

1280. *Pteridine Studies. Part XXX.*<sup>1</sup> *Some Michael-type Addition Reactions of 7-Hydroxypteridine*

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7-Hydroxypteridine, which has no tendency to add water or ethanol across a double-bond, nevertheless readily adds various types of Michael reagents, not only in substantially neutral solution, but also at pH 2. Sodium hydrogen sulphite forms a similar 1 : 1 adduct.

BOTH 2- and 6-hydroxypteridine add water covalently<sup>2</sup> (across the 3,4- and 7,8-double bonds respectively<sup>3-5</sup>) and undergo Michael-type addition reactions in the same positions with carbanion reagents such as acetylacetone and ethyl cyanoacetate.<sup>4</sup> Although covalent hydration of 7-hydroxypteridine has not been observed,<sup>6</sup> it seemed possible that 7-hydroxypteridine might form adducts with stronger nucleophilic agents. For example, acridine does not add water covalently (Dr. D. D. Perrin, personal communication), but nevertheless undergoes Michael-type additions.<sup>7</sup>

We have now found that 7-hydroxypteridine readily forms adducts with appropriate nucleophilic agents in aqueous solution. Thus, with sodium hydrogen sulphite, 7-hydroxypteridine forms a 1 : 1 adduct having ultraviolet spectral characteristics closely resembling those of 5,6-dihydro-7-hydroxypteridine;<sup>8</sup> accordingly the structure of the adduct is formulated as (I; R = -SO<sub>3</sub>Na). This adduct reverts, within a few seconds, to 7-hydroxypteridine on treatment with cold dilute aqueous sodium hydroxide, but is much more stable to dilute acids.

7-Hydroxypteridine also reacts readily with such potentially carbanionic reagents as

<sup>1</sup> Part XXIX, D. J. Brown and N. W. Jacobsen, *J.*, 1965, 1175.

<sup>2</sup> For a review of covalent hydration see A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1; D. D. Perrin, *ibid.*, p. 43.

<sup>3</sup> D. J. Brown and S. F. Mason, *J.*, 1956, 3443.

<sup>4</sup> (a) A. Albert and F. Reich, *J.*, 1961, 127; (b) A. Albert and C. F. Howell, *J.*, 1962, 1591.

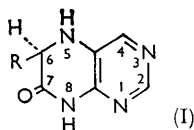
<sup>5</sup> Y. Inoue and D. D. Perrin, *J.*, 1963, 3936, 4803.

<sup>6</sup> Y. Inoue and D. D. Perrin, *J.*, 1962, 2600.

<sup>7</sup> F. Kröhnke and H. L. Honig, *Annalen*, 1959, **624**, 97.

<sup>8</sup> (a) A. Albert, D. J. Brown, and G. Cheeseman, *J.*, 1952, 1620; (b) A. Albert and S. Matsuura, *J.*, 1962, 2162.

acetylacetonone, dimedone, ethyl acetoacetate, and diethyl acetonedicarboxylate. Without exception the products isolated were 1:1 adducts, and in each instance the ultraviolet absorption spectrum of the adduct was similar to that of 5,6-dihydro-7-hydroxypteridine (see Table). Attention is directed particularly to the large bathochromic shift ( $\sim 50 \text{ m}\mu$ ) of the band at longest wavelength, seen on passing from the cation of 7-hydroxypteridine to the cation of its 5,6-dihydro derivative and those of the adducts. Steric hindrance by a 6-methyl group confirms that, in these reactions, addition occurs across the 5,6-double bond. Thus 7-hydroxy-6-methylpteridine failed to react appreciably with dimedone under conditions in which 7-hydroxypteridine (and its 2- and 4-methyl derivatives) rapidly formed adducts. Hindrance exerted by a methyl group situated at the position of nucleophilic attack is a well-known phenomenon in the covalent hydration of pteridines and other heteroaromatic substances;<sup>2</sup> that dimedone is able to condense with aldehydes, but not with ketones,<sup>9</sup> is relevant.



## Spectral properties of pteridines

Pteridine	Ionisation <sup>a</sup> (H <sub>2</sub> O; 20°)			Spectrometry <sup>e</sup>	
	Charge	pK <sub>a</sub>	$\lambda_{\text{max}}$ (m $\mu$ )	log $\epsilon$	Solvent
7-Hydroxy- <sup>b</sup>	+ <sup>f</sup>	1.2	303	3.89	pH 1.1
	0	—	227, 248 + 256, 303	3.79, 3.44 + 3.45, 4.00	pH 4.0
5,6-Dihydro-7-hydroxy-	+ <sup>g</sup>	3.36	223, 284, 352	4.47, 3.74, 3.71	pH 1.0
	0	—	211, 271, 319	4.47, 3.58, 3.70	pH 6.0
Sodium 5,6-dihydro-7-hydroxy-6-sulphonate	+ <sup>a</sup>	—	226, 284, 348	4.45, 3.78, 3.78	pH 1.0
	0 <sup>e</sup>	—	216, 270, 325	4.47, 3.68, 3.82	pH 5.5
6-Diacetylmethyl-5,6-dihydro-7-hydroxy-	+ <sup>a</sup>	—	223, 284, 349	4.42, 3.76, 3.70	pH 1.0
	0 <sup>e</sup>	—	214, 232, 274, 322	4.34, 3.93, 3.98, 3.78	Ethanol
6-(4,4-Dimethyl-2,6-dioxocyclohexyl)-5,6-dihydro-7-hydroxy-	+	3.35 <sup>g</sup>	223, 250, 286, 359	4.48, 4.15, 4.02, 3.68	pH 1.0
	0	—	215, 286, 334	4.46, 4.19, 3.75	Ethanol
6-(1-Ethoxycarbonyl-2-oxopropyl)-5,6-dihydro-	+ <sup>g</sup>	3.16 <sup>g</sup>	223, 285, 350	4.47, 3.75, 3.72	pH 1.0
	0	—	214, 275, 325	4.55, 3.67, 3.77	Ethanol
6-(4,6-Dihydroxypyrimidin-5-yl)-5,6-dihydro-	+ <sup>a</sup>	—	223, 254, 293, 352	4.39, 4.01, 3.94, 3.72	pH 1.0
	+ <sup>a</sup>	—	220, 258, 288, 346	4.50, 3.93, 3.89, 3.51	pH 1.0
6-(2,4,6-Trihydroxypyrimidin-5-yl)-5,6-dihydro-	+ <sup>a</sup>	—	223, 285, 351	4.61, 3.86, 3.85	pH 1.0
	0 <sup>e</sup>	—	214, 232, 275, 322	4.66, 3.81, 3.79, 3.95	Ethanol
6-(1,3-Diethoxycarbonyl-2-oxopropyl)-5,6-dihydro-	+ <sup>a</sup>	—	223, 286, 351	4.78, 4.08, 4.08	pH 1.0
6-(4,4-Dimethyl-2,6-dioxocyclohexyl)-5,6-dihydro-2-methyl-	+ <sup>a</sup>	—	224, 250, 285, 359	4.51, 4.20, 4.08, 3.68	pH 1.0
	+ <sup>a</sup>	—	223, 250, 288, 358	4.53, 4.16, 4.05, 3.75	pH 1.0

<sup>a</sup> Determined spectrometrically at 10<sup>-4</sup>M. <sup>b</sup> Reference 8a. <sup>c</sup> Inflections in italics. <sup>d</sup> Charge assigned to pteridine portion by analogy with the dimedone and ethyl acetoacetate adducts. <sup>e</sup> Refers to pteridine portion only. <sup>f</sup> Actually, a mixture of neutral molecule (44%) and cation (56%); at lower pH values decomposition occurs (J. Bunting, personal communication). <sup>g</sup> Analytical wavelength, 360 m $\mu$ .

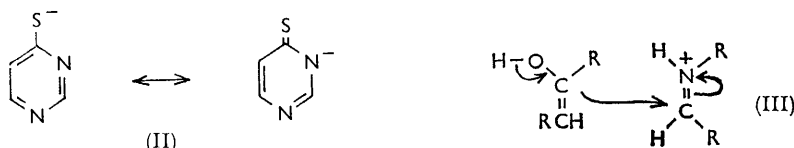
Although 7-hydroxypteridine did not react with the feebly acidic diethyl malonate in water, the desired 1:1 adduct [I; R = CH(CO<sub>2</sub>Et)<sub>2</sub>] was readily prepared in tributylamine. Acetone failed to add to 7-hydroxypteridine under any of the conditions employed. The rather low pK<sub>a</sub> values<sup>10</sup> for the methylene group of barbituric acid (4.12) and 2-thio-barbituric acid (3.75) suggested that these substances, with their high potential for forming

<sup>9</sup> F. Wild, "Characterisation of Organic Compounds," Cambridge University Press, Cambridge, 2nd edn., 1958, p. 136.

<sup>10</sup> H. G. Mautner and E. M. Clayton, *J. Amer. Chem. Soc.*, 1959, **81**, 6270.

anions, should be capable of undergoing particularly easy adduct formation with 7-hydroxypteridine in water. Indeed each compound reacted readily to yield a 1 : 1 adduct in excellent yield. That this reaction requires the presence of a mobile hydrogen at position 5 of the barbiturate nucleus is indicated by the failure of 5,5-diethylbarbituric acid to undergo adduct formation with 7-hydroxypteridine. 4,6-Dihydroxypyrimidine, which has a  $pK_a$  value (5.4) close to that of barbituric acid and which forms a "Claisen-type" adduct with benzaldehyde,<sup>11</sup> was also found to add readily to 7-hydroxypteridine. The ultraviolet absorption spectra (in 0.1N-hydrochloric acid) of the adducts of barbituric acid and 4,6-dihydroxypyrimidine with 7-hydroxypteridine exhibited maxima characteristic not only of the 5,6-dihydro-7-hydroxypteridine structure, but also of the pyrimidine substituent ( $\sim 260 m\mu$ ).

The strongly nucleophilic character of certain thio anions<sup>12,13</sup> suggested that it might be worthwhile to investigate the reaction of 7-hydroxypteridine with thiophenol ( $pK_a$  6.5).<sup>14</sup> This agent reacted smoothly with 7-hydroxypteridine in aqueous ethanol to give 5,6-dihydro-7-hydroxy-6-phenylthiopteridine (I;  $R = -S-C_6H_5$ ); 4-mercaptopyrimidine did not undergo this type of reaction, apparently because of the lowering of the nucleophilicity of its anion resulting from the "thioamide" resonance in the heterocyclic system (II). The failure of phenol to react with 7-hydroxypteridine, under conditions in which



the thiophenol adduct was prepared, is consistent with the weaker nucleophilic character of phenoxy compared to phenylthio anions.<sup>13</sup>

Although 2- and 6-hydroxypteridines form adducts when heated under reflux with methanol or ethanol,<sup>4</sup> 7-hydroxypteridine could not be induced to add these reagents under identical conditions. This observation, together with the known inability to add water,<sup>6</sup> indicate that 7-hydroxypteridine is considerably less susceptible to attack by nucleophilic agents than are the 2- and the 6-isomers. 7-Hydroxypteridine did not form isolable adducts when treated with aqueous solutions of hydrazine or hydroxylamine, but underwent extensive decomposition, presumably involving cleavage of the pteridine nucleus.

*Addition Reactions at pH 2.*—Certain Michael reagents can form adducts with 6-hydroxypteridine in the presence of acid (pH 2).<sup>15</sup> We find that 7-hydroxypteridine readily forms the above 1 : 1 adducts with dimedone, acetylacetone, barbituric acid, and ethyl acetoacetate in dilute sulphuric acid (pH 2.0) at 20—25°. Steric hindrance is exerted by a 6-methyl group as before; 7-hydroxy-6-methylpteridine fails to react with dimedone at pH 2.0, although 7-hydroxy-2-methyl- and 7-hydroxy-4-methylpteridine form adducts as readily as does 7-hydroxypteridine. Although dimedone ( $pK_a \sim 5.3$ )<sup>16</sup> and barbituric acid may well react as carbanionic species at pH 2.0,<sup>17,18</sup> it appears unlikely that a reagent such as acetylacetone ( $pK_a$  9.0)<sup>19</sup> or ethyl acetoacetate ( $pK_a$  11)<sup>19</sup> would add to 7-hydroxypteridine at this pH via the carbanion.<sup>20</sup> It seems more reasonable that enolic tautomers are the true reactive species and that these add, as shown in (III), to the 5,6-double bond of

<sup>11</sup> D. J. Brown and T. Teitei, *Austral. J. Chem.*, 1964, **17**, 567.

<sup>12</sup> J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.

<sup>13</sup> J. F. Bunnett and G. T. Davis, *J. Amer. Chem. Soc.*, 1954, **76**, 3011; *ibid.*, 1958, **80**, 4337.

<sup>14</sup> A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962.

<sup>15</sup> A. Albert and E. P. Serjeant, *J.*, 1964, 3357.

<sup>16</sup> R. P. Bell and G. C. Davis, *J.*, 1965, 353.

<sup>17</sup> M. J. Kamlet, *J. Amer. Chem. Soc.*, 1955, **77**, 4896.

<sup>18</sup> M. J. Kamlet and D. J. Glover, *J. Amer. Chem. Soc.*, 1956, **78**, 4556.

<sup>19</sup> R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, 1953, **75**, 2439.

<sup>20</sup> E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, New York, 1959 374.

7-hydroxypteridine (activated by protonation, possibly on N-5). Such a mechanism would resemble that involved in alkylation by enamines.<sup>21</sup> Our postulated involvement of the cation takes into account the many Michael reactions described for quaternised heterocyclic systems.<sup>22-24</sup> A recent report<sup>25</sup> of the addition of ketonic Michael reagents to Schiff bases, under acidic conditions, might be interpreted similarly.

### EXPERIMENTAL

Elemental analyses were carried out by the Analytical Section of this department, under Dr. J. E. Fildes. Ultraviolet (u.v.) spectra were measured on a Perkin-Elmer Spectracord (model 4000 A) recording spectrophotometer and the  $\lambda_{\text{max}}$  and extinction values were checked on an Optica CF4 manual instrument. Infrared (i.r.) spectra (Nujol) were obtained with a Unicam model S.P.200 instrument. Ionization constants were determined spectrophotometrically in Dr. D. D. Perrin's section, using the same techniques as in earlier parts of this Series. All stirring was carried out magnetically.

*Condensation with Sodium Hydrogen Sulphite.*—A solution of 7-hydroxypteridine<sup>8a</sup> (0.30 g.) and sodium hydrogen sulphite (0.60 g.) in water (6 ml.) was shaken vigorously at 20° for 5 min., and set aside for 30 min. The white solid was collected, suspended in 50% aqueous ethanol (20 ml.) and chilled to 5°. The white solid product was filtered off and washed successively with 60% aqueous ethanol, absolute ethanol, and finally diethyl ether. The washed solid, sodium 5,6-dihydro-7-hydroxypteridine-6-sulphonate, (68%) darkened slowly above 160° without melting (Found, for material dried at 20°/10 mm. over P<sub>2</sub>O<sub>5</sub>: C, 24.9; H, 3.2; N, 19.3. C<sub>8</sub>H<sub>5</sub>N<sub>4</sub>NaO<sub>4</sub>S·2H<sub>2</sub>O requires C, 25.0; H, 3.1; N, 19.45%).

*Condensation with Acetylacetone.*—7-Hydroxypteridine (0.22 g.) in water (30 ml.) and acetylacetone (2.5 ml.) were stirred at 20° for 90 min. and set aside overnight. The white solid, recrystallised from methanol (100 parts), gave 6-diacetylmethyl-5,6-dihydro-7-hydroxypteridine (65%), m. p. 189° (Found, for material dried at 20°/10 mm. over P<sub>2</sub>O<sub>5</sub>: C, 53.2; H, 5.05; N, 22.4. C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub> requires C, 53.25; H, 4.8; N, 22.55%).

When this reaction was repeated in 0.01N-sulphuric acid, stirred vigorously for the first 20 min. and gently for 20 hr., at 70% yield of the same product was obtained (mixed m. p., u.v., and i.r. spectra).

*Condensations with Dimedone.*—7-Hydroxypteridine (0.12 g.), dimedone (0.20 g.), and water (30 ml.) were stirred at 20° for 2 hr. and set aside overnight. The mixture was filtered, and the residue (67% yield) was dried (20°/10 mm.) and recrystallised from methanol (150 parts) giving colourless, hygroscopic plates of 6-(4,4-dimethyl-2,6-dioxocyclohexyl)-5,6-dihydro-7-hydroxypteridine, m. p. 212—215° (decomp.) (Found, for material dried at 105°: C, 58.45; H, 5.6; N, 19.5. C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub> requires C, 58.2; H, 5.6; N, 19.45%).

This reaction, repeated by stirring overnight in 0.01N-sulphuric acid, gave a 75% yield of material identical with the above.

*Condensations with Ethyl Acetoacetate.*—7-Hydroxypteridine (0.20 g.) and water (20 ml.) were heated on the steam-bath for 5 min. Ethyl acetoacetate (2 ml.) was added to the warm suspension, and the mixture was heated for an additional 5 min. and set aside at 20—25° for 24 hr. (swirling occasionally). The white crystalline precipitate of 6-(1-ethoxycarbonyl-2-oxopropyl)-5,6-dihydro-7-hydroxypteridine was isolated by filtration and washed with light petroleum (b. p. 40—60°) and then chloroform (76%; m. p. 179°) (Found, for material recrystallised from 50 parts ethanol and dried at 20°/10 mm.: C, 51.9; H, 4.9; N, 19.8. C<sub>12</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub> requires C, 51.8; H, 5.0; N, 20.1%).

This reaction repeated at pH 2 (0.01N-sulphuric acid), stirring for 3 days, gave a 65% yield of the same substance.

*Condensation with 4,6-Dihydroxypyrimidine.*—7-Hydroxypteridine (0.11 g.), 4,6-dihydroxypyrimidine (0.12 g.), and water (30 ml.) were stirred vigorously at 20° for 24 hr. The precipitate of 6-(4,6-dihydroxypyrimidin-5-yl)-5,6-dihydro-7-hydroxypteridine was collected by filtration, suspended in water (20 ml.), and dissolved by adding 0.5N-potassium hydroxide. Acidification

<sup>21</sup> J. Szmuszkovicz, *Adv. Org. Chem.*, 1963, **4**, 1.

<sup>22</sup> F. Kröhnke and H. L. Honig, *Chem. Ber.*, 1957, **90**, 2215.

<sup>23</sup> N. J. Leonard and R. L. Foster, *J. Amer. Chem. Soc.*, 1952, **74**, 3671.

<sup>24</sup> J. Van Eys and N. O. Kaplan, *J. Biol. Chem.*, 1957, **223**, 305.

<sup>25</sup> A. H. Blatt and N. Gross, *J. Org. Chem.*, 1964, **29**, 3306.

to pH 4 with glacial acetic acid, and chilling, furnished a 98% yield of buff crystals which decomposed gradually above 250° (Found, for material dried at 105°: C, 46.3; H, 3.2; N, 32.3.  $C_{10}H_8N_6O_3$  requires C, 46.1; H, 3.1; N, 32.3%).

*Condensations with Barbituric Acid.*—Barbituric acid (0.27 g.) was shaken vigorously in water (30 ml.) for 5 min.; 7-hydroxypteridine (0.095 g.) was added, and the mixture shaken for 30 min. The light yellow solid, filtered off and suspended in 20 ml. water, was dissolved and adjusted to pH 5 by the careful addition of *n*-potassium hydroxide, then filtered. 2*N*-Hydrochloric acid was added until the filtrate became cloudy; it was then chilled. The light yellow crystals of 6-(2,4,6-trihydroxypyrimidin-5-yl)-5,6-dihydro-7-hydroxypteridine (dried at 105°; 90%) decomposed gradually above 290° (Found: C, 42.3; H, 3.3; N, 30.0.  $C_{10}H_8N_6O_4 \cdot 0.5H_2O$  requires C, 42.1; H, 3.2; N, 29.5%).

7-Hydroxypteridine (0.22 g.), shaken for 5 hr. with a solution of barbituric acid (0.20 g.) in 0.01*N*-sulphuric acid (30 ml.), gave a 97% yield of an identical product.

*Condensation with 2-Thiobarbituric Acid.*—2-Thiobarbituric acid (0.30 g.) and water (30 ml.) were shaken vigorously at 20° for 10 min., the solution was clarified by filtration, and 7-hydroxypteridine (0.12 g.) was added. The mixture was shaken gently for 48 hr.; a yellow solid was collected by filtration, suspended in hot water (20 ml.) and dissolved by adding *n*-potassium hydroxide. Acidification to pH 2 with 2*N*-hydrochloric acid and subsequent chilling gave yellow crystals of 6-(4,6-dihydroxy-2-mercaptopyrimidin-5-yl)-5,6-dihydro-7-hydroxypteridine (dried at 105°; 98%). It decomposed gradually in the range 240–260° (Found: C, 38.6; H, 3.4; N, 27.35.  $C_{10}H_8N_6O_3S \cdot H_2O$  requires C, 38.7; H, 3.2; N, 27.1%).

*Condensation with Diethyl Acetonedicarboxylate.*—7-Hydroxypteridine (0.20 g.), diethyl acetonedicarboxylate (2 ml.), and 50% aqueous ethanol (20 ml.) were stirred at 20° for 5 days and set aside for an additional 2 days. The white solid (51%), suspended in cold ethanol (5 ml.), filtered off, and washed with ether, gave 6-(1,3-diethoxycarbonyl-2-oxopropyl)-5,6-dihydro-7-hydroxypteridine, m. p. 129° (Found, for material dried at 20°/10 mm. over  $P_2O_5$ : C, 50.2; H, 5.2; N, 15.6.  $C_{15}H_{18}N_4O_6 \cdot 0.5H_2O$  requires C, 50.15; H, 5.3; N, 15.6%).

*Condensation with Thiophenol.*—7-Hydroxypteridine (0.10 g.) and 66% aqueous ethanol (30 ml.) were stirred at 20° for 4 hr., and clarified by filtration. Thiophenol (1 ml.) was added and the solution stirred for 72 hr. After filtration and washing with benzene, the 5,6-dihydro-7-hydroxy-6-phenylthiopteridine (24%) had m. p. 255–257° (decomp.) (Found, for material dried at 20°/10 mm.: C, 55.75; H, 3.9; N, 21.7.  $C_{12}H_{10}N_4OS$  requires C, 55.4; H, 4.1; N, 21.9%).

*Condensation with Diethyl Malonate.*—7-Hydroxypteridine (0.12 g.), diethyl malonate (1 ml.), and tri-*n*-butylamine (2 ml.) were shaken at 20° for 8 days. Water (5 ml.) was added, and the pH adjusted to 2.0 by the careful addition of conc. hydrochloric acid. The resulting white solid was filtered off, recrystallised from ethanol, and dried at 20°/10 mm. giving 6-dicarbethoxymethyl-5,6-dihydro-7-hydroxypteridine (62%), m. p. 168–170° (Found: C, 50.7; H, 5.2; N, 18.1.  $C_{13}H_{16}N_4O_5$  requires C, 50.6; H, 5.2; N, 18.2%).

*Condensation of C-Methylated 7-Hydroxypteridines with Dimedone.*—7-Hydroxy-2-methylpteridine <sup>4a</sup> (0.08 g.) and dimedone (0.10 g.) were stirred with water (30 ml.) at 25° for 5 hr. The mixture was set aside overnight and the 6-(4,4-dimethyl-2,6-dioxocyclohexyl)-5,6-dihydro-7-hydroxy-2-methylpteridine, filtered off and dried at 105° (79%), had m. p. 221–223° (decomp.) (Found: C, 59.45; H, 6.05; N, 18.45.  $C_{16}H_{18}N_4O_2$  requires C, 59.3; H, 5.9; N, 18.5%).

7-Hydroxy-4-methylpteridine <sup>4a</sup> (0.05 g.), dimedone (0.07 g.), and water (30 ml.) similarly treated gave 6-(4,4-dimethyl-2,6-dioxocyclohexyl)-5,6-dihydro-7-hydroxy-4-methylpteridine (dried at 105°; 67%). It decomposes gradually above 215° (Found: C, 59.3; H, 6.01; N, 18.4%).

7-Hydroxy-6-methylpteridine <sup>4a</sup> (0.07 g.) and dimedone (0.175 g.) were stirred in water (30 ml.) at 25° for 72 hr.; that no appreciable adduct formation occurred was shown by the unchanged u.v. absorption spectrum (in 0.1*N*-hydrochloric acid) of the reaction mixture.

We thank Dr. D. J. Brown for kindly supplying several pyrimidine intermediates, and Mr. J. M. Culnane for able technical assistance. This investigation was supported (in part) by a United States Public Health Service Research Fellowship (5-F2-CA-22, 175-02) awarded to J. J. McC. by the National Cancer Institute.

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[Received, June 14th, 1965.]