subsequent methylation by MeI.

The homolytic nucleophilic acylations of **11**, **13**, **15**, **18**, and **20** at C(6) were then performed with the system aldehyde/$Fe^{++}$/*tert*-butyl hydroperoxide, which generated the acyl radicals nicely and gave relatively high yields of the corresponding 6-propionyl-(**21**–**25**) and 6-(dihydrocinnamoyl) derivatives (**26**, **27**).

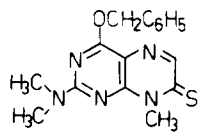
Studies for the removal of the 7-(alkylthio) groups by *Raney*-Ni desulfurization indicated that either low yields of complex mixtures are obtained or complete decomposition of the pteridine nucleus takes place. A less reactive metal like *Raney*-Co revealed better results since **21** gave a 44% yield of 2-amino-4-(pentyloxy)-6-propionylpteridine (**28**) on reflux of the components in EtOH. The best conditions, however, for the reductive cleavage of the C–S bond have been found by short treatment of an alcoholic solution of the 7-(alkylthio)pteridine with Cu-Al alloy in presence of alkali. In EtOH **21** was converted in 71% yield to a 7:1 mixture of 2-amino-4-(pentyloxy)-(**28**) and 2-amino-4-ethoxy-6-propionylpteridine (**29**), from which **28** could be isolated in pure form by fractional crystallization. An exchange of the 4-MeO group against the EtO group was also observed on desulfurization of **22** in alkaline EtOH giving **31**, whereas analogous treatment of **22** in MeOH proceeded in 38% yield to 2-(dimethylamino)-4-methoxy-6-



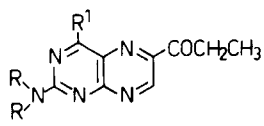
| | R | $R^1$ |
|---|---|---|
| **4** | H | $OC_5H_{11}$ |
| **5** | $CH_3$ | $OCH_3$ |
| **6** | $CH_3$ | $OCH_2C_6H_5$ |
| **7** | H | $NH_2$ |
| **8** | $CH_3$ | $NH_2$ |

| | R | $R^1$ | $R^2$ |
|---|---|---|---|
| **10** | H | $OC_5H_{11}$ | Cl |
| **11** | H | $OC_5H_{11}$ | $SC_3H_7$ |
| **12** | $CH_3$ | $OCH_3$ | SH |
| **13** | $CH_3$ | $OCH_3$ | $SCH_3$ |
| **14** | $CH_3$ | $OCH_2C_6H_5$ | SH |
| **15** | $CH_3$ | $OCH_2C_6H_5$ | $SCH_3$ |
| **16** | H | $NH_2$ | Cl |
| **17** | H | $NH_2$ | SH |
| **18** | H | $NH_2$ | $SCH_3$ |
| **19** | $CH_3$ | $NH_2$ | SH |
| **20** | $CH_3$ | $NH_2$ | $SCH_3$ |

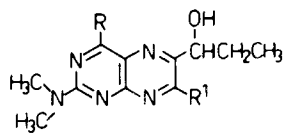
| | R | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|
| **21** | H | $OC_5H_{11}$ | $C_3H_7$ | H |
| **22** | $CH_3$ | $OCH_3$ | $CH_3$ | H |
| **23** | $CH_3$ | $OCH_2C_6H_5$ | $CH_3$ | H |
| **24** | H | $NH_2$ | $CH_3$ | H |
| **25** | $CH_3$ | $NH_2$ | $CH_3$ | H |
| **26** | H | $NH_2$ | $CH_3$ | $C_6H_5$ |
| **27** | $CH_3$ | $NH_2$ | $CH_3$ | $C_6H_5$ |



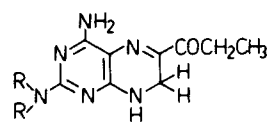
**9**



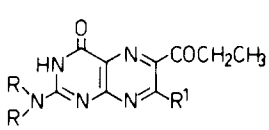
| | R | $R^1$ |
|---|---|---|
| **28** | H | $OC_5H_{11}$ |
| **29** | H | $OC_2H_5$ |
| **30** | $CH_3$ | $OCH_3$ |
| **31** | $CH_3$ | $OC_2H_5$ |
| **32** | H | $NH_2$ |
| **33** | $CH_3$ | $NH_2$ |



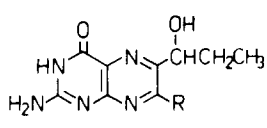
| | R | $R^1$ |
|---|---|---|
| **34** | $OCH_3$ | H |
| **35** | $NH_2$ | $SCH_3$ |



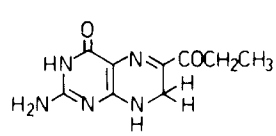
| | R |
|---|---|
| **36** | H |
| **37** | $CH_3$ |



| | R | $R^1$ |
|---|---|---|
| **38** | H | H |
| **39** | H | $SCH_3$ |
| **40** | $CH_3$ | H |
| **41** | $CH_3$ | $SCH_3$ |



| | R |
|---|---|
| **42** | H |
| **43** | $SCH_3$ |



**2**

propionylpteridine (**30**) and a small amount fo the 6-(1-hydroxypropyl) derivative **34**. Another example of desulfurization was achieved with 2-(dimethylamino)-7-(methylthio)-6-propionylpteridine-4(3*H*)-one (**41**) giving **40** in 26% yield and indicating that the presence of an amide function does not favour this interconversion. The starting (methylthio) derivative **41** resulted either from alkaline hydrolysis of **23** or acid treatment of **25**.

Table 1. *Physical Data of Pteridines*

| | $pK_a$ | UV Spectra | | pH | Molecular form[a]) |
|---|---|---|---|---|---|
| | | $\lambda_{max}$ [nm] | lg $\varepsilon$ | | |
| **11** | 3.37 | 240, 273, 370 (sh), 377 | 4.53, 4.01, 4.26, 4.27 | MeOH | 0 |
| | | 223, 277, 365, 374 | 4.46, 3.69, 4.39, 4.38 | 1.0 | + |
| | | 238, 271, 368 (sh), 376 | 4.43, 3.88, 4.23, 4.24 | 6.0 | 0 |
| **13** | 3.55 | 246, 286, 388 | 4.57, 4.24, 4.20 | MeOH | 0 |
| | | 236, 283, 369, 386 | 4.46, 3.74, 4.38, 4.37 | 0 | + |
| | | 246, 287, 318 (sh), 390 | 4.50, 4.14, 3.57, 4.17 | 6.0 | 0 |
| **14** | 7.34 | 250, 306, 426 | 4.52, 3.92, 4.36 | MeOH | 0 |
| | | 249, 306, 430, 453 (sh) | 4.50, 3.91, 4.39, 4.27 | 4.0 | 0 |
| | | 262, 292, 396, 400 (sh) | 4.51, 3.88, 4.32, 4.29 | 11.0 | – |
| **9** | –2.37 | 250, 307, 416 | 4.53, 3.91, 4.39 | MeOH | 0 |
| | | 251, 302, 455, 482 (sh) | 4.43, 3.94, 4.26, 4.19 | – 4.0 | + |
| | | 251, 309, 421, 438 (sh) | 4.51, 3.91, 4.39, 4.33 | 7.0 | 0 |
| **15** | | 206, 246, 288, 388 | 4.33, 4.53, 4.18, 4.16 | MeOH | 0 |
| | | 237, 282, 340 (sh), 370, 387 | 4.45, 3.79, 4.03, 4.36, 4.35 | 2.0 | + |
| | | 206, 246, 288, 391 | 4.32, 4.48, 4.10, 4.15 | 6.0 | 0 |
| **16** | | 222, 262, 280 (sh), 371 | 4.05, 4.31, 3.71, 3.94 | MeOH | 0 |
| **17** | 2.02 | 221, 244, 311, 403 | 4.01, 4.09, 3.78, 4.06 | 0.0 | + |
| | 7.02 | 230, 276, 297 (sh), 399 | 4.11, 3.69, 3.66, 4.05 | 4.0 | 0 |
| | | 243, 290 (sh), 385 | 4.23, 3.63, 4.08 | 10.0 | – |
| **18** | 5.26 | 225, 262, 365 | 4.35, 4.09, 4.32 | 2.0 | + |
| | | 240, 261, 308 (sh), 375 | 4.40, 4.14, 3.52, 4.19 | 8.0 | 0 |
| **19** | 2.26 | 220, 251, 264, 315, 415 | 4.09, 4.35, 4.34. 4.08, 4.32 | 0.0 | + |
| | 7.42 | 206, 241, 288, 408, 430 | 4.34, 4.33, 4.04, 4.20, 4.21 | 5.0 | 0 |
| | | 214, 258, 298 (sh), 398 | 4.24. 4.52, 3.84, 4,28 | 10.0 | – |
| **20** | 5.33 | 244, 275, 388 | 4.43, 4.37, 4.15 | MeOH | 0 |
| | | 230, 266, 364, 376 | 4.41, 4.12, 4.33, 4.34 | 2.0 | + |
| | | 244, 275, 390 | 4.41, 4.32, 4.15 | 8.0 | 0 |
| **21** | 2.89 | 247 (sh), 272, 304, 388 | 4.18, 4.45, 4.11, 4.28 | MeOH | 0 |
| | | 244 295 (sh), 308, 380 | 4.38, 3.97, 4.03, 4.21 | 1.0 | + |
| | | 244 (sh), 271, 304, 389 | 4.09, 4.35, 4.03, 4.21 | 6.0 | 0 |
| **22** | 2.89 | 274, 315, 402 | 4.23, 3.93, 4.10 | MeOH | 0 |
| | | 212, 252, 308, 389 | 4.05, 4.40, 4.06, 4.34 | 1.0 | + |
| | | 222, 273, 319, 405 | 4.05, 4.38, 4.09, 4.31 | 6.0 | 0 |
| **23** | 2.49 | 208, 274, 315, 403 | 4.24, 4.45, 4.13, 4.31 | MeOH | 0 |
| | | 254, 312, 392 | 4.40, 4.07, 4.34 | 0.0 | + |
| | | 248 (sh), 276, 318, 404 | 4.08, 4.44, 4.13, 4.33 | 6.0 | 0 |
| **24** | 4.67 | 222 (sh), 268, 304, 389 | 3.86, 4.48, 4.02, 4.24 | MeOH | 0 |
| | | 250, 288, 376 | 4.42, 4.14, 4.21 | 2.0 | + |
| | | 268, 310 (sh), 392 | 4.46, 3.97, 4.25 | 7.0 | 0 |
| **25** | 4.45 | 227, 275, 298, 405 | 4.01, 4.45, 4.27, 4.34 | MeOH | 0 |
| | | 256, 292, 384 | 4.36, 4.24, 4.33 | 2.0 | + |
| | | 228, 277, 300 (sh), 406 | 4.00, 4.42, 4.23, 4.35 | 7.0 | 0 |
| **26** | 4.41 | 269, 304 (sh), 392 | 4.45, 4.03, 4.20 | MeOH | 0 |
| | | 252, 287, 375 | 4.36, 4.11, 4.16 | 2.0 | + |
| | | 269, 310 (sh), 392 | 4.40, 3.98, 4.07 | 7.0 | 0 |
| **27** | 4.41 | 227, 275, 299, 406 | 4.02, 4.44, 4.27, 4.35 | MeOH | 0 |
| | | 255, 295, 385 | 4.35, 4.24, 4.31 | 2.0 | + |
| | | 229, 278, 302 (sh), 409 | 4.00, 4.42, 4.22, 4.37 | 7.0 | 0 |

*Table 1* (cont.)

| | p$K_a$ | UV Spectra | | | | | pH | Molecular form[a]) |
|---|---|---|---|---|---|---|---|---|
| | | $\lambda_{max}$ [nm] | | | | lg $\varepsilon$ | | |
| **39** | 1.91 | 214, | 272, | 308, | 374 | 3.88, 4.31, 3.99, 4.08 | MeOH | 0 |
| | 7.56 | | 251, | 311, | 365 | 4.39, 4.13, 4.18 | 0 | + |
| | | | 273, | 310, | 378 | 4.46, 4.18, 4.26 | 4.0 | 0 |
| | | | 266, | 300 (sh), | 384 | 4.52, 4.11, 4.33 | 10.0 | – |
| **41** | 1.30 | 218 (sh), | 278, | 320, | 384 | 4.03, 4.43, 4.20, 4.26 | MeOH | 0 |
| | 7.27 | | 256, | 311, | 367 | 4.42, 4.11, 4.19 | – 1.0 | + |
| | | | 278, | 321, | 384 | 4.41, 4.21, 4.16 | 5.0 | 0 |
| | | 225, | 271, | 300 (sh), | 396 | 4.01, 4.41, 4.18, 4.39 | 10.0 | – |
| **28** | 2.58 | | 252, | 301, | 363 | 4.21, 4.18, 4.12 | MeOH | 0 |
| | | 224, | 246, | 270 (sh), | 334 | 4.21, 4.25, 3.98, 4.20 | 0.0 | + |
| | | 230 (sh), | 252, | 300, | 366 | 4.04, 4.19, 4.13, 4.14 | 5.0 | 0 |
| **30** | | 225, | 242, | 314, | 389 | 4.06, 4.06, 4.13, 4.08 | MeOH | 0 |
| | | 231, | 260, | | 349 | 4.19, 4.01, 4.13 | 0.0 | + |
| | | 225, | 240, | 316, | 395 | 4.12, 4.08, 4.12, 4.10 | 5.0 | 0 |
| **31** | 2.39 | 226, | 242, | 316, | 393 | 4.07, 4.09, 4.22, 4.08 | MeOH | 0 |
| | | 230, | 262, | | 348 | 4.20, 4.12, 4.16 | 0.0 | + |
| | | 228, | 239 (sh), | 317, | 398 | 4.11, 4.10, 4.18, 4.14 | 5.0 | 0 |
| **32** | 4.04 | | 262, | | 335 | 4.21, 4.05 | 1.0 | + |
| | | 224 (sh), | 277, | 312 (sh), | 373 | 3.92, 4.21, 3.82, 3.98 | 7.0 | 0 |
| **33** | 3.91 | 223, | 273, | | 344 | 4.22, 4.21, 4.16 | 1.0 | + |
| | | 241, | | 303, | 398 | 4.04, 4.21, 4.14 | 7.0 | 0 |
| **38** | 1.44 | 230 (sh), | 268, | 320 | | 3.96, 4.06, 4.04 | – 1.0 | + |
| | 7.12 | 239, | | 303, | 347 | 3.96, 4.17, 3.96 | 3.0 | 0 |
| | | | 275, | 307 (sh), | 369 | 4.22, 3.87, 4.06 | 10.0 | 0 |
| **40** | 1.03 | 212, | 274, | 332, | 418 | 4.15, 4.12, 4.14, 3.43 | – 2.0 | + |
| | 6.94 | 225, | 266, | 318, | 360 | 4.10, 3.79, 4.31, 4.02 | 4.0 | 0 |
| | | 238, | | 301, | 389 | 4.00, 4.17, 4.20 | 10.0 | – |
| **35** | 5.33 | 243, | 276, | | 389 | 4.37, 4.43, 4.13 | MeOH | 0 |
| | | 232, | 265, | 365, | 378 | 4.44, 4.18, 4.33, 4.34 | 2.0 | + |
| | | 244, | 276, | | 389 | 4.39, 4.38, 4.14 | 8.0 | 0 |
| **42** | 2.27 | | 247, | 322 | | 4.04, 3.92 | 0.0 | + |
| | 7.97 | 236, | 273 | | 345 | 4.03, 4.15, 3.79 | 5.0 | 0 |
| | | 220 (sh), | 254, | | 364 | 3.92, 4.,35, 3.86 | 10.0 | – |
| **43** | 2.53 | 229, | 264 (sh), | 282, | 354 | 4.39, 3.76, 3.81, 4.30 | 0.0 | + |
| | 8.68 | 226 (sh), | 242, | 280, | 362 | 4.24, 4.34, 4.16, 4.20 | 5.0 | 0 |
| | | 236, | 258, | | 370 | 4.42, 4.18, 4.18 | 12.0 | – |
| **36** | –0.40 | 204, | 271, | 314, | 415 | 4.30, 4.31, 3.35, 4.08 | MeOH | 0 |
| | 5.30 | 220 (sh), | | 298, | 382 | 4.11, 4.21, 3.83 | – 3.0 | ++ |
| | | 219, | 268, | 291, | 397 | 4.27, 4.18, 4.00, 3.94 | 2.0 | + |
| | | | 272, | | 420 | 4.30, 4.06 | 8.0 | 0 |
| **37** | –0.77 | 206, | 276, | 326 (sh), | 412 | 4.30, 4.22, 3.75, 4.18 | MeOH | 0 |
| | 5.18 | 236, | | 299, | 382 | 4.16, 4.18, 3.96 | – 3.0 | ++ |
| | | 232, | 280, | | 388 | 4.22, 4.18, 4.04 | 2.0 | + |
| | | | 278, | 325 (sh), | 415 | 4.21, 3.75, 4.18 | 8.0 | 0 |
| **2** | 1.35 | 212, | 264, | 285, | 404 | 4.20, 4.11, 3.90, 3.85 | MeOH | 0 |
| | 10.05 | 232, | 284, | 330 (sh), | 395 | 4.14, 4.10, 3.35, 3.89 | – 1.0 | + |
| | | 213, | 265, | 286 (sh), | 410 | 4.22, 4.23, 3.89, 4.01 | 5.0 | 0 |
| | | | 267, | 312, | 430 | 4.22, 3.28, 4.10 | 13.0 | – |

[a]) ++ = Dication; + = cation; 0 = neutral form; – = monoanion.

Tab. 2. *$^1$H-NMR Data of Pteridine Derivatives*[a])

| | $\delta$(H) of substituents at C(*i*) | | | | $\delta$(H) of H–N(8) | Solvent |
|---|---|---|---|---|---|---|
| | C(2) | C(4) | C(6) | C(7) | | |
| **11** | 5.65 (br. *s*, 2 H) | 4.52 (*t*, 2 H), 2.0–0.8 (*m*, 9 H) | 8.28 (*s*, 1 H) | 3.32 (*t*, 2 H) 2.98–0.8 (*m*, 5 H) | | $CDCl_3$ |
| **13** | 3.36 (*s*, 6 H) | 4.18 (*s*, 3 H) | 8.21 (*s*, 1 H) | 2.70 (*s*, 3 H) | | $CDCl_3$ |
| **14** | 3.18 (*s*, 6 H) | 7.42 (*m*, 5 H), 5.50 (*s*, 2 H) | 7.97 (*s*, 1 H) | | 14.11 (*s*, 1 H) | $(D_6)$DMSO |
| **9** | 3.22 (*s*, 3 H), 3.24 (*s*, 3 H) | 7.44 (*m*, 5 H), 5.54 (*s*, 2 H) | 8.20 (*s*, 1 H) | | 3.90 (*s*, 3 H)[b]) | $(D_6)$DMSO |
| **15** | 3.22 (*s*, 6 H) | 7.44 (*m*, 5 H), 5.56 (*s*, 2 H) | 8.29 (*s*, 1 H) | 2.59 (*s*, 3 H) | | $(D_6)$DMSO |
| **17** | 7.36 (br. *s*, 2 H) | 6.97 (br. *s*, 2 H) | 7.86 (*s*, 1 H) | | | $(D_6)$DMSO |
| **18** | 7.52 (br. *s*, 2 H) | 6.60 (br. *s*, 2 H) | 8.16 (*s*, 1 H) | 2.56 (*s*, 3 H) | | $(D_6)$DMSO |
| **19** | 3.14 (*s*, 6 H) | 7.58 (br. *s*, 1 H) | 8.13 (*s*, 1 H) | | | $(D_6)$DMSO |
| **20** | 3.14 (*s*, 6 H) | 7.58 (br. *s*, 1 H) | 8.14 (*s*, 1 H) | 2.57 (*s*, 3 H) | | $(D_6)$DMSO |
| **21** | 6.22 (br. *s*, 2 H) | 4.58 (*t*, 2 H), 2.1–0.8 (*m*, 9 H) | 3.20 (*m*, 2 H), 2.10–0.8 (*m*, 3 H) | 3.20 (*m*, 2 H) 2.1–0.8 (*m*, 5 H) | | $CDCl_3$ |
| **22** | 3.58 (*s*, 6 H) | 4.20 (*s*, 3 H) | 3.26 (*q*, 2 H), 1.20 (*t*, 3 H) | 2.64 (*s*, 3 H) | | $CDCl_3$ |
| **23** | 3.32 (*s*, 3 H), 3.29 (*s*, 3 H) | 7.44 (*m*, 5 H), 5.65 (*s*, 2 H) | 3.10 (*q*, 2 H), 1.05 (*t*, 3 H) | 2.46 (*s*, 3 H) | | $(D_6)$DMSO |
| **24** | 9.04 (br. *s*, 2 H) | 8.28 (br. *s*, 2 H) | 3.50 (*q*, 2 H), 1.34 (*t*, 3 H) | 2.76 (*s*, 3 H) | | TFA |
| **25** | 3.44 (*s*, 6 H) | | 3.40 (*q*, 2 H), 1.32 (*t*, 3 H) | 2.60 (*s*, 3 H) | | TFA |
| **26** | 7.12 (br. *s*, 2 H) | 8.02 (br. *s*, 1 H), 7.92 (br. *s*, 1 H) | 7.28 (*m*, 5 H), 3.56 (*t*, 2 H), 2.90 (*t*, 2 H) | 2.39 (*s*, 3 H) | | $(D_6)$DMSO |
| **27** | 3.31 (*s*, 3 H), 3.19 (*s*, 3 H) | 8.03 (br. *s*, 1 H), 7.94 (br. *s*, 1 H) | 7.28 (*m*, 5 H), 3.56 (*t*, 2 H), 2.89 (*t*, 2 H) | 2.42 (*s*, 3 H) | | $(D_6)$DMSO |
| **39** | | | 3.40 (*q*, 2 H), 1.24 (*t*, 3 H) | 2.63 (*s*, 3 H) | | TFA |

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|---|---|---|---|---|---|---|
| **41** | 3.31 (*s*, 3 H), 3.18 (*s*, 3 H) | 11.64 (*s*, 1 H) | 3.10 (*q*, 2 H), 1.06 (*t*, 3 H) | 2.43 (*s*, 3 H) | | $(D_6)$DMSO |
| **28** | 8.20 (br. *s*, 1 H), 7.80 (br. *s*, 1 H) | 4.93 (*t*, 2 H), 2.2–0.8 (*m*, 9 H) | 3.50 (*q*, 2 H), 2.2–0.8 (*m*, 3 H) | 9.62 (*s*, 1 H) | | $CDCl_3$ |
| **30** | 3.40 (*s*, 3 H), 3.37 (*s*, 3 H) | 4.22 (*s*, 3 H) | 3.26 (*q*, 2 H), 1.23 (*t*, 3 H) | 9.40 (*s*, 1 H) | | $CDCl_3$ |
| **31** | 3.31 (*s*, 6 H) | 4.63 (*q*, 2 H), 1.46 (*t*, 3 H) | 3.14 (*q*, 2 H), 1.10 (*t*, 3 H) | 9.21 (*s*, 1 H) | | $(D_6)$DMSO |
| **32** | | | 3.48 (*q*, 2 H), 1.37 (*t*, 3 H) | 9.58 (*s*, 1 H) | | (D)TFA |
| **33** | 3.20 (*s*, 6 H) | 8.08 (br. *s*, 2 H) | 3.30 (*q*, 2 H), 1.08 (*t*, 3 H) | 9.08 (*s*, 1 H) | | $(D_6)$DMSO |
| **38** | 9.20 (br. *s*, 2 H) | | 3.50 (*q*, 2 H), 1.39 (*t*, 3 H) | 9.64 (*s*, 1 H) | | TFA |
| **40** | 3.68 (*s*, 3 H), 3.63 (*s*, 3 H) | | 3.82 (*q*, 2 H), 1.49 (*t*, 3 H) | 9.42 (*s*, 1 H) | | (D)TFA |
| **35** | 3.15 (*s*, 6 H) | 7.75 (br. *s*, 1 H), 7.59 (br. *s*, 1 H) | 4.63 (*m*, 1 H), 1.85 (*m*, 1 H), 1.61 (*m*, 1 H), 0.88 (*t*, 3 H), 5.15 (*d*, 1 H, OH) | 2.56 (*s*, 3 H) | | $(D_6)$DMSO |
| **42** | | | 5.33 (br. *s*, 1 H), 2.20 (*m*, 2 H), 1.20 (*t*, 3 H) | 9.15 (*s*, 1 H) | | (D)TFA |
| **43** | | | 5.26 (br. *s*, 1 H), 1.90 (*m*, 2 H), 1.10 (*t*, 3 H) | 2.76 (*s*, 3 H) | | (D)TFA |
| **36** | | | 3.12 (*q*, 2 H), 1.20 (*t*, 3 H) | 4.62 (*s*, 2 H) | | (D)TFA |
| **37** | 3.33 (*s*, 3 H), 3.20 (*s*, 3 H) | 6.96 (*s*, 1 H), 6.40 (*s*, 1 H) | 2.90 (*q*, 2 H), 0.96 (*t*, 3 H) | 4.12 (*s*, 2 H) | 7.96 (*s*, 1 H) | $(D_6)$DMSO |
| **2** | 6.80 (br. *s*, 2 H) | | 2.85 (*q*, 2 H), 1.00 (*t*, 3 H) | 4.14 (br. *s*, 2 H) | 7.34 (br. *s*, 1 H) | $(D_6)$DMSO |

[a]) Chemical shifts $\delta$(H) in ppm relative to TMS ( = 0 ppm).
[b]) Signal of $CH_3$–N(8).

Reduction of 2,4-diamino-7-(methylthio)-6-propionylpteridine (**24**) with an excess of Cu-Al alloy in alkaline EtOH led directly to the yellow-fluorescent 2,4-diamino-7,8-dihydro-6-propionylpteridine (**36**) in 49% yield, and similarly, **25** was transformed by a smaller amount of reducing agent to a mixture of 42% of 4-amino-2-(dimethylamino)-6-propionylpteridine (**33**) and 20% of its 7,8-dihydro derivative **37**. Treatment of 7-(methylthio)-6-propionylpterin (**39**), which was prepared by selective acid hydrolysis of **24**, under analogous conditions afforded a complex mixture from which deoxysepiapterin (**2**) and 6-(1-hydroxypropyl)pterin (**42**) were isolated in 28 and 48% yield, respectively; other blue fluorescent compounds were identified as 6-propionylpterin (**38**) and 6-(1-hydroxypropyl)-7-(methylthio)pterin (**43**) by chromatographical comparison with authentic samples derived from alkaline hydrolysis of **28** and $NaBH_4$ reduction of **39**, respectively. An improved yield of 37% of deoxysepiapterin (**2**) was obtained by Al-amalgam reduction of 7-(methylthio)-6-propionylpterin (**39**), whereas the partial reduction of **38** to **2** by the same reducing agent gave rise to an isolated yield of 32%.

The following further transformations were achieved. Alkaline hydrolysis of the mixture **28**/**29** led to 6-propionylpterin (**38**). Oxidation of **36** in $AcOH/H_2O$ with little $H_2O_2$ afforded 2,4-diamino-6-propionylpteridine (**32**). Furthermore, **42** was oxidized by $CrO_3$ to 6-propionylpterin (**38**) and the $NaBH_4$ reduction of **25** resulted in a high yield of 4-amino-2-(dimethylamino)-6-(1-hydroxypropyl)-7-(methylthio)pteridine (**35**).

**3. Physical Data.** – The newly synthesized compounds have been characterized by physical means. The purity was checked by TLC and the composition by elemental analysis. The structures have been proven by UV and $^1$H-NMR spectra, and the $pK_a$ determinations gave more information about the various molecular species (*Tables 1* and *2*).

It is interesting to know that the basic properties of **9** and **15** differ by almost 6 $pK_a$ units proving the much weaker basic properties of a thioamide over an *S*-alkyl-thioimidate function and their influence on the $\pi$-system of the heterocycle. The strong bathochromic shift of the long-wavelength absorption of **9** on cation formation and the low basic $pK_a$ of $-2.37$ indicate that the site of protonation is very much likely N(5) and not, as usual, N(1) for steric reasons. Furthermore, the $pK$ values and UV spectra of **17** and **19** show, in comparison with those of **18** and **20**, that the pteridine-7(8*H*)-thione form predominates clearly as neutral species in the tautomeric equilibria. Introduction of an acyl substituent into position 6 is associated with a red-shift in the UV spectrum. Another bathochromic shift is also observed on reduction of **32**, **38**, and **40** to their 7,8-dihydro derivatives **36**, **2**, and **37**, respectively, which is a characteristic feature of this type of compounds and shows that, in the reduced stage, a linear merocyanine-type resonance is an energetically favoured stabilization [15]. The $^1$H-NMR data do not reveal much additional structural information. In some cases like **9**, **23**, **30**, **37**, and **40**, the two $CH_3$ groups at $N$–C(2) appear as *s*'s with different chemical shifts indicating a coplanar arrangement with the nucleus. The spectra taken in TFA for solubility reasons show the expected signals at somewhat lower field due to cation formation under these conditions.

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## Experimental Part

*General.* TLC: precoated silica-gel thin-layer sheets *F 1500 LS 254* and cellulose thin-layer sheets *F 1440* from *Schleicher & Schüll.* Prep. TLC: silica gel *60 $PF_{254}$ (Merck).* Column chromatography: silica gel *Merck 60* (0.063–0.2 mesh) and *Florisil* (0.15–0.25 mm, *Serva*). Paper chromatography (PC): sheets *2043 bgl* from *Schleicher & Schüll.* M.p.: *Büchi* apparatus, model Dr. *Tottoli;* not corrected. UV/VIS: *Cary* recording spectrometer, model *118, Applied Phys. Corp.,* and *Uvikon 820, Kontron;* $\lambda_{max}$ in nm (lg $\varepsilon$). $^1$H-NMR: *Bruker WM-250;* $\delta$ in ppm relative to TMS ( = 0 ppm).

1. *2-Amino-7,8-dihydro-6-propionylpteridin-4(3*H*)-one* ( = *Deoxysepiapterin;* **2**). a) To a soln. of 50 mg of **38** in 50 ml of 1N $NH_3$ are added at r.t. 0.25 g of amalgamated Al-powder with stirring. After 35 min, it is filtered and washed with dil. $NH_3$, and the filtrate is stirred vigorously on air for 30 min. The soln. is evaporated, the residue extracted thrice with each 100 ml of hot EtOH and then concentrated to a small volume. This extract is put on 2 sheets of paper and chromatographed with PrOH/$H_2O$/20% aq. $NH_3$ 50:46:4. The intense yellow band is eluted with 200 ml of 1N $NH_3$, evaporated, and the residue recrystallized from 10 ml of EtOH/$H_2O$ 1:1 to give 16 mg (32%) of **2** as yellow crystals, chromatographically and spectrophotometrically identical with an authentic sample [15].

b) Small pieces of Al-foil (0.5 g) are immersed into an aq. soln. of $HgCl_2$ (50 mg) for 15 min. The soln. is decanted, the Al-foil washed several times with $H_2O$, and then a soln. of 0.3 g (1.13 mmol) of **39** in 200 ml of 1M aq. $NH_3$ added. The mixture is stirred at r.t. for 1.5 h, then filtered, concentrated under reduced pressure to 150 ml, and adjusted by AcOH addition to pH 3–4. This soln. is passed through a *Florisil* column (25 × 3 cm) which is treated with $H_2O$ to elute blue-fluorescing compounds. Then, the yellow-fluorescing compound is eluted with 1 l of an aq. acetone gradient (0–10%) and the main fraction collected. After evaporation to a small volume and another chromatographical separation on *Florisil* in the same manner, a yellow residue is obtained, which is extracted 3 times each with 70 ml of hot MeOH. Evaporation and crystallization from $H_2O$ give 92 mg (37%) of **2** as yellow needles which shows the same physical data as an authentic sample.

2. *4-(Benzyloxy)-2-(dimethylamino)-8-methylpteridine-7(8*H*)-thione* (**9**). A soln. of 3.13 g (0.01 mol) of **14** in 500 ml of MeOH and 1.1 g of KOH is treated with 1.5 g of dimethyl sulfate under stirring at r.t. over night. The resulting yellow precipitate is filtered off (1.76 g) and yields, on recrystallization from 400 ml of MeOH, 0.86 g (26%) of **9** as yellow needles. M.p. 210–211°. Anal. calc. for $C_{16}H_{17}N_5OS$ (327.3): C 58.70, H 5.23, N 21.39; found: C 58.43, H 5.01, N 21.39.

3. *2-Amino-4-(pentyloxy)-7-(propylthio)pteridine* (**11**). To a mixture of 100 ml of $POCl_3$ and 5.0 g of KCl are added 4.89 g (0.05 mol) of **4** [26], and then the flask is put in a hot oil bath (140°). After heating for 12 min with stirring, the mixture is cooled with ice, the excess of $POCl_3$ evaporated in vacuum, and the residue treated with 100 g of ice and 150 ml of $CHCl_3$. The org. layer is separated, the aq. soln. extracted twice with $CHCl_3$, and the combined org. extract dried ($Na_2SO_4$) and evaporated. The residue, which consists of **10**, is then treated with a soln. of 15 ml of propanethiol in 250 ml of 0.25N NaOMe. The soln. is stirred for 1 h at r.t., then neutralized with AcOH, and evaporated. The residue is treated with 100 ml of $H_2O$ and the precipitate collected and purified by chromatography on a silica-gel column with 4.5 l of $CHCl_3$. The product is eluted with the last 2 l to yield, after recrystallization from EtOH/$H_2O$ 1:1, 4.36 g (71%) of **11** as colourless needles. M.p. 154–155°. Anal. calc. for $C_{14}H_{21}N_5OS$ (307.4): C 54.70, H 6.89, N 22.78; found: C 54.72, H 6.80, N 22.54.

4. *2-(Dimethylamino)-4-methoxy-7-(methylthio)pteridine* (**13**). In 200 ml of anh. dioxane are heated 1.0 g (4.5 mmol) of **5** [27] and 2.0 g of $P_4S_{10}$ for 5 min under reflux. After cooling, 500 ml of $H_2O$ are added, and the soln. is extracted several times with $CHCl_3$. The org. layers are dried ($Na_2SO_4$) and evaporated to yield crude *2-(dimethylamino)-4-methoxypteridine-7-thiol* (**12**). The residue is then treated with 300 ml of 0.5N KOH, insoluble material filtered off, and to the filtrate 5 ml of $CH_3I$ are added. The mixture is vigorously stirred for 1 h at r.t. and then the precipitate filtered off by suction. Recrystallization from $H_2O$/MeOH yielded 0.65 g (57%) of **13** as yellowish crystals. M.p. 160°. Anal. calc. for $C_{10}H_{13}N_5OS$ (251.3): C 47.79, H 5.21, N 27.87; found: C 47.60, H 5.07, N 28.04.

5. *4-(Benzyloxy)-2-(dimethylamino)pteridine-7-thiol* (**14**). A mixture of 5.0 g (16.8 mmol) of **6** [28] and 10.0 g of $P_4S_{10}$ is stirred in 100 ml of dry pyridine at 60° for 22 h. After cooling, the soln. was concentrated *in vacuo* to *ca.* 30 ml, then mixed well with 300 ml of ice-cold $H_2O$ and the precipitate collected. Recrystallization from acetone yielded 3.8 g (72%) of **14** as brownish crystals. M.p. 232–234° (dec.). Anal. calc. for $C_{15}H_{15}N_5OS$ (313.3): C 57.49, H 4.82, N 22.35; found: C 57.38, H 4.80, N 22.26.

6. *4-(Benzyloxy)-2-(dimethylamino)-7-(methylthio)pteridine* (**15**). The reaction filtrate of *Exper. 2* is concentrated to *ca.* 100 ml to form a yellow precipitate. The material is filtered off and yields on recrystallization from

MeOH/$H_2O$ 0.55 g (17%) of **15** as yellow needles. M.p. 176°. Anal. calc. for $C_{16}H_{17}N_5OS$ (327.3): C 58.70, H 5.23, N 21.39; found: C 58.67, H 5.20, N 21.19.

7. *2,4-Diaminopteridine-7-thiol* (**17**). A mixture of 20.0 g (0.11 mol) of **7** [29] and 30 g of KCl is heated under reflux in 500 ml of $POCl_3$ for 2 h till all starting material has dissolved. The excess of $POCl_3$ is evaporated and the residue treated with 400 ml of ice-water. After stirring for 15 min, the soln. is adjusted to pH 7 with $NH_3$, whereby a pale yellowish precipitate of *2,4-diamino-7-chloropteridine* (**16**) separates. The solid is collected and added to a soln. of 30 g of NaSH in 900 ml of $H_2O$. The mixture is heated under reflux for 2 h, treated with charcoal, filtered, and then adjusted to pH 3 with AcOH to give 19.0 g (86%) of **17** as an orange powder. M.p. > 300°. Anal. calc. for $C_6H_6N_6S$ (194.2): C 37.11, H 3.12, N 43.29; found: C 37.26, H 3.08, N 43.39.

8. *2,4-Diamino-7-(methylthio)pteridine* (**18**). To a soln. of 9.2 g (47 mmol) of **17** in 500 ml of 1% aq. KOH soln. are added 10 g of $CH_3I$ with stirring at r.t. After 15 h, the precipitate is collected by suction and washed with $H_2O$ and acetone to yield, after drying at 100°, 8.5 g (86%) of **18** as yellowish crystals. M.p. 250°. Anal. calc. for $C_7H_8N_6S$ (208.2): C 40.38, H 3.87, N 40.37; found: C 40.35, H 3.89, N 40.50.

9. *4-Amino-2-(dimethylamino)pteridine-7-thiol* (**19**). A suspension of 3.0 g (13.5 mmol) of **8** [29] and 6 g of $P_4S_{10}$ is heated with stirring in 75 ml of pyridine at 80° for 7 h. To the resulting clear soln. are aded 20 ml of $H_2O$ after cooling, and then the soln. is evaporated. The residue is treated with 50 ml of $H_2O$, filtered, and dried at 100° to yield 3.1 g (96%) of **19** as an orange powder. M.p. 281°. Anal. calc. for $C_8H_{10}N_6S$ (222.2): C 43.24, H 4.54, N 37.82; found: C 43.24, H 4.54, N 37.76.

10. *4-Amino-2-(dimethylamino)-7-(methylthio)pteridine* (**20**). A soln. of 4.0 g (17 mmol) of **19** in 100 ml of 4% aq. KOH soln. is treated with 4.0 g of $CH_3I$ and stirred at r.t. over night. The precipitate is collected, washed with $H_2O$ and dried at 100° to give 3.5 g (82%) of **20** as yellow crystals. M.p. 226–227°. Anal. calc. for $C_9H_{12}N_6S$ (236.2): C 45.76, H 5.12, N 35.58; found: C 45.77, H 5.13, N 35.59.

11. *2-Amino-4-(pentyloxy)-6-propionyl-7-(propylthio)pteridine* (**21**). To the soln. of 5.0 g (16.3 mmol) of **11** and 20 ml of propionaldehyde in 400 ml of AcOH/$H_2O$ 3:1 are added dropwise and simultaneously 28.5 g of $FeSO_4 \cdot 7\ H_2O$ in 130 ml of $H_2O$ and 13 ml of *tert*-butyl hydroperoxide with vigorous stirring within 30 s. After stirring for 1 min, 800 ml of $H_2O$ are added, the precipitate is collected by suction, washed with $H_2O$, and dried to give 4.86 g (79%) of **21** as yellow, chromatographically pure crystals. A small amount is recrystallized from EtOH/$H_2O$: yellow needles. M.p. 200–201°. Anal. calc. for $C_{17}H_{25}N_5O_2S$ (363.5): C 56.17, H 6.93, N 19.27; found: C 56.01, H 6.85, N 19.33.

12. *2-(Dimethylamino)-4-methoxy-7-(methylthio)-6-propionylpteridine* (**22**). To the soln. of 2.0 g (8 mmol) of **13** and 7.5 ml of propionaldehyde in 150 ml of AcOH/$H_2O$ 2:1 are added simultaneously 13.3 g of $FeSO_4 \cdot 7\ H_2O$ in 56 ml of $H_2O$ and 5.6 ml of *tert*-butyl hydroperoxide with vigorous stirring within 60 s. After stirring for 1 min, the soln. is diluted with 500 ml of $H_2O$ and then extracted 3 times with each 200 ml of $CHCl_3$. The org. extracts are united, dried ($Na_2SO_4$), and evaporated. The residue is purified by chromatography over a silica-gel column (20 × 2.5 cm) with $CHCl_3$. The product fraction is evaporated and the residue recrystallized from 120 ml of EtOH/benzene 2:1 to yield 0.89 g (40%) of **22** as orange needles. M.p. 213–214°. Anal. calc. for $C_{13}H_{17}N_5O_2S$ (307.4): C 50.80, H 5.57, N 22.78; found: C 50.79, H 5.64, N 22.64.

13. *4-(Benzyloxy)-2-(dimethylamino)-7-(methylthio)-6-propionylpteridine* (**23**). To the soln. of 1.3 g (4.2 mmol) of **15** and 2 g of propionaldehyde in 17 ml of AcOH/1N $H_2SO_4$ 15:2 are added dropwise at 15–20° simultaneously a soln. of 7.0 g $FeSO_4 \cdot 7\ H_2O$ in 30 ml of $H_2O$ and 4.0 g of *tert*-butyl hydroperoxide within 30 min with vigorous stirring. After 1 h stirring at r.t., the mixture is diluted with 100 ml of $H_2O$ and then cooled with ice. The precipitate is collected, washed with $H_2O$, and recrystallized from EtOH to yield 0.67 g (44%) of yellow needles. M.p. 237–238°. Anal. calc. for $C_{19}H_{21}N_5O_2S$ (383.5): C 59.51, H 5.52, N 18.26; found: C 59.28, H 5.65, N 18.35.

14. *2,4-Diamino-7-(methylthio)-6-propionylpteridine* (**24**). To 135 ml of AcOH/1N $H_2SO_4$ 100:35 are added 4.0 g (19 mmol) of **18** and 8 g of propionaldehyde. The soln. is cooled to *ca.* 10° and then are added dropwise and simultaneously a soln. of 35 g of $FeSO_4 \cdot 7\ H_2O$ in 150 ml of $H_2O$ and 20 g of *tert*-butyl hydroperoxide within 20 min and vigorous stirring. Stirring is continued for 4 h at r.t., then the mixture is diluted with 200 ml of $H_2O$. The precipitate is collected after cooling, washed with acetone and $Et_2O$ to give 4.3 g (85%) of **24** as a chromatographically pure yellow powder. M.p. > 300°. Anal. calc. for $C_{10}H_{12}N_6OS \cdot \frac{1}{2}\ H_2O$ (276.3): C 43.94, H 4.79, N 30.75; found: C 44.18, H 4.46, N 30.61.

15. *4-Amino-2-(dimethylamino)-7-(methylthio)-6-propionylpteridine* (**25**). In 117 ml of AcOH/$H_2O$/1N $H_2SO_4$ 100:15:2 are dissolved, with gentle heating, 8.0 g (34 mmol) of **20**. The soln. is cooled to 0°, and 20 g of

propionaldehyde are added. Then, simultaneously and dropwise within 40 min, a soln. of 60 g of $FeSO_4 \cdot 7\ H_2O$ in 200 ml of $H_2O$ and 40 g of *tert*-butyl hydroperoxide are added with vigorous stirring. The soln. is partially neutralized by addition of 100 ml of 1N NaOH and evaporated and the solid dissolved in 300 ml of $H_2O$. The soln. is extracted several times with $CHCl_3$, the extract washed with $H_2O$, dried ($Na_2SO_4$), and evaporated. After recrystallization from MeOH, 3.5 g (36%) of **25** are obtained as yellow crystals. M.p. 256–257° (dec.). Anal. calc. for $C_{12}H_{18}N_6OS$ (294.4): C 48.96, H 6.16, N 28.35; found: C 49.04, H 6.08, N 28.76.

16. *2,4-Diamino-7-(methylthio)-6-(3-phenylpropionyl)pteridine* (**26**). To a soln. of 0.4 g (1.9 mmol) of **18** and 3 g of dihydrocinnamaldehyde in 90 ml of 80% AcOH soln. are added simultaneously and dropwise within 10 min 5 g of $FeSO_4 \cdot 7\ H_2O$ in 20 ml of $H_2O$ and 3 g of *tert*-butyl hydroperoxide at r.t. After stirring for 30 min, the soln. is evaporated to *ca.* 50 ml and then extracted twice with hexane to remove the excess of dihydrocinnamaldehyde. Dilution with 150 ml of $H_2O$ leads to the precipitation of a yellow solid. The material is recrystallized from EtOH to give 0.17 g (26%) of **26** as yellow prisms. M.p. 243–245° (dec.). Anal. calc. for $C_{16}H_{16}N_6OS$ (340.3): C 56.45, H 4.73, N 24.69; found: C 56.45, H 4.84, N 24.56.

17. *4-Amino-2-(dimethylamino)-7-(methylthio)-6-(3-phenylpropionyl)pteridine* (**27**). In a mixture of 25 ml of AcOH, 10 ml of $H_2O$, and 0.2 ml of conc. $H_2SO_4$ are dissolved 0.7 g (3 mmol) of **20** and 2.0 g of dihydrocinnamaldehyde. To the stirred soln. are added at 15–20° simultaneously and dropwise 10 g of $FeSO_4 \cdot 7\ H_2O$ in 30 ml of $H_2O$ and 4.5 g of *tert*-butyl hydroperoxide within 15 min. The mixture is stirred for 7 h at r.t., then extracted twice with each 100 ml of $CHCl_3$, the extract washed with $H_2O$, dried ($Na_2SO_4$), and evaporated to *ca.* 25 ml. This soln. is chromatographed on a silica-gel column (8 × 3 cm) with $CHCl_3$/hexane 1:1 and then with $CHCl_3$/MeOH 10:1. The product fraction is recrystallized from MeOH to yield 0.26 g (24%) of **27** as yellow needles. M.p. 216–217°. Anal. calc. for $C_{18}H_{20}N_6OS$ (368.5): C 58.68, H 5.47, N 22.81; found: C 58.41, H 5.47, N 22.79.

18. *2-Amino-4-(pentyloxy)-6-propionylpteridine* (**28**) *and 2-Amino-4-ethoxy-6-propionylpteridine* (**29**). a) To a soln. of 1.0 g (2.6 mmol) of **21** in 160 ml of EtOH, 12.0 g of Cu-Al alloy are added. The mixture is heated with stirring to boiling, and then 18 ml of 5N NaOH are added at once. A vigorous reaction with foaming occurs, and after exactly 15 s, the reaction is stopped by addition of 20 ml of AcOH. The mixture is filtered hot, the insoluble material washed with 200 ml of hot EtOH, and then the united filtrate evaporated. The residue is extracted with hot $CHCl_3$ several times, filtered, and after concentration to a small volume, chromatographed on a silica-gel column (10 × 3 cm) with $CHCl_3$. The product fraction is recrystallized from EtOH/DMF to yield 0.58 g (71%) of **28**/**29** as yellow crystals which consist, according to $^1$H-NMR, of 85% of **28** and 15% of **29**. This mixture has not been separated since it can be used for base hydrolysis to form 6-propionylpterin **38** (*cf. Exper. 26a*).

b) In 90 ml of DMF are treated 0.3 g (0.825 mmol) of **21** with 1.5 g of NaSH at 55° for 4 h. The soln. is neutralized with AcOH, 150 ml of $H_2O$ are added, and the orange-red precipitate is collected, washed, and dried to give 0.2 g of crude *2-amino-4-(pentyloxy)-6-propionylpteridine-7-thiol*. This material is refluxed in 100 ml of EtOH and 50 ml of $H_2O$ with 5.0 g of *Raney*-Co for 1 h. It is filtered hot, washed with hot EtOH, and then the org. solvent is evaporated in vacuum. The remaining aq. layer is extracted 3 times with 50 ml of $CHCl_3$, dried ($Na_2SO_4$), and then concentrated to a smaller volume for chromatography *via* a silica-gel column (2 × 8 cm) with $CHCl_3$. The product fraction is recrystallized from EtOH/$H_2O$ to yield 0.08 g (44%) of **28** as a yellowish powder. M.p. 246°. Anal. calc. for $C_{14}H_{19}N_5O_2$ (289.3): C 58.12, H 6.62, N 24.21; found: C 58.25, H 6.81, N 24.40.

19. *2-(Dimethylamino)-4-methoxy-6-propionylpteridine* (**30**). To a soln. of 0.153 g (0.5 mmol) of **22** in 100 ml of MeOH, 4 g of Cu-Al alloy are added. The stirred and refluxing soln. is then treated with 2 ml of 5N KOH by dropwise addition within 10 min. The mixture is filtered, the filtrate neutralized and evaporated, and the residue separated by prep. TLC on 40 × 20 × 0.2 cm silica-gel plates in $CHCl_3$/AcOEt 1:1. The yellow band yields 0.05 g (38%) of **30** as a yellow powder. M.p. 168°. Anal. calc. for $C_{12}H_{15}N_5O_2$ (261.3): C 55.16, H 5.79, N 26.81; found: C 55.31, H 5.58, N 26.70.

20. *2-(Dimethylamino)-4-ethoxy-6-propionylpteridine* (**31**). To a soln. of 1.49 g (4.9 mmol) of **22** in 400 ml of hot EtOH in an open beaker (2 l), 18 g of Cu-Al alloy are added, followed by 27 ml of 5N NaOH with stirring. There is a vigorous reaction with foaming, which is quenched after 1 min with 30 ml of AcOH. The mixture is filtered, the solid washed with $CHCl_3$, and the filtrate evaporated. The residue is distributed between 300 ml of $CHCl_3$ and 150 ml of $H_2O$, the aq. layer, after separation, again extracted with $CHCl_3$, and the combined $CHCl_3$ fraction dried ($Na_2SO_4$) and concentrated to a small volume for chromatography on a silica-gel column (30 × 2.5 cm) with $CH_2Cl_2$/MeOH 100:1. The main product fraction shows, on chromatography, the two products **30** and **31**. The mixture is separated on 2 prep. silica-gel plates (40 × 20 × 0.2 cm) with $C_6H_6$/acetone 8:1. The slower moving band is eluted with $CHCl_3$/MeOH and yielded, after evaporation and recrystallization from $H_2O$, 0.315 g (24%) of **31** as yellow crystals. M.p. 150°. Anal. calc. for $C_{13}H_{17}N_5O_2$ (275.3): C 56.71, H 6.22, N 25.44; found: C 56.31, H 6.10, N 25.48.

21. *2,4-Diamino-6-propionylpteridine* (**32**). To a soln. of 55 mg (0.25 mmol) of **36** in 6 ml of AcOH/$H_2O$ 5:1, 2 drops of 30% $H_2O_2$ are added, and the soln. is stirred over night (yellowish→blue fluorescence). The soln. is evaporated and the residue recrystallized from $H_2O$ to give 20 mg (37%) of a brownish powder. M.p. > 300°. Anal. calc. for $C_9H_{10}N_6O$ (218.2): C 49.53, H 4.62, N 38.52; found: C 49.35, H 4.59, N 36.27.

22. *4-Amino-2-(dimethylamino)-6-propionylpteridine* (**33**). To a soln. of 1.8 g (6.1 mmol) of **25** in 600 ml of boiling EtOH are added 40 g of Cu-Al alloy and then dropwise with stirring within 10 min 15 ml of 5N NaOH. After boiling for another 10 min, the reaction is quenched by addition of AcOH. The mixture is filtered hot, the filtered cake washed with hot EtOH, and then the combined filtrate evaporated. The residue is treated with $H_2O$ and then extracted several times with $CHCl_3$. The $CHCl_3$ extract is dried ($Na_2SO_4$), concentrated to a small volume, and chromatographed on a silica-gel column (3 × 40 cm) with $CHCl_3$. Two major fractions are obtained, of which the first shows a blue and the second a yellow fluorescence (see *Exper. 25*). From the first fraction, after recrystallization of the residue from MeOH, are obtained 0.64 g (42%) of **33** as yellow needles. M.p. > 315°. Anal. calc. for $C_{11}H_{14}N_6O$ (246.3): C 53.65, H 5.73, N 34.13; found: C 53.62, H 5.60, N 34.06.

23. *4-Amino-2-(dimethylamino)-6-(1-hydroxypropyl)-7-(methylthio)pteridine* (**35**). A mixture of 0.48 g (1.6 mmol) of **25** and 0.5 g of $NaBH_4$ in 200 ml of EtOH is heated under reflux for 1 h. The soln. is adjusted to pH 4 with AcOH, then evaporated, and the residue recrystallized from $H_2O$ to give 0.37 g (77%) of ivory needles. M.p. 205–206°. Anal. calc. for $C_{12}H_{18}N_6OS$ (294.3): C 48.96, H 6.16, N 28.55; found: C 48.99, H 6.41, N 28.56.

24. *2,4-Diamino-7,8-dihydro-6-propionylpteridine* (**36**). To a boiling soln. of 2.0 g (7.2 mmol) of **24** in 1.5 l of EtOH are added 60 g of Cu-Al alloy and then dropwise with vigorous stirring 40 ml of 5N NaOH within 45 min. The mixture is then adjusted to pH 6 with AcOH, filtered hot, and the filter cake washed with hot EtOH till a colourless filtrate is obtained. The combined filtrate is evaporated and the residue first recrystallized from $H_2O$ and then from MeOH to give 0.81 g (49%) of **36** as orange needles. M.p. > 300°. Anal. calc. for $C_9H_{12}N_6O$ (220.2): C 49.08, H 5.49, N 38.16; found: C 48.99, H 5.55, N 38.19.

25. *4-Amino-2-(dimethylamino)-7,8-dihydro-6-propionylpteridine* (**37**). The 2nd, yellow-fluorescing fraction of *Exper. 22* is evaporated and the residue recrystallized from MeOH to give 0.3 g (20%) of **37** as orange needles. M.p. 196–198° (dec.). Anal. calc. for $C_{11}H_{16}N_6O$ (248.3): C 53.20, H 6.49, N 33.85; found: C 53.30, H 6.62, N 33.78.

26. *2-Amino-6-propionylpteridin-4(3H)-one* (**38**). a) In 36 ml of 1N NaOH/dioxane 5:1 are heated under reflux 0.29 g (1 mmol) of **28** for 20 min. The soln. is treated with charcoal and filtered hot and then the filtrate added dropwise to a boiling soln. of 35 ml of $H_2O$/AcOH 6:1. The precipitate is filtered, washed with $H_2O$ and EtOH, and yielded, after drying at 100°, 0.19 g (85%) of **38** as a slightly yellowish powder. M.p. > 300°.

b) A soln. of 1.0 g (4.3 mmol) of **42** in 200 ml of 85% AcOH soln. is treated with 1.0 g of $CrO_3$ for 10 min under reflux. After cooling, the precipitate is collected, washed with $H_2O$, and then recrystallized from $H_2O$ to yield 0.8 g (81%) of **38** as a slightly yellowish powder. M.p. > 300°. Anal. calc. for $C_9H_9N_5O_2$ (219.2): C 49.13, H 4.14, N 31.95; found: C 49.02, H 4.12, N 32.08.

27. *2-Amino-7-(methylthio)-6-propionylpteridin-4(3H)-one* (**39**). A suspension of 1.5 g (5.5 mmol) of **24** in 60 ml of 6N HCl is boiled under reflux for 6 h. The precipitate is collected after cooling, then dissolved in 200 ml of 0.1N NaOH and, after treatment with charcoal and filtration, the hot soln. is acidified with HCOOH to form 1.21 g (82%) of **39** as yellowish needles. M.p. > 300°. Anal. calc. for $C_{10}H_{11}N_5O_2S$ (265.2): C 45.27, H 4.18, N 26.40; found: C 45.00, H 4.22, N 26.15.

28. *2-(Dimethylamino)-6-propionylpteridin-4(3H)-one* (**40**). To a boiling soln. of 0.47 g (1.6 mmol) of **41** in 500 ml of EtOH are added 10 g of Cu-Al alloy and then dropwise with stirring 6 ml of 5N NaOH within 5 min. The mixture is refluxed for another 10 min, filtered hot, and the precipitate washed twice with hot EtOH. The combined filtrate is acidified with AcOH to pH 3 and evaporated and the residue dissolved in 40 ml of $H_2O$. This soln. is separated on a *Florisil* column (10 × 3 cm). The by-products are eluted with $H_2O$ and the yellow-fluorescing product with 0.1N aq. $NH_3$. After evaporation, the product is treated with 20 ml of 0.1N AcOH, evaporated again, and then the residue recrystallized from $H_2O$ to give 0.1 g (26%) of **40** as sand-coloured needles. M.p. 315–316° (dec.). Anal. calc. for $C_{11}H_{13}N_5O_2$ (247.3): C 53.43, H 5.30, N 28.32; found: C 53.21, H 5.67, N 28.13.

29. *2-(Dimethylamino)-7-(methylthio)-6-propionylpteridin-4(3H)-one* (**41**). a) In 50 ml of 0.2N NaOH/EtOH 1:1 are boiled under reflux 0.81 g (2.1 mmol) of **23** for 2 h. The soln. is then concentrated to *ca.* 20 ml, acidified with AcOH to pH 3, the precipitate collected and washed with $H_2O$. The product is then dissolved in 100 ml of 0.1N NaOH, treated with charcoal, filtered, and the filtrate added dropwise to a hot soln. of 50 ml of 1N AcOH with stirring. The precipitate is collected by suction, washed with $H_2O$ and EtOH, and dried at 100° to yield 0.53 g (85%) of **41** as yellowish needles. M.p. 335–336°.

b) In 30 ml of 6N HCl are boiled under reflux 1.6 g (5.4 mmol) of **25** for 10 h. The soln. is evaporated, the residue dissolved in 0.1N NaOH and the workup done analogously to the preceding procedure to yield 0.3 g (20%) of **41**. M.p. 335–336°. Anal. calc. for $C_{12}H_{15}N_5O_2S$ (293.3): C 49.13, H 5.15, N 23.87; found: C 49.23, H 5.18, N 23.95.

30. *2-Amino-6-(1-hydroxypropyl)pteridin-4(3H)-one* (**42**). To a soln. of 0.22 g (1 mmol) of **38** in 30 ml of 0.2N NaOH, 0.2 g of $NaBH_4$ are added. The soln. is stirred at r.t. for 1 h, then acidified with AcOH and the colourless precipitate collected. The material is dissolved in 100 ml of 0.1N NaOH by heating, treated with charcoal, and filtered. The hot filtrate is added dropwise with stirring to boiling 1N AcOH. The precipitate is collected after cooling, washed with $H_2O$, and yields, after recrystallization from $H_2O$, 0.15 g (65%) of **42** as colourless crystals. M.p. > 300°. Anal. calc. for $C_9H_{11}N_5O_2 \cdot \frac{1}{2} H_2O$ (230.2): C 46.95, H 5.25, N 30.42; found: C 46.74, H 5.06, N 30.37.

31. *2-Amino-6-(1-hydroxypropyl)-7-(methylthio)pteridin-4(3H)-one* (**43**). To a soln. of 0.16 g (0.6 mmol) of **39** in 20 ml of 0.2N NaOH, 0.2 g of $NaBH_4$ are added. The soln. is stirred for 1 h at r.t. and then acidified with HCOOH to separate a colourless precipitate. This material is collected, then dissolved in 100 ml of 0.1N NaOH, treated with charcoal, filtered, and then added dropwise to a hot soln. of 1N HCOOH. The precipitate is collected, washed with $H_2O$, and dried at 100° to yield 0.085 g (53%) of **43** as colourless needles. M.p. > 300°. Anal. calc. for $C_{16}H_{13}N_5O_2S \cdot \frac{1}{2} H_2O$ (280.3): C 43.47, H 5.11, N 25.35; found: C 43.87, H 4.53, N 25.47.

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