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CHEMICAL SYNTHESIS OF DEOXYSEPIAPTERIN

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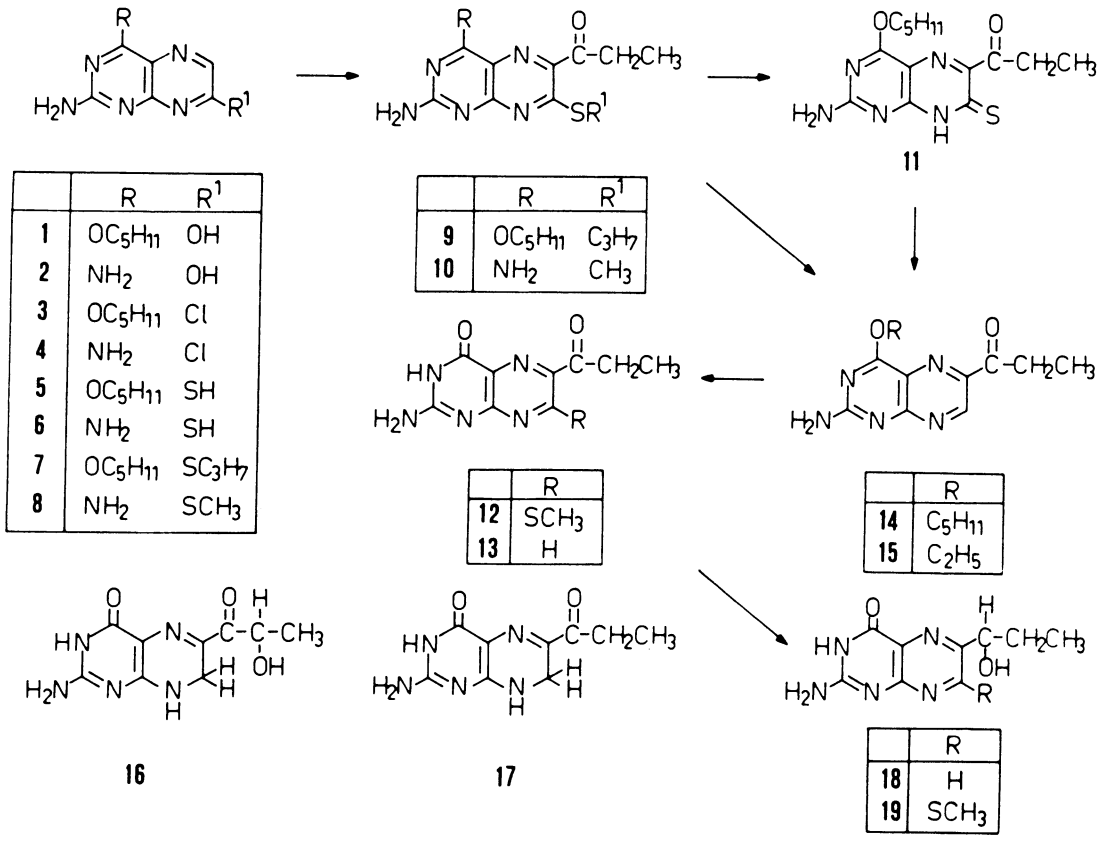
A chemical synthesis of the yellow eye pigment deoxysepiapterin of Drosophila melanogaster has been achieved from 7-alkylthio pteridines by homolytic nucleophilic acylation at C-6 and subsequent hydrolyses to 6-propionylpterin derivatives followed by desulfurizations with copper-aluminum alloy.

Sepiapterin (16)[1,2] and deoxysepiapterin (17) (formerly called isosepiapterin) may be regarded as the main yellow eye pigments of Drosophila melanogaster, whereby the latter compound has been isolated for the first time from the mutant sepia.[3] Another natural source of 17 has been found in the blue-green alga Anacystus nidulans[4] and its formation is also observed on oxidation of 5,6,7,8-tetrahydrobiopterin glucoside.[5] Chemical syntheses of substantial amounts of these pigments have so far not been reported although reaction of 7,8-dihydropterin with α-ketobutyric acid and thiamine led to deoxysepiapterin[6] and with α-keto-β-hydroxybutyric acid in the presence of zinc chloride gave sepiapterin.[7] Finally both compounds are also formed on air oxidation in a phosphate buffer (pH 4) from the hardly accessible 5,6,7,8-tetrahydrobiopterin[8,9] or by acid catalyzed dehydration of 7,8-dihydrobiopterin.[10]

A new chemical approach to the synthesis of deoxysepiapterin (17) is now derived from the possibility of homolytic nucleophilic substitution of the pteridine nucleus by acyl radicals.[11] Since 6,7-unsubstituted pteridine



	R	R^1
1	OC_5H_{11}	OH
2	NH_2	OH
3	OC_5H_{11}	Cl
4	NH_2	Cl
5	OC_5H_{11}	SH
6	NH_2	SH
7	OC_5H_{11}	SC_3H_7
8	NH_2	SCH_3

	R	R^1
9	OC_5H_{11}	C_3H_7
10	NH_2	CH_3

	R
12	SCH_3
13	H

	R
14	C_5H_{11}
15	C_2H_5

	R
18	H
19	SCH_3

derivatives react under these conditions preferentially at the most electron-deficient 7-position, analogous homolytic nucleophilic attack at the adjacent C-6 atom can only be achieved with 7-substituted pteridine derivatives.

A useful protecting group with the potential of removal is obviously in the nitrogen-heterocyclic series the thio-function, which prompted us to synthesize deoxysepiapterin from 2-amino-4-n-pentyloxy-7-n-propylthiopteridine (7) and 2,4-diamino-7-methylthiopteridine (8), respectively. Both starting materials can be obtained from the corresponding 7-hydroxy derivatives 1 and 2 via $POCl_3$ chlorination (3,4), thiation with sodium hydrogen sulfide (5,6), and subsequent alkylation.

Table 1. Physical Data of Pteridine Derivatives

Compound	pK_a in H_2O	UV - Absorption Spectra λ_{max}/nm				UV - Absorption Spectra log ε				pH	Molecular Form
7		240	273	[370]	377	4.53	4.01	[4.26]	4.27	MeOH	o
8		241	263	312	371	4.43	4.19	3.51	4.18	MeOH	o
9		[247]	272	304	388	[4.18]	4.45	4.11	4.28	MeOH	o
10		224	269	[306]	392	3.83	4.51	[4.04]	4.27	MeOH	o
14		252		301	363	4.21		4.18	4.12	MeOH	o
12	2.03	252		311	365	4.39		4.13	4.18	0.0	+
	7.81		273	310	378		4.46	4.18	4.26	4.0	o
			266	[300]	384		4.52	[4.11]	4.33	10.0	-
13	1.44	[230]	268	320		[3.96]	4.06	4.04		-1.0	+
	7.12	239		303	347	3.96		4.17	3.96	4.0	o
			275	[307]	369		4.22	[3.87]	4.06	10.0	-
18	2.27	247		322		4.04		3.92		0.0	+
	7.97	236	273		345	4.03	4.15		3.79	5.0	o
		[220]	254		364	[3.92]	4.35		3.86	10.0	-
19	2.64	230	[266]	284	355	4.39	[3.76]	3.80	4.29	0.0	+
	8.39	[230]	243	280	363	[4.23]	4.33	4.15	4.19	5.0	o
		237	258		369	4.42	4.18		4.18	12.0	-
17	1.35	232	284	[330]	395	4.14	4.10	[3.35]	3.89	-1.0	+
	10.05	213	265	[286]	410	4.22	4.23	[3.89]	4.01	5.0	o
			267	312	430		4.22	3.28	4.10	13.0	-

[ ] = Shoulder; + = cation; o = neutral molecule; - = monoanion.

Homolytic acylation of 7 and 8 with the system propionaldehyde/Fe^{++}/t-butylhydroperoxide proceeded in good yields to give 2-amino-4-n-pentyloxy-7-n-propylthio-6-propionylpteridine (9, 79%) and 2,4-diamino-7-methylthio-6-propionylpteridine (10, 85%), respectively. Treatment of 9 with NaSH in DMF afforded the 7-thioxo-7,8-dihydro analog (11), which showed then no desulfurization with Raney-nickel but decomposition. However, Raney-cobalt in ethanol could solve the problem and converted 11 in 44% yield to 2-amino-4-n-pentyloxy-6-propionylpteridine (14). Finally it was found that desulfurization of 9 itself works best with copper-aluminum alloy in ethanol and in the presence of base to

form in 71% yield a mixture of 14 and 15, which on subsequent alkaline hydrolysis afforded 6-propionylpterin (13). Partial reduction to deoxysepiapterin (17) was somewhat tricky and could only be achieved in 32% yield with amalgamated aluminum powder in aqueous ammonia.

In a second route 10 was first selectively hydrolyzed by 6 M HCl to give 7-methylthio-6-propionylpterin (12, 80%), which was then subjected to copper-aluminum alloy treatment in alkaline ethanol. From the complex mixture, 28% of deoxysepiapterin (17) and 48% of 6-(1-hydroxypropyl)pterin (18) have been isolated, whereas 6-propionylpterin (13) and 6-(1-hydroxypropyl)-7-methylthiopteridine (19) have been detected in the filtrate and identified by chromatographical comparisons.

Structural assignments were based on elementary analyses, NMR-spectra as well as UV-spectra and pK_a determinations, which are in this field especially informative (Table 1).

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