THE SYNTHESIS AND PROPERTIES OF SOME DERIVATIVES OF 2-OXO-4-THIOXO-AND 2, 4-DITHIOXO-1H, 3H-PTERIDINES

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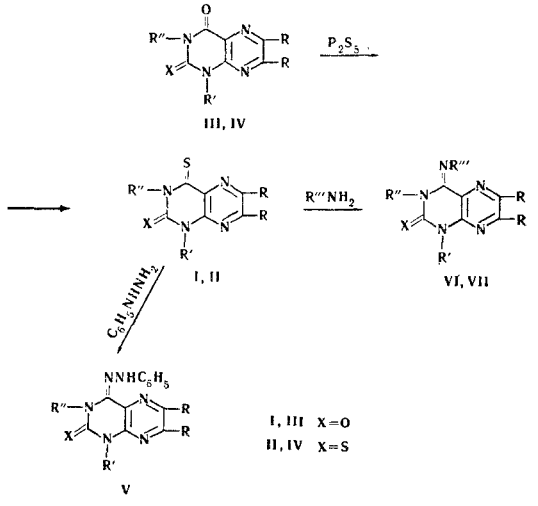
Some new derivatives of 2-oxo-4-thioxo- (I) and 2,4-dithioxo-1H, 3H-pteridine (II) have been prepared by treatment of 2,4-dioxo- (III) and 2-thioxo-4-oxo-1H,3H-pteridines (IV) with P_2S_5 in dioxane solution. The corresponding 4-phenylhydrazones, and the products of reaction of the pteridinethiones with aliphatic and aromatic amines and amino acids, have been obtained.

It is known that the sulfur in the 4-position in 2,4-dithiouracil [1], 2,4-dithiobarbituric acid [2], 2,4-dithiohydantoin [3], and some other heterocyclic compounds [4, 5] exhibits thioketonic properties, and is readily exchanged for the amino and alkyl or arylamino groups. Taylor et al. [6] have shown that 4-thioxo-6,7-diphenyl-3H-pteridine reacts with benzylamine and butylamine in boiling alcohol in presence of mercuric oxide, and with alcoholic ammonia in a sealed tube, with the formation of the corresponding 4-amino-derivatives. In order to study this problem in greater detail, we have synthesized eight pteridine derivatives of types I and II by known methods [7]. The reaction of III with P_2S_5 leads to the replacement of only one oxygen atom. Replacement of the 2-oxygen atom would give the known 2-thioxo-4-oxo-compounds [8, 9], while replacement of the 4-oxygen atom would lead to the new isomeric compounds. The compounds obtained differed in color, melting point, and UV absorption spectra from the 2-thioxo-4-oxo- derivatives, showing that the oxygen atom in the 4-position has been replaced, with the formation of I. Reaction of IV with P_2S_5 led to the formation of II.



Compounds I and II were high-melting, well-crystalline compounds of an orange or red color. Their UV absorption maxima in 0.1 N NaOH were substantially shifted toward longer wavelengths in comparison with those of the 2-thioxo-4-oxo- isomers.

On heating I with phenylhydrazine in alcohol or acetic acid, copious evolution of H_2S occurs with the formation of dark red crystals of the 4-phenylhydrazino-derivatives of the pteridines (V). When the reaction is carried out in acetic acid, simultaneous acetylation occurs to give the acetyl-derivatives of V. Compounds I and II react with ammonia, primary and secondary aliphatic amines, and primary aromatic amines, and with aliphatic amino acids. The reaction with ammonia and amines proceeds on heating in acetic acid or alcohol, and is accompanied by the evolution of H_2S, giving 4-amino-, 4-alkylamino-, 4-dialkylamino-, and 4-arylamino-derivatives (VI). The reaction with amino acids proceeds in boiling alcoholic solution in presence of sodium acetate to give the 4-carboxyalkylamino-derivatives of pteridine (VII).

Reaction of II with phenylhydrazine or with amines leads to replacement of the sulfur atom in the 4-position only, since under similar conditions the sulfur atom in 2-thioxo-4-oxo-1H, 3H-pteridine does not react either with amines or with phenylhydrazine. The 2-sulfur atom reacts only under much more severe conditions [10, 11]. The compounds were high-melting substances with a neutral reaction. The 4-arylamino-compounds were yellow, but the alkylamino-derivatives and VII were almost colorless.

EXPERIMENTAL

Pteridine-4-thiones. A suspension of 0.0025 moles of III or IV and 0.005 moles of P_2S_5 in 25 ml of anhydrous dioxane was boiled on an oil bath under reflux for from 15 min to 1.5 hr. The mixture was treated with charcoal, filtered, and the filtrate poured into an equal volume of water. The precipitate which separated was purified by recrystallization.

4-Phenylhydrazinopteridines. A solution of 0.001 moles of I or II and 0.2 ml of phenylhydrazine in 10 ml of alcohol or acetic acid was boiled under reflux until evolution of H_2S ceased (from 10 to 30 min). The product which crystallized was purified by recrystallization.

4-Aminopteridines. 0.001 moles of I or II, 0.001 moles of the aromatic amine or aminoethanol, and 10 ml of alcohol or acetic acid (or 0.001 mole I, 0.002 mole aliphatic amine hydrochloride, 0.002 mole of sodium acetate and 10 ml of alcohol) were boiled until evolution of H_2S had ceased (1–3 hr). The solid which separated on cooling or dilution with water was filtered off and purified by recrystallization.

4-Carboxyalkylaminopteridines. A mixture of 0.001 mole of the amino acid and I or II was boiled with 10 ml of alcohol and 0.5 g of sodium acetate until no more H_2S was evolved (3–7 hr). The reaction mixture was diluted with an equal volume of water, acidified with 10% HCl, and the precipitated product filtered off.

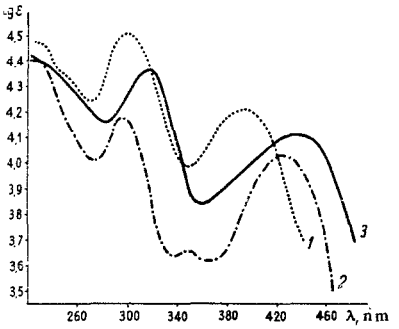
Data on the compounds obtained are given in the table.

2-Oxo-4-thioxo- and 2, 4-Dithioxo-1H, 3H-pteridines and Their Derivatives

Compound	Pteridine	Solvent[1*]; duration of heating, hr	Mp, °C	Mol. formula	Found, %		Calculated, %		Yield, %
					N	S	N	S	
1	2-Oxo-4-thioxo-6,7-diphenyl-1H,3H-	Dioxane 0.25	270	$C_{18}H_{12}N_4OS$	16.35	9.96	16.85	9.66	89
2	2,4-Dithioxo-6,7-diphenyl-1H,3H-	Dioxane 0.5	268	$C_{18}H_{12}N_4S_2$	15.84	18.27	16.09	18.43	86
3	1-p-Anisyl-2-oxo-4-thioxo-6,7-diphenyl-1H,3H-	Dioxane 1.0	>275	$C_{25}H_{18}N_4O_2S$	12.82	6.99	12.78	7.31	85
4	1-p-Anisyl-3-methyl-2-oxo-4-thioxo-6,7-diphenyl-1H,3H-	Dioxane 1.0	209—210	$C_{26}H_{20}N_4O_2S$	12.42	7.15	12.38	7.08	90
5	1,3-Dimethyl-2-oxo-4-thioxo-6,7-diphenyl-1H,3H-	Dioxane 0.5	220—221	$C_{20}H_{16}N_4OS$	15.73	9.13	15.55	8.90	90
6	2-Oxo-4-thioxo-6,7-dimethyl-1H,3H-	Dioxane 1.0	>275	$C_8H_8N_4OS$	26.45	15.09	26.91	15.40	90
7	2,4-Dithioxo-6,7-dimethyl-1H,3H-	Dioxane 1.5	252	$C_8H_8N_4S_2$					84
8	1-p-Anisyl-2-oxo-4-thioxo-6,7-dimethyl-1H,3H-	Dioxane 1.0	238—239	$C_{15}H_{14}N_4O_2S$	17.61	10.42	17.82	10.20	85
9	2-Oxo-4-phenylhydrazino-6,7-diphenyl-1H,3H-	CH_3OH; 0.5	245	$C_{24}H_{18}N_6O$	21.01	—	20.70	—	81
10	4-Thiosemicarbazone of compound I	C_2H_5OH: 3.0 CH_3COONa:	209	$C_{19}H_{15}N_7OS$	25.59	8.41	25.18	8.23	95
11	2-Thioxo-4-phenylhydrazino-6,7-diphenyl-1H,3H-	C_2H_5OH: 0.5	279—280	$C_{24}H_{18}N_6S$	19.96	7.70	19.90	7.58	84
12	2-Thioxo-4-p-nitrophenylhydrazino-6,7-diphenyl-1H,3H-	CH_3COOH: 6.0	281 (decomp.)	$C_{24}H_{17}N_7O_2S$	20.75	6.92	20.97	6.86	90
13	1-p-Anisyl-2-oxo-4-phenylhydrazino-6,7-diphenyl-1H,3H-	C_2H_5OH: 0.5	285 (decomp.)	$C_{31}H_{24}N_6O_2$	15.99	—	16.40	—	92
14	1-p-Anisyl-3-methyl-2-oxo-4-phenylhydrazino-6,7-diphenyl-1H,3H-	CH_3COOH: 1.0	248	$C_{32}H_{26}N_6O_2$	15.49	—	15.90	—	91
15	1,3-Dimethyl-2-oxo-4-phenylhydrazino-6,7-diphenyl-1H,3H-	Propan-2-ol 0.5	292—293	$C_{26}H_{22}N_6O$	19.35	—	19.34	—	88
16	2-Oxo-4-phenylhydrazino-6,7-dimethyl-1H,3H-	C_2H_5OH: 0.5	247	$C_{14}H_{14}N_6O$	29.45	—	29.79	—	94
17	2-Oxo-4-(α-acetylphenylhydrazino)-6,7-dimethyl-1H,3H-	CH_3COOH: 0.5	267	$C_{16}H_{16}N_6O_2$	26.15	—	25.93	—	87
18	2-Thioxo-4-phenylhydrazino-6,7-dimethyl-1H,3H-	Propan-2-ol 0.5	274	$C_{14}H_{14}N_6S$	28.00	10.64	28.17	10.74	92
19	2-Thioxo-4-(α-acetylphenylhydrazino)-6,7-dimethyl-1H,3H-	CH_3COOH: 0.5	279 (decomp.)	$C_{16}H_{16}N_6OS$	24.37	9.65	24.69	9.42	81

Compound	Pteridine	Solvent [1]*; duration of heating, hr	Mp, °C	Mol. formula	Found, %		Calculated, %		Yield, %
					N	S	N	S	
20	2-Oxo-4-amino-6,7-diphenyl-1H- [13]	NH_4OH. 0.25	320—325 (decomp.)	$C_{18}H_{13}N_5O$	—	—	—	—	70
21	2-Oxo-4-ethylamino-6,7-diphenyl-1H-	Propan-2-ol. CH_3COONa 2.0	>300	$C_{20}H_{17}N_5O$	20.40	—	20.40	—	40
22	2-Oxo-4-dimethylamino-6,7-diphenyl-1H-	Propan-2-ol. CH_3COONa 1.0	>300	$C_{20}H_{17}N_5O$	20.22	—	20.40	—	95
23	2-Oxo-4-(β-hydroxyethylamino)-6,7-diphenyl-1H-	C_2H_5OH. 3.0	>300	$C_{20}H_{17}N_5O_2$	19.41	—	19.49	—	68
24	2-Oxo-4-benzylamino-6,7-diphenyl-1H-	CH_3COOH. 1.5	298—300	$C_{25}H_{19}N_5O$	17.02	—	17.28	—	80
25	2-Oxo-4-anilino-6,7-diphenyl-1H-	CH_3COOH. 2.0	>300	$C_{24}H_{17}N_5O$	17.65	—	17.89	—	66
26	2-Thioxo-4-anilino-6,7-diphenyl-1H-	C_2H_5OH. 25.0	266—267	$C_{24}H_{17}N_5S$	17.09	7.53	17.19	7.87	86
27	1,3-Dimethyl-2-oxo-4-phenylimino-6,7diphenyl-1H,3H-	Propan-2-ol.	186—187	$C_{26}H_{21}N_5O$	16.95	—	16.70	—	60
28	2-Oxo-4-(o-tolylamino)-6,7-diphenyl-1H-	CH_3COOH. 2.0	>300	$C_{25}H_{19}N_5O$	17.29	—	17.28	—	70
29	2-Oxo-4-(p-tolylamino)6,7-diphenyl-1H-	CH_3COOH. 2.0	>300	$C_{25}H_{19}N_5O$	17.07	—	17.28	—	75
30	2-Oxo-4-(o-anisylamino)-6,7-diphenyl-1H-	CH_3COOH. 1.5	>300	$C_{25}H_{19}N_5O_2$	16.61	—	16.62	—	87
31	2-Oxo-4-(p-anisylamino)-6,7-diphenyl-1H-	CH_3COOH. 2.0	>300	$C_{25}H_{19}N_5O_2$	16.22	—	16.62	—	82
32	2-Oxo-4-carboxymethylamino-6,7-diphenyl-1H-	C_2H_5OH. CH_3COONa 3.5	216—217	$C_{20}H_{15}N_5O_3$ [2]*	18.47	—	18.76	—	93
33	2-Oxo-4-(α-carboxyethylamino)-6,7-diphenyl-1H-	C_2H_5OH. CH_3COONa 7.0	244 (decomp.)	$C_{21}H_{17}N_5O_3$ [3]*	18.03	—	18.08	—	82
34	2-Oxo-4-(α-carboxypropylamino)-6,7-diphenyl-1H-	C_2H_5OH. CH_3COONa 6.0	235 (decomp.)	$C_{22}H_{19}N_5O_3$ [4]*	17.15	—	17.45	—	99
35	2-Oxo-4-(α-carboxypentyl-amino)-6,7-diphenyl-1H-	C_2H_5OH. CH_3COONa 4.0	178—179	$C_{24}H_{23}N_5O_3$ [5]*	16.15	—	16.31	—	80
36	2-Thioxo-4-ethoxycarbonylamino-6,7-diphenyl-1H-	C_2H_5OH. CH_3COONa 5.0	142—143	$C_{22}H_{19}N_5O_2S$	16.81	7.70	16.78	7.68	90

1* Pteridines 1-4, 8-11, 14, 17, 22, 26, 29, 32-34 and 36 were recrystallized from acetic acid; 5, 13, 16, 19-21, 24, 25 and 28 from butanol; 6, 7, 18, 23 and 35 from ethanol; 12 from dichloroethane; 15 from propan-2-ol; 27 from methanol; and 30 and 31 from dimethylformamide. 2* Found, %: COOH 12.00. Calc., %: COOH 12.06. 3* Found, %: COOH 11.91. Calc., %: COOH 11.63. 4* Found, %: COOH 11.41. Calc., %: COOH 11.22. 5* Found, %: COOH 10.16. Calc., %: COOH 10.49.



UV Absorption spectra (in 0.1 N NaOH): 1) 2-thioxo-4-oxo-6, 7-diphenyl-1H, 3H-pteridine; 2) 2-oxo-4-thioxo-6, 7-diphenyl-1H,3H-pteridine; 3) 2, 4-dithioxo-6, 7-diphenyl-1H,3H-pteridine.

REFERENCES

1. P. B. Russel, G. B. Elion, E. A. Faleo, and G. H. Hitchings, J. Am. Chem. Soc., 71, 2279, 1949.

2. H. C. Carrington, J. Chem. Soc., 124, 1944.

3. H. C. Carrington, J. Chem. Soc., 684, 1947.

4. N. I. Leonard and D. Y. Curtin, J. Org. Chem., 11, 349, 1946.

5. A. I. Tomisek and B. E. Christensen, J. Am. Chem. Soc., 70, 2423, 1948.

6. E. C. Taylor, I. A. Carbon and D. R. Hoff, J. Am. Chem. Soc., 75, 1904, 1953.

7. A. P. Grishchuk, T. E. Gorizdra, I. D. Komaritsa, and S. N. Baranov, USSR patent no. 172808, Byull. Izobret., no. 14, 1965.

8. M. Polonovski, M. Pesson, and R. Viellefosse, C. r., 218, 796, 1944.

9. M. Matsuura, S. Nawa, H. Kakizawa, and J. Hirata, J. Am. Chem. Soc., 75, 4446, 1953.

10. E. C. Taylor and C. K. Cain, J. Am. Chem. Soc., 74, 1644, 1952.

11. E. C. Taylor and C. K. Cain, J. Am. Chem. Soc., 73, 4384, 1951.

12. J. W. Daly and B. E. Christensen, J. Am. Chem. Soc., 78, 225, 1956.

13. E. C. Taylor and C. K. Cain, J. Am. Chem. Soc., 71, 2538, 1949.

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