39013-84-8; **32**, 39008-25-8; **34**, 39062-23-2; **35**, 39008-26-9; **36**, 39008-27-0; 4,5-diamino-1-methyl-2methylthio-6-oxopyrimidine, 39008-28-1; carbon disulfide, 75-15-0; 9-methyl-2,8-dithiouric acid, 39008-29-2; 9-methyl-8-thiouric acid, 39008-30-5; 3-methyl6,8-dimethylthiopurine, 39008-31-6; 7-methyl-2,6,8-trimethylthiopurine, 39008-32-7.

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## Pteridines. I. β-Keto Sulfoxides and α-Keto Aldehyde Hemithioacetals as Pteridine Precursors. A New Selective Synthesis of 6- and 7-Substituted Pteridines<sup>1</sup>

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Alkyl and aralkyl  $\beta$ -keto sulfoxides are converted into 2-amino-4-hydroxypteridines on treatment with 2,4,5-triamino-6-hydroxypyrimidine sulfate and sodium acetate in glacial acetic acid at room temperature for 0.5–1.0 hr followed by refluxing for 1 hr. The only pteridines isolated under these specific conditions are the 6 isomers, with no 7 isomers detected by uv or nmr analysis. In order to account for the positional selectivity of the reaction, a mechanism is proposed wherein  $\beta$ -keto sulfoxides are viewed as "latent"  $\alpha$ -keto aldehydes. A region specific synthesis of the isomeric 7-substituted pteridines is also described, involving the use of  $\alpha$ -keto aldehyde hemithioacetals. Nmr spectra of the 6- and 7-substituted pteridines in FSO<sub>3</sub>H and in 1:4 FSO<sub>3</sub>H-CF<sub>4</sub>CO<sub>2</sub>H solution are reported.

The problem of devising a direct and unequivocal route to 6-substituted pteridines has long challenged the imagination of synthetic organic chemists.<sup>2</sup> In the classical approach, condensation of  $\alpha$ -keto aldehydes with 4,5-diaminopyrimidines leads to varying mixtures of 6- and 7-substituted products, even in the presence of "aldehyde-protecting" reagents such as sodium bisulfite,<sup>3,4</sup> hydrazine,<sup>5,6</sup> or 2-mercaptoethanol.<sup>7</sup> Similarly,  $\alpha$ -keto aldehyde derivatives with the aldehyde function blocked in the form of an acetal<sup>8</sup> or hydrazone<sup>8</sup> afford mixtures because acid-catalyzed partial dissociation to the free aldehyde cannot be completely prevented.<sup>6</sup> Although several alternatives have been developed in order to circumvent these difficulties, they all involve lengthy and sometimes inefficient reaction schemes. Familiar examples include several variants<sup>9,10</sup>

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of the homofolic and bishomofolic acid synthesis,<sup>11</sup> and also the ingenious pyrazine route devised recently by Taylor and coworkers.<sup>12</sup> This report describes a new pteridine synthesis which is notable for its simplicity and appears to proceed with remarkable positional selectivity. The key element in our approach was the novel use of  $\beta$ -keto sulfoxides,<sup>13</sup> a readily accessible class of compounds whose acid-catalyzed transformations<sup>14,15</sup> allow them to be viewed as "latent"  $\alpha$ -keto aldehydes.<sup>16,17</sup>

A representative group of  $\beta$ -keto sulfoxides (1a-f), obtained from the appropriate esters *via* the dimethyl sulfoxide-sodium hydride procedure,<sup>18,15</sup> was allowed to react with 2,4,5-triamino-6-hydroxypyrimidine. In every instance the pteridine products were identified as 6-substituted derivatives (2a-f), with no evidence for the formation of 7 isomers.

In accord with considerations of a possible mechanism (see Chart I), the reaction was conducted in two stages. After equimolar amounts of each  $\beta$ -keto sulfoxide and of the pyrimidine (in the form of its sulfate salt) were suspended in glacial acetic acid containing 2 molar equiv of sodium acetate, the heterogeneous mixture was

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(16) In the context of this work, use of the term "latent" is intended to denote the fact that in  $\beta$ -keto sulfoxides, as opposed to acetals, hydrazones, or other true aldehyde derivatives, the carbon destined to become an aldehyde is not yet in the aldehyde oxidation state at the start of the reaction.

(17) Following the completion of this work an interesting example illustrating the use of a  $\beta$ -keto sulfoxide as a "latent"  $\alpha$ -keto aldehyde appeared; see M. von Strandtman, D. Connor, and J. Shavel, Jr., J. Heterocycl. Chem., **9**, 175 (1972).



stirred at room temperature for 0.5-1.0 hr in order to form the putative Schiff base intermediate (stage 1) shown in Chart I, and then under reflux for 1 hr to effect a Pummerer-like rearrangement and concomitant ring closure (stage 2). Pteridine formation was signaled by copious evolution of methyl mercaptan as soon as heating was begun. Purification of the resultant 6-substituted pteridines (2a-f) was achieved very effectively in most instances by a single crystallization from 80%formic acid.

In order to assess the synthetic validity of the keto sulfoxide approach, we also carried out parallel experiments with other potential pteridine precursors, including the parent  $\alpha$ -keto aldehyde itself. The *n*hexyl series was selected for this purpose. Keto sulfoxide 1a was converted into 1,1-dimethoxy-2-octanone (3, 91% yield) by reaction with methanol and iodine<sup>15</sup> and into 1-methylthio-1-octanol-2-one (4a, 79% yield) on treatment with HCl in DMSO.14b Heating 4a under reduced pressure, in an attempted distillation, unexpectedly led to the formation of 1,2-octanedione (5, 39% yield). This provided a straightforward alternative to the reported copper acetate technique.<sup>14b</sup> The identity and purity of each compound was established rigorously by nmr. Dimethyl acetal 3 displayed sharp singlets at  $\delta$  4.43 for the methinyl proton and at  $\delta$  3.42 for the methoxy proton, whereas methyl hemithioacetal 4a showed singlets at  $\delta$  5.30 and 3.62 for the methinyl and methylthic protons, respectively. Keto aldehyde 5, on the other hand, exhibited a typical sharp singlet at  $\delta$  9.21 which was totally absent in 3 and 4a. The latter were thus entirely free of keto aldehyde.



When dimethyl acetal **3** was allowed to react with 2,4,5-triamino-6-hydroxypyrimidine under the same conditions as had been used with 1a the product was found on the basis of uv and nmr analysis (see Experimental Section) to contain both pteridine 2a and its 7 isomer 6a. In the reaction of **3** the proportion of 6a was estimated to be only 10-15% (nonetheless a trouble-some contamination in view of the known difficulty of separation of pteridine isomers), whereas with **5** the two products were formed in approximately equal amounts. When the same reaction was carried out with hemithio-acetal **4a**, however, the sole product (74% yield) proved to be **6a**. We thus had at our disposal, complementing the keto sulfoxide technique, a second route capable of giving 7 isomers exclusively.

As a further illustration of the general utility of the hemithioacetal route to 7-substituted pteridines, keto sulfoxides 1e and 1f were converted into hemithioacetals 4b and 4c (70-80% yield) and these stable crystalline derivatives were in turn allowed to react with 2,4,5triamino-6-hydroxypyrimidine in order to form 6b and 6c, respectively. A reasonable mechanism for this reaction is shown in Chart II. The unidirectional course



of the reaction may be due mostly to the ease of breakage of the C-S bond, methyl mercaptan formation thereby taking precedence over Schiff base formation in the first step.

Because all the pteridines prepared in this work were high-melting compounds, melting point determinations were of little value in establishing identity or purity. Paper chromatography was likewise considered a dubious criterion in view of the very close  $R_{\rm f}$  values reported by other workers for 6 and 7 isomers in various solvent systems.<sup>8,18</sup> Uv and nmr spectra, on the other hand, provided an effective tool for this purpose and were in qualitative accord with the literature. Thus,

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uv spectra of the 6-substituted pteridines 2a-f measured in 0.1 N NaOH solution all had  $E_{255}/E_{365}$  values (extinction coefficient ratios)<sup>5b,6-8</sup> of 3,4-3.6, whereas those of the 7 isomers 6a-c all showed  $E_{255}/E_{365}$  values of 2.4-2.5. Moreover, nmr spectra determined in a 1:4 FSO<sub>3</sub>H-CF<sub>3</sub>CO<sub>2</sub>H mixture or in certain instances in  $FSO_3H$  alone were consistent with the findings of Dieffenbacher and Philipsborn,<sup>19a</sup> who reported a chemical shift difference of 0.6 ppm between 2-amino-4hydroxy-6-methylpteridine and 2-amino-4-hydroxy-7methylpteridine. This increment, which is greater than can be observed with trifluoroacetic acid<sup>19b</sup> or in 0.1 N NaOD solution,<sup>7</sup> has been ascribed to the ability of FSO<sub>3</sub>H to diprotonate the pteridine ring at N-1 and N-8. Because of the proximity of a positive charge in the dication, the C-7 proton in a 6-substituted pteridine gives rise to a resonance signal at a lower magnetic field than the 6 proton in the corresponding 7 isomer. In the present series the 6-alkylpteridines 2a-d gave spectra with sharp singlets at  $\delta$  9.7 in 1:4 FSO<sub>8</sub>H- $CF_{3}CO_{2}H$  and at 9.9 in  $FSO_{3}H$  alone. In contrast, the spectrum of 7-alkylpteridine 6a in 1:4 FSO<sub>3</sub>H-CF<sub>3</sub>CO<sub>2</sub>H solution displayed a sharp singlet at  $\delta$  9.0.<sup>20</sup>

Although nmr spectra could also be used to distinguish 6- and 7-aralkyl derivatives, the presence of phenyl groups susceptible to electrophilic attack was a complicating factor.<sup>21</sup> Thus, a sample of 2f freshly dissolved in 1:4 FSO<sub>3</sub>H-CF<sub>3</sub>CO<sub>2</sub>H showed the C-7 proton and phenyl protons as singlets at  $\delta$  8.6 and 7.3, respectively. However, an almost immediate change began to occur in the spectrum. The C-7 proton signal at  $\delta$ 8.6 decreased rapidly and was replaced by another singlet at  $\delta$  9.6. At the same time the phenyl singlet gave way to an AB quartet at  $\delta$  7.8 consistent with para substitution on the aromatic ring. The spectral transformation was complete after 2 hr at magnet temperature (ca. 40°). A fresh solution of 6c in 1:4 FSO<sub>3</sub>H- $\rm CF_3CO_2H$  also showed singlets at  $\delta$  8.7 (C-6 proton) and 7.3 (phenyl protons) which decreased rapidly in intensity with the emergence of a new singlet at  $\delta$  9.0 and an AB quartet at  $\delta$  7.8 (the change was complete in this instance after only 45 min). It is possible that the  $\delta$ 8.7 singlet in the spectra of 2e and 6c represents a transient monoprotonated species, since a spectrum of 2e in  $CF_3CO_2H$  alone likewise contained a singlet at δ 8.7.

In addition to the foregoing uv and nmr spectral data, more direct chemical evidence was obtained with several compounds. Oxidation of pteridines 2a, 2c, and 2d with alkaline potassium permanganate afforded 2-amino-4hydroxypteridine-6-carboxylic acid, identified by comparison (ir, uv, and paper chromatography) with an authentic specimen derived from 2-amino-4-hydroxy-6methylpteridine.<sup>6</sup> Similar oxidation of **6a** furnished 2amino-4-hydroxypteridine-7-carboxylic acid, shown to

(20) The nmr spectrum of 6a in FSO3H alone underwent progressive changes, the initial C-7 methylene triplet at  $\delta$  3.6 giving way to a new triplet at § 5.5 suggestive of a vinvl proton. The transformation was essentially It appears therefore that, whereas 6-alkyl compounds complete after 3 hr. are stable in FSO<sub>8</sub>H solution, the 7 isomers are not.

(21) It is reasonable to suppose that 1:4 FSO<sub>2</sub>H-CF<sub>5</sub>CO<sub>2</sub>H mixtures ontain significant amounts of the known mixed anhydride CF3C(O)OSO2F [D. D. DesMarteau and G. H. Cady, Inorg. Chem., 5, 169 (1966)], which could serve as a powerful electrophilic reagent [cf. F. Carré, R. Corriu, and G. Dabosi, Bull. Soc. Chim. Fr., 2905 (1967), and M. H. Karger and Y. Mazur, J. Org. Chem., 36, 540 (1971)].

be identical with an authentic specimen prepared by oxidation of 2-amino-4-hydroxy-7-methylpteridine.6 Control experiments with mixtures of 2a and its 7 isomer 6a yielded mixtures of the 6- and 7-carboxylic acids whose ir and uv spectral characteristics were readily distinguishable from those of either pure acid alone.

The yields of pteridines obtained via the  $\beta$ -keto sulfoxide route (9-17%) and the  $\alpha$ -keto aldehyde hemithioacetal route (45-75%) merit some discussion. For reasons of convenience, all the reactions were carried out under uniform conditions, which may not necessarily have been optimal for each compound. With both types of precursors there was considerable formation of nonpteridine by-products which remained in solution during recrystallization from 80% formic acid. In addition, however, there was some decomposition of the  $\beta$ -keto sulfoxides, as judged from the malodorous character of the mother liquors. We conclude that the higher yield of 7 isomers is a consequence of the fact that the hemithioacetals are less prone than the  $\beta$ -keto sulfoxides to undergo side reactions. It might be possible to lessen the impact of these side reactions by altering various parameters such as the duration of stage 1 or the pH. However, it is important to stress that, even with yields not exceeding 20%, the  $\beta$ -keto sulfoxide route nonetheless compares quite favorably with older methods wherein removal of small quantities of 7 isomer by repetitive fractional crystallization is extremely laborious and is known to result frequently in large material losses. A fuller assessment of the synthetic potential of  $\beta$ -keto sulfoxides and  $\alpha$ -keto aldehyde hemithioacetals as pteridine precursors awaits investigation.

## Experimental Section<sup>22</sup>

1-Methylsulfinyl-2-octanone (1a) (Procedure A).—NaH (21 g of 57% mineral oil dispersion, 0.5 mol) was placed in a 500-ml three-necked flask equipped with a mechanical stirrer, pressureequalized dropping funnel, reflux condenser, and T tube leading to a nitrogen cylinder and water aspirator. After repeated treatment with n-hexane to remove the mineral oil, DMSO (250 ml, dried over Linde 3A Molecular Sieves) was added and the stirred mixture was heated to ca. 75° by means of an oil bath, a positive nitrogen atmosphere being maintained. When hydrogen evolution was complete (2-3 hr) the dark gray solution was cooled to room temperature, ethyl n-heptanoate (40 g, 0.25 mol) was added dropwise, and the mixture was stirred for 1 hr and poured into ice-water (450 ml). After Et<sub>2</sub>O extraction to remove unreacted ester the aqueous phase was cooled and acidified to pH 2 with 12 N HCl (50 ml). Extraction with CHCl<sub>3</sub> (700 ml), washing with H<sub>2</sub>O and saturated NaCl, drying, and evaporation under reduced pressure left a solid which crystallized from i-Pr<sub>2</sub>O in the form of colorless prisms (38 g, 81%), mp 63-64°. Anal. Calcd for  $C_9H_{18}O_2S$ : C, 56.80; H, 9.53; S, 16.85.

Found: C, 57.02; H, 9.73; S, 17.05.

1-Methylsulfinyl-2-nonanone (1b).-This compound was prepared in 76% yield via procedure A, starting from ethyl n-octanoate, as colorless prisms, mp 63-64° (i-Pr<sub>2</sub>O-n-hexane).

<sup>(19) (</sup>a) A. Dieffenbacher and W. von Philipsborn, Helv. Chim. Acta, 52, 743 (1969); (b) A. Dieffenbacher, R. Mondelli, and W. von Philipsborn, ibid., 49, 1355 (1966).

<sup>(22)</sup> Ir spectra were taken with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Quantitative uv spectra were measured on Cary Model 11 and 15 spectrophotometers. Nmr spectra were determined on a Varian A-60 instrument with MeaSi as the reference. When FSO3H was used as the solvent a sealed capillary containing Me<sub>4</sub>Si was placed in the nmr sample tube. For paper chromatography by the ascending or descending technique the following solvent systems were used: (1) n-BuOH-morpholine-H<sub>2</sub>O (3:1:2); (2) *i*-PrOH-1 N NH<sub>4</sub>OH (7:3); (3) 5% Na<sub>2</sub>CO<sub>3</sub>: (4) i-PrOH-concentrated NH4OH-H2O (7:2:1); (5) n-BuOH-AcOH-H2O (4:1:5); (6) i-PrOH-concentrated NH4OH-H2O (5:1:2). Melting points were measured in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.) and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Werby Laboratories, Boston, Mass.

Anal. Calcd for  $C_{10}H_{20}O_2S$ : C, 58.72; H, 9.86; S, 15.66. Found: C, 58.57; H, 10.00: S, 15.60.

1-Methylsulfinyl-4-phenyl-2-butanone (1e) .-- This compound was prepared from methyl hydrocinnamate via procedure A: 55% yield; mp 54-56° (i-Pr<sub>2</sub>O-CHCl<sub>3</sub>); nmr (CDCl<sub>3</sub>) δ 3.70 (d, 1.0 Hz, 2, COCH<sub>2</sub>SO), 2.93 (s, 4, CH<sub>2</sub>CH<sub>2</sub>), 2.58 (s, 3, CH<sub>3</sub>SO).

Anal. Calcd for C11H14O2S: C, 62.84; H, 6.71; S, 15.22. Found: C, 62.58; H, 6.77; S, 15.50.

1-Methylsulfinyl-5-phenyl-2-pentanone (1f).-This compound was prepared from methyl 4-phenylbutyrate via procedure A: 85% yield; mp 44-47° (*i*-Pr<sub>2</sub>O-CHCl<sub>3</sub>); nmr (CDCl<sub>3</sub>)  $\delta$  3.70 (s, 2,  $COCH_2SO$ ), 2.4-2.9 (m, 4) and 1.7-2.2 (m, 2) (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.63 (s, 3, CH<sub>3</sub>SO).

Anal. Calcd for C<sub>12</sub>H<sub>16</sub>O<sub>2</sub>S: C, 64.27; H, 7.19; S, 14.26. Found: C, 64.42; H, 7.38; S, 14.49.

1-Methylthio-4-phenyl-1-butanol-2-one (4b) (Procedure B).-A mixture of le (5 g, 0.024 mol), DMSO (9.1 ml), H<sub>2</sub>O (68 ml), and 12 N HCl (9.1 ml) was stirred at room temperature for 24 hr. Extraction with  $Et_2O$  (100 ml), washing with 5% NaHCO<sub>3</sub> and  $\mathrm{H}_{2}\mathrm{O},$  drying, evaporation under reduced pressure, and recrystallization of the residue (3.5 g, 70%) from CHCl<sub>3</sub>-petroleum ether (bp  $30-60^{\circ}$ ) gave colorless prisms: mp  $49-50^{\circ}$ ; nmr (CDCl<sub>3</sub>)  $\delta$  5.18 (d, 1, methine H), 4.08 (s, 1, OH), 2.97 (m, 4, CH<sub>2</sub>CH<sub>2</sub>), 1.82 (s, 3, CH<sub>3</sub>S), in accord with assignments reported for arylglyoxal hemithioacetals.14b

Anal. Calcd for C11H14O2S: C, 62.84; H, 6.71; S, 15.22. Found: C, 62.98; H, 6.76; S, 15.17.

1-Methylthio-5-phenyl-1-pentanol-2-one (4c).—This compound was prepared from  $\beta$ -keto sulfoxide 1f via procedure B: 76% yield; mp 83-84.5° (CHCl<sub>3</sub>-petroleum ether); nmr (CDCl<sub>3</sub>) δ 5.2 (broad s, 1, methine H), 4.1 (broad s, 1, OH), 1.7-3.0 (m, 6, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.92 (s, 3, CH<sub>3</sub>S).

Anal. Calcd for C<sub>12</sub>H<sub>16</sub>O<sub>2</sub>S: C, 64.27; H, 7.19; S, 14.26. Found: C, 64.56; H, 7.29; S, 14.00.

1,2-Octanedione (5).—Starting from  $\beta$ -keto sulfoxide 1a, procedure B gave a 79% yield of 1-methylthio-1-octanol-2-one (4a) as an oil (solidifying on refrigeration) which was subjected directly to vacuum distillation through a short Vigreux column. The  $\alpha$ -keto aldehyde 5 was obtained as a bright yellow volatile fraction: bp 38–42° (0.8 mm); yield 1.1 g (38%); nmr (CDCl<sub>3</sub>)  $\delta$  9.23 (s, 1, CHO), 2.71 (t, 2, CH<sub>2</sub>CO), 0.8–2.0 (m, 11, remaining protons). The hemithioacetal 4a was sufficiently pure to be used directly in subsequent reactions.

Anal. Calcd for C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>: C, 67.63; H, 10.14. Found: C, 67.57; H, 9.92.

2-Amino-6-n-hexyl-4-hydroxypteridine (2a) (Procedure C).-A mixture of  $\beta$ -keto sulfoxide 1a (20 g, 0.1 mol), 2,4,5-triamino-6hydroxypyrimidine sulfate monohydrate (26 g, 0.1 mol), and NaOAc (16 g, 0.2 mol) in glacial AcOH (600 ml) was stirred at room temperature for 0.5 hr and then under reflux for 1 hr. Evolved methyl mercaptan was absorbed by passage through concentrated NaOH. Cooling and filtration gave a yellow solid, which was washed with H<sub>2</sub>O, EtOH, and Et<sub>2</sub>O. A single crystallization of this solid (12 g) from 80% formic acid<sup>28</sup> yielded 3.6 g (15%) of pale yellow powder: mp >360°; nmr (CF<sub>3</sub>CO<sub>2</sub>H)  $\delta$ 9.9 (s, C-7 proton), 8.2 (s, amidinium), 3.6 (t, C-6 methylene); uv (0.1 N NaOH) 253 nm ( $\epsilon$  20,625), 363 (5935),  $E_{265}/E_{365} =$ 3.4;  $R_{\rm f}$  (1) 0.88,  $R_{\rm f}$  (2) 0.77,  $R_{\rm f}$  (3) 0.55.

Anal. Calcd for C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O: C, 58.28; H, 6.92; N, 28.31. Found: 58.53; H, 7.16; N, 28.57.

2-Amino-6-n-heptyl-4-hydroxypteridine (2b).—This compound was obtained from  $\beta$ -keto sulfoxide 1b via procedure C: 17% yield after one crystallization from 80% formic acid; mp >360°; mmr (FSO<sub>6</sub>H) δ 9.9 (s, C-7 proton), 7.7 (s, amidinium), 3.6 (t, C-6 methylene); uv (0.1 N NaOH) 253 nm (ε21,918), 363 (6320),

 $E_{255}/E_{355} = 3.4$ ;  $R_{\rm f}$  (3) 0.54,  $R_{\rm f}$  (4) 0.85,  $R_{\rm f}$  (5) 0.87. Anal. Calcd for  $C_{13}H_{19}N_{\rm b}O$ : C, 59.74; H, 7.32; N, 26.79. Found: C, 59.85; H, 7.22; N, 27.05.

2-Amino-4-hydroxy-6-n-nonylpteridine (2c).-This compound was obtained from  $\beta$ -keto sulfoxide 1c via procedure C: 9% yield after one crystallization from 80% formic acid; mp >360°; nmr (FSO<sub>3</sub>H) δ 9.9 (s, C-7 proton), 7.7 (s, amidinium), 3.6 (t, C-6 methylene); uv  $(0.1 N \text{ NaOH}) 253 \text{ nm} (\epsilon 21,981), 362 (6170),$  $E_{255}/E_{365} = 3.5; R_{\rm f}(5) 0.94, R_{\rm f}(6) 0.91.$ 

Anal. Calcd for C<sub>15</sub>H<sub>23</sub>N<sub>5</sub>O: C, 62.25; H, 8.01; N, 24.20. Found: C, 62.01; H, 8.00; N, 24.03.

2-Amino-6-cyclohexylmethyl-4-hydroxypteridine(2d).-This compound was obtained from  $\beta$ -keto sulfoxide 1d via procedure C. The keto sulfoxide was prepared from ethyl cyclohexylacetate according to procedure A and was used without purification. Crystallization of a small sample of 1d from  $i-\Pr_2O-n$ -hexane yielded colorless prisms which melted on filtration at room temperature. The pteridine, mp >360°, was obtained in 9% overall yield after one crystallization from 80% formic acid: nmr (FSO<sub>3</sub>H)  $\delta$  9.9 (s, C-7 proton), 7.8 (s, amidinium), 3.6 (d, J = 7 Hz, C-6 methylene); uv (0.1 N NaOH) 252 nm (\$\epsilon 24,140\$), 363  $(6794), E_{255}/E_{365} = 3.5; R_{\rm f} (3) 0.52.$ 

Anal. Calcd for C<sub>13</sub>H<sub>17</sub>N<sub>5</sub>O: C, 60.21; H, 6.60; N, 27.00. Found: C, 60.34; H, 6.57; N, 27.06.

2-Amino-4-hydroxy-6-(2-phenylethyl)pteridine (2e).—This compound was obtained from  $\beta$ -keto sulfoxide 1e via procedure C: 17% yield after one crystallization from 80% formic acid; mp >360°; nmr (CF<sub>3</sub>CO<sub>2</sub>H) & 8.5 (s, C-7 proton), 7.1 (s, aromatic protons), 3.2 (m, CH2CH2);24 uv (0.1 N NaOH) 254 nm (e 23,-012), 363 (6376),  $E_{255}/E_{365} = 3.6$ .

Anal. Calcd for C14H13N5O: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.66; H, 4.82; N, 25.95.

2-Amino-4-hydroxy-6-(3-phenylpropyl)pteridine (2f).—This compound was prepared from  $\beta$ -keto sulfoxide 1f via procedure C: 14% yield after one crystallization from 80% formic acid; mp  $>360^{\circ}$ ; nmr (1:4 FSO<sub>3</sub>H-CF<sub>3</sub>CO<sub>2</sub>H, 2 hr equilibration time)  $\delta$ 9.6 (s, C-7 proton), 8.1 (s, amidinium), 7.8 (q,  $J_{AB}/\delta_A - \delta_B =$ 0.35, aromatic protons), 3.5 (m, C-6 methylene);<sup>24</sup> uv (0.1 N NaOH) 254 nm ( $\epsilon$  21,543), 364 (6083),  $E_{255}/E_{385} = 3.5$ .

Anal. Calcd for C<sub>15</sub>H<sub>15</sub>N<sub>5</sub>O: C, 64.04; H, 5.37; N, 24.89. Found: C, 63.90; H, 5.40; N, 24.73.

2-Amino-7-n-hexyl-4-hydroxypteridine (6a).—This compound was prepared from hemithioacetal 4a (used without purification, as in the synthesis of 5) via procedure C: 74% yield after one crystallization from 80% formic acid; mp >360°; nmr (1:4  $FSO_{3}H-CF_{3}CO_{2}H)$   $\delta$  9.0 (s, C-6 proton), 8.1 (s, amidinium), 3.4 (t, C-7 methylene); uv (0.1 N NaOH) 251 nm ( $\epsilon$  19,954), 355  $(8505), E_{255}/\check{E}_{365} = 2.4.$ 

Anal. Calcd for C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O: C, 58.28; H, 6.92; N, 28.31. Found: C, 57.98; H, 6.72; N, 28.04.

2-Amino-4-hydroxy-7-(2-phenylethyl)pteridine (6b).-This compound was prepared from hemithioacetal 4b via procedure C: 59% yield after one crystallization from 80% formic acid; mp  $>360^{\circ}$ ; nmr (1:4 FSO<sub>3</sub>H-CF<sub>3</sub>CO<sub>2</sub>H, 1 hr equilibration time)  $\delta$ 9.0 (s, C-6 proton), 8.2 (s, amidinium), 7.8 (q,  $J_{AB}/\delta_A$  – δв 0.33, aromatic protons), 3.4 (m, CH<sub>2</sub>CH<sub>2</sub>);<sup>24</sup> uv (0.1 N NaOH)  $252 \text{ nm} (\epsilon 20,702), 357 (8648), E_{255}/E_{365} = 2.5.$ 

Anal. Calcd for C14H13N5O: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.99; H, 4.79; N, 26.07.

2-Amino-4-hydroxy-7-(3-phenylpropyl)pteridine (6c).-This compound was prepared from hemithioacetal 4c via procedure C: 43% yield after one crystallization from 80% formic acid; mp >360°; nmr (1:4 FSO<sub>3</sub>H-CF<sub>3</sub>CO<sub>2</sub>H, 45 min equilibration time)  $\delta$  9.0 (s, C-6 proton), 8.2 (s, amidinium), 7.8 (q,  $J_{AB}/\delta_A - \delta_B =$ 0.35, aromatic proton), 3.2 (e, animumini), 7.3 (q, 5AB/0A - bB = 0.35, aromatic protons), 3.4 (m, C-7 methylene);<sup>24</sup> uv (0.1 N NaOH) 252 nm ( $\epsilon$  18,047), 358 (7497),  $E_{255}/E_{365} = 2.5$ . Anal. Calcd for C<sub>15</sub>H<sub>15</sub>N<sub>5</sub>O: C, 64.04; H, 5.37; N, 24.89.

Found: C, 63.80; H, 5.28; N, 24.62.

2-Amino-6-(and 7-)n-hexyl-4-hydroxypteridines (2a and 6a). Via Dimethyl Acetal 3.—A solution of  $\beta$ -keto sulfoxide la (5 Α. g, 0.026 mol) and iodine (4.1 g, 0.016 mol) in absolute MeOH (53 ml) was stirred under reflux for 90 min, cooled, and concen-trated to dryness under reduced pressure. The oily residue was taken up in CHCl<sub>3</sub> (50 ml) and excess iodine was destroyed by shaking with saturated sodium thiosulfate  $(2 \times 50 \text{ ml})$ . Drying and solvent evaporation gave 4.5 g (91%) of the dimethyl acetal  ${f 3}$ as a clear, amber-colored liquid: nmr (CDCl<sub>3</sub>)  $\delta$  4.4 (s, 1, meth-ine H), 3.4 (s, 6, CH<sub>3</sub>O), 2.3–2.7 (m, 4, CH<sub>2</sub>CO), 0.7–2.7 (m, 11, remaining protons). Without further purification, 3 was allowed

<sup>(23)</sup> Control experiments with mixtures of 6 and 7 isomers indicated that crystallization from 80% formic acid could not effect isomer separation and was not selectively destructive to the 7 isomer. Hence, isolation of 6 isomer as the sole product does not seem to be an experimental artifact. Rather, low material recovery during recrystallization apparently results from the fact that much of the crude solid filtered from the original reaction mixture consists of compounds which are soluble in 80% formic acid and are not pteridines.

<sup>(24)</sup> Spectra taken in freshly prepared 1:4  $FSO_3H-CF_3CO_2H$  solutions contained prominent singlets at  $\delta$  8.6 and 7.3 which diminished rapidly on standing. Although it is possible, as one of the referees has suggested, that this is a consequence of covalent solvation, this phenomenon was observed only with the aralkyl derivatives. Nmr spectra of the alkyl-substituted pteridines did not exhibit a time-dependent character.

## 6-SUBSTITUTED trans-2α-DECALYL TOSYLATES

to react with 2,4,5-triamino-6-hydroxypyrimidine sulfate according to procedure C. The product obtained after one crystallization from 80% formic acid (1.7 g, 23%, mp  $>360^\circ$ ) was a mixture of pteridines 2a and 6a: uv (0.1 N NaOĤ)  $E_{255}/E_{865} = 3.3$ ; nmr (1:4 FSO<sub>3</sub>H-CF<sub>3</sub>CO<sub>2</sub>H) § 9.7 and 9.0 (C-7 and C-6 protons, relative peak areas ca. 8:1). The spectral data indicate the 7 isomer 6a to be present to the extent of 10-15%.

Via Keto Aldehyde 5.—Treatment of 1,2-octanedione (5) В. with 2,4,5-triamino-6-hydroxypyrimidine sulfate according to procedure C gave a mixture of 2a and 6a: uv (0.1 N NaOH)  $E_{255}/E_{365} = 3.1$ ; mrr (1:4 FSO<sub>3</sub>H-CF<sub>3</sub>CO<sub>2</sub>H)  $\delta$  9.7 and 9.0 (C-7 and C-6 protons, relative peak areas *ca*. 3:2).

Oxidation Experiments .- Pteridines 2a, 2c, 2d, and 6a were oxidized with  $KMnO_4$  according to the following typical procedure. A solution of the pteridine (0.1 g) in 0.1 N NaOH (20 ml)was heated to 70° on the steam bath and treated dropwise with 5% KMnO<sub>4</sub> (10 ml) over a 5-hr period. The mixture was kept at 70° overnight and excess oxidant was destroyed by adding a few drops of 50% NaHSO3. Filtration through Celite and acidification of the yellow filtrate to pH 2 with 2 N HCl afforded a fine yellow solid which was collected by centrifugation, washed with  $H_2O$ , and dried: yield 0.04 g. On the basis of uv spectral comparison with authentic samples,6 the product obtained from pteridines 2a, 2c, and 2d was identified as 2-amino-4-hydroxypteridine-6-carboxylic acid, uv (0.1 N NaOH) 262, 364 nm. The product derived from pteridine 6a, on the other hand, was identified as 2-amino-4-hydroxypteridine-7-carboxylic acid, uv (0.1 N NaOH) 266, 372 nm. Ir spectra (KCl) of the two acids were clearly distinguishable and were in accord with published curves.28

Registry No.—1a, 39276-30-6; 1b, 39267-31-7; 1c, 13133-44-3; 1d, 39267-33-9; 1e, 30780-46-2; 1f, 39267-35-1; 2a, 39267-36-2; 2b, 39267-37-3; 2c, 39267-38-4; 2d, 39267-39-5; 2e, 4215-03-6; 2f, 31419-67-7; 3, 6956-55-4; 4a, 39267-67-9; 4b, 39267-68-0; 4c, 39267-69-1; 5, 2363-86-2; 6a, 39267-71-5; 6b, 39267-72-6; 6c, 39267-73-7; ethyl n-heptanoate, 106-30-9; ethyl n-octanoate, 106-32-1; methyl hydrocinnamate, 103-25-3; methyl 4-phenylbutyrate, 2046-17-5; 2,4,5-triamino-6-hydroxypyrimidine sulfate, 39267-74-8.

(25) C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Inc., 1970, p 1034, spectra A and B.

## Solvolyses of 6-Substituted trans- $2\alpha$ -Decalyl Tosylates. **Remote Inductive Effects and Their Solvent Effects**<sup>1</sup>

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A series of 6-substituted  $trans-2\alpha$ -decalyl tosylates was solvolyzed in trifluoroacetic acid, acetic acid, and ethanol. The relative rates of trifluoroacetolysis of the parent H, 6(eq)-CH<sub>3</sub>O, 6(ax)-CH<sub>3</sub>O, 6(eq)-C<sub>6</sub>H<sub>5</sub>, 6(ax)-C<sub>6</sub>H<sub>5</sub>, and. The relative rates of trimuoroacetolysis of the parent H,  $0(eq)-Ch_{3}O$ ,  $0(ax)-Ch_{3}O$ ,  $0(eq)-C_{6}H_{5}$ ,  $0(ax)-C_{6}H_{5}$ , 0(ax)-C $10^{-1}$ ,  $3.95 \times 10^{-1}$ ,  $7.80 \times 10^{-1}$ , and  $6.28 \times 10^{-1}$ , respectively. The acetolyses gave mainly a mixture of the  $\Delta^1$  and  $\Delta^2$  olefins and the inverted  $2\beta$ -acetates with the minor retained  $2\alpha$ -acetate. Satisfactorily linear correlations were obtained by treatment of the rate data with the Hammett-Taft equation. The  $\rho^*$  values obtained for all the tosylates vary with solvent: -4.47 in trifluoroacetolysis, -2.05 in acetolysis, and -0.867 in ethanolysis. These results are explained in terms of remote inductive effects operating between the  $C_6$  substituents noises. These results are explained in terms of remote inductive energy operating between the  $C_8$  substituents and the  $C_2$  reaction center. Plotting values for only the 6(eq) compounds and the 6(ax) compounds, respec-tively, yields significantly different  $\rho^*$  values: in acetolysis, -1.98 for eq and -2.63 for ax; in ethanolysis, -0.735 for eq and -1.30 for ax. The difference is explained in terms of a dipole-dipole interaction acting through the field between the  $C_6$  substituents and the reaction site.

Investigation of remote substituent effects provides much useful information on the structural influence on chemical reactivity, and steroidal compounds have provided some suitable model systems for such investigation.<sup>2-7</sup> The significant factors governing the effects have been suggested by several groups and may be classified as (1) inductive effects, (2) electrostatic field effects, and (3) conformational transmission.<sup>2,5,7</sup> In a previous paper,<sup>4</sup> we demonstrated that the rate of acetolysis of A-ring substituted A/B-trans- and -cis- $11\alpha$ -p-toluenesulfonyloxy sapogenin derivatives decreases as the A-ring substituent becomes increasingly

electronegative, and that the main cause of the rate variation is the transmission of inductive effects of the A-ring substituents through the carbon-carbon chains composing the sapogenin molecules. However, the concept of long-range inductive effects is a matter of considerable argument to the organic chemist, who traditionally expects to find significant inductive effects operating over short ranges only.<sup>8</sup> Our pre-



vious results have been accepted as important in connection with this argument.<sup>2,5-7</sup> We have therefore undertaken a study of the solvolysis of C<sub>6</sub>-substituted

<sup>(1)</sup> Presented in part at the 23rd Symposium on Organic Reaction Mechanisms, Kobe, Japan, Oct 3, 1972.

<sup>(2)</sup> D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," (2) D. N. KIRK and M. F. Hartshorn, "Steroid Reaction Mechanisms, Elsevier, Amsterdam, 1968, pp 16-20 and 234-235.
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<sup>(7)</sup> D. N. Jones and R. Grayshan, J. Chem. Soc. C, 2421 (1970).

<sup>(8)</sup> For example, E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 200-209.