(**4b**) (9.31 g, 0.05 mol) and zinc dust (15 g) were added in portions over 10–12 min to a magnetically stirred solution of 2-acetylcyclopentanone (**19c**) (6.28 g, 0.05 mol) in glacial acetic acid (50 mL) such that the solution reached reflux spontaneously. Water (10 mL) was added when zinc acetate began to separate. Stirring was maintained for 15 min; then the reaction mixture was diluted with H_2O (400 mL) and extracted with CH_2Cl_2. The product was extracted into aqueous Na_2CO_3 and back into CH_2Cl_2 after acidification with 6 N HCl. Upon evaporation of solvent, an oil was obtained that gradually crystallized solid upon standing in a warm location for several weeks. Yield: 6.72 g (48.2%). A sample was recrystallized from aqueous acetic acid for analysis, mp 98–99 °C. Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.41; H, 8.70; N, 10.03. ^{1}H NMR ($CDCl_3$): δ 1.17 (6 H, t, J = 7 Hz, NEt), 1.69–1.91 (2 H, m, chain: 2′), 2.02 (3 H, s, 3-Me), 2.15 (3 H, s, 5-Me), 2.22–2.49 (4 H, m, chain: 1′,3′), 3.54 (4 H, q, J = 7 Hz, NEt), 9.85 (2 H, br s, NH, CO_2H). ^{13}C NMR ($CDCl_3$ at 77.31): δ 177.91 (COOH), 166.42 (CON), 128.01 (5), 120.16 (2), 119.56 (3), 118.80 (4), 41.39 (2C: NCH_2CH_3), 33.70 (3′), 25.84 (2′), 23.62 (1′), 13.49 (2C: NCH_2CH_3), 11.05 (2C: 3,5-CH_3).

***N*,*N*,5-Triethyl-4-(3-carboxypropyl)-3-methyl-2-pyrrolecarboxamide (22d)** was prepared similarly to **22c**, starting with 2-propionylcyclopentanone (**19d**) (6.94 g, 49.6 mmol), as an oil, 2.27 g (15.6%). Characterized only by NMR. ^{1}H NMR ($CDCl_3$): δ 1.17 (9 H, t, J = 7 Hz, 2 NEt, 5-Et), 1.67–1.94 (2 H, m, chain: 2′), 2.02 (3 H, s, 3-Me), 2.27–2.67 (6 H, m) [includes 2.34 (4 H, t, J = 7 Hz, chain: 1′,3′) and 2.54 (2 H, q, J = 7 Hz, 5-Et)], 3.54 (4 H, q, J = 7 Hz, NEt), 9.77 (1 H, s, NH), 10.19 (1 H, br s, CO_2H). ^{13}C NMR ($CDCl_3$ at 77.25): δ 177.91 (COOH), 166.42 (CON), 133.92 (5), 120.32 (2), 119.45 (3), 118.15 (4), 41.39 (2C: NCH_2CH_3), 33.80 (3′), 26.17 (2′), 23.62 (1′), 19.12 (5-CH_3CH_2), 14.03 (5-CH_3CH_2), 13.54 (2C: NCH_2CH_3), 10.94 (3-CH_3).

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Pteridines. 51. A New and Unequivocal Route to C-6 Carbon-Substituted Pterins and Pteridines[1]

Edward C. Taylor* and Partha S. Ray

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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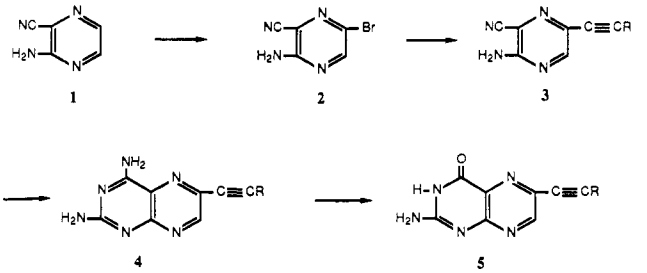
Coupling of terminal acetylenes with 2-amino-3-cyano-5-bromopyrazine in the presence of catalytic amounts of palladium(II) salts and Cu(I) gave a series of 5-ethynyl derivatives which were cyclized with guanidine to 2,4-diamino-6-ethynyl-substituted pteridines. Alkaline hydrolysis yielded 6-ethynyl-substituted pterins, which were prepared independently by analogous palladium-catalyzed coupling of the same terminal acetylenes with 2-pivaloyl-6-chloropterin, followed by alkaline removal of the 2-pivaloyl grouping.

A vast majority of biologically significant naturally occurring pterins and chemotherapeutically useful pteridine derivatives carry carbon substituents at position 6 (e.g., biopterin, folic acid, methotrexate). A major challenge in pteridine synthesis has been the unequivocal preparation of 6-substituted derivatives unaccompanied by 7-substituted isomers.[2] Several years ago we described a versatile solution to this problem which involved the preparation of 2-amino-3-cyano[and (ethoxycarbonyl)]-5-substituted pyrazines via their 1-oxides which were accessible by an unambiguous route by condensation of α-keto aldoximes with aminomalonitrile tosylate. Subsequent manipulation of these pyrazine intermediates and final annulation of the pyrimidine ring then led to 6-substituted pteridines and pterins.[3] Since its introduction, this procedure has been extensively used for the construction of a wide variety of C-6-substituted derivatives.[4] A potential drawback of this methodology, however, is the relative inaccessibility of complex α-keto aldoximes (the origin of the eventual C-6 substituents). We describe in this paper an alternative synthetic strategy which should permit the preparation of a wide diversity of pteridines carrying multifunctional carbon side chains at position 6.

Scheme I



	Yields, %		
	3	4	5
a, R = C_6H_5	75	88	87
b, R = $(CH_2)_3CH_3$	60	85	86
c, R = $C(CH_3)_3$	65	90	90
d, R = CH_2OCH_3	54	82	88

We have previously described the synthesis of 2-amino-3-cyano-5-(bromomethyl)[and (chloromethyl)]-pyrazine by condensation of aminomalonitrile tosylate with β-bromo(and β-chloro)pyruvaldoxime, followed by PCl_3 deoxygenation of the resulting 2-amino-3-cyano-5-(halomethyl)pyrazine 1-oxides.[5] Subsequent displacement of

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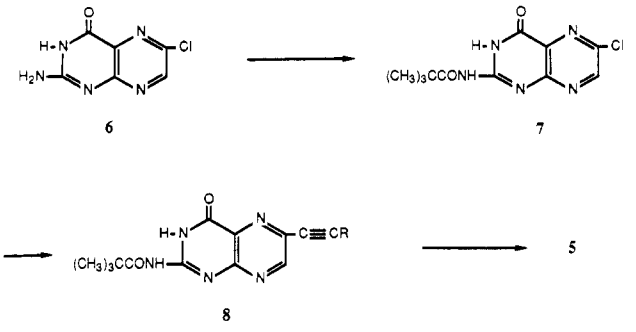
the halide by nitrogen, oxygen, sulfur, and carbon nucleophiles followed by pyrimidine ring annulation leads to 6-substituted 2,4-diaminopteridines.[6] The construction of 6-alkenylpteridines, precursors to polyhydroxy derivatives such as biopterin and neopterin, was accomplished by a Wittig route utilizing the triphenylphosphonium salt derived by displacement with triphenylphosphine.[5,7]

At the time the above work was carried out we also described a straightforward synthesis of 2-amino-3-cyanopyrazine by condensation of aminomalonitrile tosylate with the monooxime of glyoxal followed by PCl_3 deoxygenation of the resulting 1-oxide.[3b] This compound undergoes smooth bromination at position 5 with bromine in acetic acid at 60 °C.[8] We have now found that the resulting 2-amino-3-cyano-5-bromopyrazine readily undergoes carbon–carbon bond formation with acetylenes in the presence of palladium catalysts (the Heck reaction[9,10]). The best conditions in our hands proved to be addition of the appropriate acetylene to a mixture of 2-amino-3-cyano-5-bromopyrazine, acetonitrile, triethylamine, and a catalytic amount of the palladium dichloride/triphenylphosphine complex prepared in situ and in the presence of cuprous iodide.[11] All of the coupling reactions summarized in Scheme I were complete at room temperature within 18 h and gave good yields of the 5-alkynylpyrazines **3a–d**. These pyrazine intermediates cyclized readily with guanidine in methanol/sodium methoxide under reflux to yield the corresponding 2,4-diamino-6-alkynylpteridines **4a–d**, which were obtained analytically pure directly from the reaction mixtures. It is worthy of note that the typical acetylenic IR absorption bands (KBr) for **4a–c** were very weak and were not present at all in the spectrum of **4d**. Alkaline hydrolysis of these 2,4-diamino-6-alkynylpteridines by heating under reflux in 1 N sodium hydroxide/50% ethanol gave the 6-alkynylpterins **5a–d** in excellent yield. The IR spectra of the 6-alkynylpterins **5a–c** showed medium to strong intensity acetylenic absorption bands; the acetylenic absorption band for **5d** was, however, very weak.

Very few methods are available for the direct attachment of C-6 carbon substituents to an intact pterin or pteridine ring. Reaction of 7,8-dihydropterin with α-ketobutyric acid and thiamine gives deoxysepiapterin[12] and with α-keto-β-hydroxybutyric acid in the presence of zinc chloride gives sepiapterin;[13] both reactions, however, proceed in extremely poor yield. Addition of methyllithium to trimethylsilylated 6-methyl-7,8-dihydropterin gives the 6,6-dimethyl derivative,[14] but this hardly represents a general procedure for C-6 functionalization. Homolytic nucleophilic acylation of pteridines at position 6 has recently been reported.[15] However, since 6,7-unsubstituted derivatives undergo acylation at the more electron deficient 7-position, it was necessary to block the 7-position with an alkylthio substituent in order to direct acylation to position 6. This strategy thus necessitates a subsequent reductive desulfurization of the 7-alkylthio blocking substituent. Homolytic 1-hydroxyalkylation at position 6 (of pteridines blocked at position 7) represents a further extension of this free radical methodology.[16]

Scheme II



	Yield, % 8	5
a, R = C_6H_5	55	92
b, R = $(CH_2)_3CH_3$	71	86
c, R = $C(CH_3)_3$	70	85
d, R = CH_2OCH_3	56	88

6-Chloropterin (**6**) is readily accessible from pterin 8-oxide by reaction with acetyl chloride in trifluoroacetic acid,[17] but this compound itself is much too insoluble in organic solvents to function as a substrate for Heck coupling. We have found, however, that pivaloylation of this compound by heating with pivalic anhydride in the presence of a catalytic amount of 4-(dimethylamino)pyridine yields its 2-pivaloyl derivative (**7**), which is readily soluble in a variety of organic solvents (dichloromethane, chloroform, ethyl acetate, acetonitrile, hot ethanol, and even hot benzene).[18] 2-Pivaloyl-6-chloropterin (**7**) readily undergoes Heck coupling with acetylenes to give the 2-pivaloyl-6-alkynylpterins **8a–d** (Scheme II). These Heck reactions were conducted in refluxing acetonitrile in the presence of a catalytic amount of the palladium acetate/tri-*o*-tolylphosphine complex (prepared in situ), triethylamine, and 1 equiv (relative to the palladium catalyst) of cuprous iodide. Reactions were generally complete after 8 h and (a consequence of the presence of the 2-pivaloyl substituent) were easily purified by silica gel chromatography. Recrystallization then gave analytically pure products. The acetylenic IR absorption bands (KBr) for **8a–c** were of medium intensity and not present in the spectrum of **8d**. The 2-pivaloyl group was readily removed by hydrolysis with 1.5 N sodium hydroxide/95% ethanol at reflux. Removal of the 2-pivaloyl group can also be ac-

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(18) Previous attempts to solubilize pterins have largely focused on acetylation. Although the resulting 2-acetyl derivatives are somewhat more soluble than the pterins themselves in solvents such as hot DMF, NMP, and Me_2SO, standard silica gel chromatography is usually unsuitable for such poorly soluble compounds; their purification by other techniques is a frustrating and often tedious process.

complished by stirring the above hydrolysis mixture at room temperature for several days.

We have thus described two alternate pathways, both employing palladium-catalyzed carbon–carbon coupling, for the preparation of 6-alkynylpterins and 2,4-diamino-6-alkynylpteridines. Subsequent papers will describe the utilization of these novel intermediates for the construction of a variety of 6-substituted derivatives such as 10-deazaaminopterin, 10-deazafolic acid, pterin-6-carboxaldehyde, a variety of 6-alkyl-5,6,7,8-tetrahydropterins related to BH_4, and Form A of the molybdenum cofactor.

Experimental Section

2-Amino-3-cyano-5-bromopyrazine (2). A mixture of bromine (5.2 mL, 0.1 mol) in glacial acetic acid (20 mL) was added dropwise, over a period of 2 h, to a stirred suspension of 2-amino-3-cyanopyrazine (12.0 g, 0.1 mol) in glacial acetic acid (60 mL) preheated to 60 °C. The mixture was heated at 60 °C for a further 4 h, allowed to cool to room temperature, and added to crushed ice. The suspended solid was collected by filtration, washed well with water followed by a small volume of cold ethanol, and dried in vacuo at 80 °C. The crude solid was recrystallized from benzene to give orange plates, mp 179–180 °C. A second recrystallization from carbon tetrachloride gave 16.9 g (85%) of fine yellow plates: mp 182–183 °C (lit.[8] mp 181–183 °C); NMR ($CDCl_3$) δ 5.32 (br, 2 H), 8.32 (s, 1 H); IR (KBr) 3400, 3340, 3190, 2240, 1655 cm^{-1}.

Anal. Calcd for $C_5H_3BrN_4$: C, 30.15; H, 1.51; H, 28.14; Br, 40.20. Found: C, 30.26; H, 1.52; N, 28.10; Br, 40.07.

General Procedure for Palladium-Catalyzed Coupling of 2-Amino-3-cyano-5-bromopyrazine (2) with Acetylenes. A mixture of 2-amino-3-cyano-5-bromopyrazine (200 mg, 1 mmol), palladium chloride (10 mg, 0.055 mmol), copper(I) iodide (11 mg, 0.057 mmol), triphenylphosphine (30 mg, 0.122 mmol), triethylamine (0.7 mL, 5 mmol), and the acetylene (1.1 mmol) in acetonitrile (5 mL) was stirred at room temperature for 18 h and then filtered through a pad of Celite. The solvent was removed by evaporation under reduced pressure, and the residue was triturated with ethyl acetate. The precipitated triethylamine hydrobromide was removed by filtration, the filtrate washed with water, and the organic layer separated, dried (anhydrous $MgSO_4$), and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue chromatographed over silica gel and then recrystallized from the appropriate solvent.

2-Amino-3-cyano-5-(phenylethynyl)pyrazine (3a). The residue (see above) was chromatographed on silica gel by using 1% methanol in chloroform as eluent. The fractions containing the pure product were combined (R_f 0.4 in 5% methanol in dichloromethane), and the solvent was removed under reduced pressure. Recrystallization of the residue from chloroform gave 165 mg (75%) of yellow needles: mp 188–189 °C; NMR ($CDCl_3$) δ 7.4–7.48 (m, 3 H), 7.48–7.66 (m, 2 H), 7.7 (br, 2 H), 8.49 (s, 1 H); IR (KBr) 3400, 3300, 3180, 2240, 1650 cm^{-1}.

Anal. Calcd for $C_{13}H_8N_4$: C, 70.91; H, 3.63; N, 25.45. Found: C, 70.64; H, 3.69; N, 25.36.

2-Amino-3-cyano-5-(*n*-butylethynyl)pyrazine (3b). The residue was chromatographed on silica gel by using 2% acetonitrile in chloroform as eluent. The fractions containing the product were combined (R_f 0.3 in 5% acetonitrile in chloroform) and the solvent removed by evaporation under reduced pressure. Recrystallization of the solid from carbon tetrachloride gave 120 mg (60%) of yellow microcrystals: mp 141–142 °C; NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7.0 Hz), 1.3–1.6 (m, 4 H), 2.44 (t, 2 H, J = 7 Hz), 7.53 (br, 2 H), 8.29 (s, 1 H); IR (KBr) 3400, 3330, 3190, 2240, 1655 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_4 \cdot 0.1CCl_4$: C, 65.39; H, 6.09; N, 27.73. Found: C, 65.36; H, 5.95; N, 27.72.

2-Amino-3-cyano-5-(*tert*-butylethynyl)pyrazine (3c). The residue was chromatographed on silica gel by using 2% acetonitrile in chloroform as eluent. The fractions containing the pure product were combined (R_f 0.3 in 5% acetonitrile in chloroform), and the solvent was removed by evaporation under reduced pressure. Recrystallization of the residual solid from carbon tetrachloride gave 130 mg (65%) of yellow microcrystals: mp 169–170 °C; NMR ($CDCl_3$) δ 1.26 (s, 9 H), 7.58 (br, 2 H), 8.27 (s, 1 H); IR (KBr) 3400, 3330, 3220, 2230, 1650, 1635 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_4$: C, 66.00; H, 6.00; N, 28.00. Found: C, 65.77; H, 6.10; N, 27.87.

2-Amino-3-cyano-5-[(methoxymethyl)ethynyl]pyrazine (3d). The residue was chromatographed on silica gel by using 1% methanol in chloroform as eluent. The combined fractions containing the pure product were combined (R_f 0.5 in 5% methanol in dichloromethane), and the solvent was removed under reduced pressure. Recrystallization of the residual solid from benzene gave 102 mg (54%) of yellow needles: mp 135–136 °C; NMR ($CDCl_3$) δ 3.47 (s, 3 H), 4.36 (s, 2 H), 5.44 (br, 2 H), 8.34 (s, 1 H); IR (KBr) 3500, 3320, 3180, 2240, 1660 cm^{-1}.

Anal. Calcd for $C_9H_8N_4O$: C, 57.45; H, 4.25; N, 29.79. Found: C, 57.31; H, 4.30; N, 29.72.

General Procedure for the Reaction of 2-Amino-3-cyanopyrazines 3a–d with Guanidine. Sodium (60 mg, 2.6 mmol) was dissolved in dry methanol (10 mL) under nitrogen, guanidine hydrochloride (220 mg, 2.3 mmol) was added with stirring, and after 5 min the cloudy solution was filtered into a round-bottomed flask containing the amino nitrile (1 mmol). The filter funnel was rinsed for 16 h under nitrogen. The aminonitrile soon dissolved to give a bright yellow or orange solution from which the annulated product (pteridine) gradually precipitated. The reaction mixture was cooled to room temperature, cooled at 2 °C for 5 h, and filtered, and the collected solid was washed well with water followed by cold methanol and dried at 80 °C in vacuo.

2,4-Diamino-6-(phenylethynyl)pteridine (4a): 230 mg (88%) of a bright yellow microcrystalline solid; mp >300 °C; NMR (Me_2SO-d_6) δ 6.7–7.2 (br, 2 H), 7.4–7.7 (m, 5 H), 7.7–8.0 (br, 2 H), 8.84 (s, 1 H); IR (KBr) 3500, 3430, 3310, 3140, 2230, 1630 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_6$: C, 64.12; H, 3.82; N, 32.06. Found: C, 63.89; H, 3.90; N, 31.93.

2,4-Diamino-6-(*n*-butylethynyl)pteridine (4b): 205 mg (85%) of a yellow microcrystalline powder; mp 263–265 °C; NMR (Me_2SO-d_6) δ 0.90 (t, 3 H, J = 7.18 Hz), 1.38–1.58 (m, 4 H), 2.48 (t, 2 H, J = 7.0 Hz), 6.8 (br, 2 H), 7.7 (br, 2 H), 8.64 (s, 1 H); IR (KBr) 3480, 3320, 3100, 2230, 1670, 1635 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_6 \cdot 0.2H_2O$: C, 58.62; H, 5.90; N, 34.18. Found: C, 58.72; H, 5.86; N, 34.22.

2,4-Diamino-6-(*tert*-butylethynyl)pteridine (4c): 217 mg (90%) of a bright yellow microcrystalline powder; mp >300 °C; NMR (Me_2SO-d_6) δ 1.30 (s, 9 H), 6.8 (br, 2 H), 7.7 (br, 2 H), 8.61 (s, 1 H): IR (KBr) 3480, 3320, 3130, 2230, 1675, 1630 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_6$: C, 59.50; H, 5.78; N, 34.71. Found: C, 59.39; H, 5.82; N, 34.67.

2,4-Diamino-6-[(methoxymethyl)ethynyl]pteridine (4d): 188 mg (82%) of a yellow microcrystalline powder, mp >300 °C; NMR (Me_2SO-d_6) δ 3.34 (s, 3 H), 4.38 (s, 2 H), 7.0 (br, 2 H), 8.71 (s, 1 H), 11.6 (br, 2 H); IR (KBr) 3420, 3320, 3120, 1665, 1640 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_6O$: C, 52.17; H, 4.35; N, 36.52. Found: C, 51.89; H, 4.35; N, 36.31.

General Procedure for Preparation of the Pterins 5a–d from Hydrolysis of the 2,4-Diaminopteridines 4a–d. The 2,4-diaminopteridine (0.4 mmol) was heated under gentle reflux with a 1:1 mixture of ethanol/1 N NaOH for 8 h. The solution was then cooled to room temperature and acidified with acetic acid. After 18 h at 2 °C, the mixture was filtered, and the collected solid was washed sequentially with water, ethanol, and ether and dried at 80 °C in vacuo.

6-(Phenylethynyl)pterin (5a): 92 mg (87%) of a bright yellow microcrystalline powder; mp >300 °C; NMR (Me_2SO-d_6) δ 7.0 (br, 2 H), 7.45–7.66 (m, 5 H), 8.81 (s, 1 H), 11.50 (br, 1 H); IR (KBr) 3000–3500 (br), 2220, 1700 (br) cm^{-1}.

Anal. Calcd for $C_{14}H_9N_5O \cdot 0.25H_2O$: C, 62.80; H, 3.58; N, 26.16. Found: C, 62.78; H, 3.56; N, 26.12.

6-(*n*-Butylethynyl)pterin (5b): 84 mg (86%) of a yellow microcrystalline powder, mp >300 °C; NMR (Me_2SO-d_6) δ 0.89 (t, 3 H, J = 7.26 Hz), 1.41–1.59 (m, 4 H), 2.48 (t, 2 H, J = 6.87 Hz), 8.61 (s, 1 H), 11.50 (br, 1 H). IR (KBr) 3000–3500 (br), 2230, 1600–1730 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 59.26; H, 5.35; N, 28.81. Found: C, 59.09; H, 5.38; N, 28.69.

6-(*tert*-Butylethynyl)pterin (5c): 85 mg (90%) of a pale yellow microcrystalline powder; mp >300 °C; NMR (Me_2SO-d_6) δ 1.30 (s, 9 H), 7.0 (br, 2 H), 8.58 (s, 1 H), 11.50 (br, 1 H); IR (KBr) 3000–3500 (br), 2230, 1720 (br) cm^{-1}.

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 59.26; H, 5.35; N, 28.81. Found: C, 59.15; H, 5.43; N, 28.71.

6-[(Methoxymethyl)ethynyl]pterin (5d): 82 mg (88%) of a yellow microcrystalline powder; mp >300 °C; NMR (Me_2SO-d_6) δ 3.34 (s, 3 H), 4.38 (s, 2 H), 7.0 (br, 2 H), 8.71 (s, 1 H), 11.6 (br, 1 H); IR (KBr) 3000–3500 (br), 2240 (w), 1700 (br) cm^{-1}.

Anal. Calcd for $C_{10}H_9N_5O_2 \cdot 0.35\ H_2O$: C, 50.57; H, 4.12; N, 29.49. Found: C, 50.56; H, 3.97; N, 29.47.

2-Pivaloyl-6-chloropterin (7). A suspension of 6-chloropterin (6) (10.86 g, 0.055 mol) and 4-(dimethylamino)pyridine (1 g, 8.1 mmol) in pivalic anhydride (50 mL) was heated under reflux for 6 h. The mixture was cooled to room temperature, diluted with ether (300 mL), and then held at 2 °C for 2 h. The precipitated solid was collected by filtration, dissolved in dichloromethane, and passed through a pad of silica gel, by eluting with 2% methanol in dichloromethane. Evaporation of the filtrate under reduced pressure and recrystallization of the residual solid from ethanol gave 11.1 g (72%) of cream-colored microcrystals: mp 272–273 °C; NMR ($CDCl_3$) δ 1.36 (s, 9 H), 8.50 (br, 1 H), 8.80 (s, 1 H), 12.3 (br, 1 H) [the presence of a very small amount of ethanol in the sample was readily apparent from the NMR spectrum and confirmed by microanalysis]; IR (KBr) 3020–3350 (br), 1730, 1610 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}ClN_5O_2 \cdot 0.35C_2H_5OH$: C, 47.18; H, 4.77; N, 23.51; Cl, 11.90. Found: C, 47.44; H, 4.70; N, 23.70; Cl, 11.77.

General Procedure for Palladium-Catalyzed Coupling of 2-Pivaloyl-6-chloropterin with Acetylenes. A mixture of 2-pivaloyl-6-chloropterin (1 g, 3.552 mmol), palladium acetate (100 mg, 0.445 mmol), tri-*o*-tolylphosphine (277 mg, 0.91 mmol), copper(I) iodide (85 mg, 0.445 mmol), triethylamine (5 mL), the appropriate acetylene (4 mmol), and acetonitrile (20 mL) was heated under nitrogen at reflux for 8 h. The solvent was removed by evaporation under reduced pressure, and the residue was chromatographed on silica gel, by eluting with 1% methanol in chloroform. The fractions containing the product were combined, the solvent was removed in vacuo, and the residual solid was recrystallized.

2-Pivaloyl-6-(phenylethynyl)pterin (8a). Recrystallization from absolute ethanol gave 678 mg (55%) of cream-colored microcrystals: mp 284–285 °C; NMR ($CDCl_3$) δ 1.37 (s, 9 H), 7.38–7.45 (m, 3 H), 7.62–7.65 (m, 2 H), 8.41 (br, 1 H), 8.96 (s, 1 H), 12.30 (br, 1 H); IR (KBr) 3020–3360 (br), 2220, 1680, 1620 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}N_5O_2$: C, 65.71; H, 4.90; N, 20.17. Found: C, 65.70; H, 4.95; N, 20.14.

2-Pivaloyl-6-(*n*-butylethynyl)pterin (8b). Recrystallization from absolute ethanol gave 824 mg (71%) of yellow microcrystals: mp 242–243 °C; NMR ($CDCl_3$) δ 0.96 (t, 3 H, J = 7.16 Hz), 1.35 (s, 9 H), 1.42–1.64 (m, 4 H), 2.50 (t, 2 H, J = 7.18 Hz), 8.39 (br, 1 H), 8.80 (s, 1 H), 12.37 (br, 1 H); IR (KBr) 3020–3320 (br), 2240, 1690, 1620 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.38; H, 6.42; N, 21.40. Found: C, 62.26; H, 6.49; N, 21.36.

2-Pivaloyl-6-(*tert*-butylethynyl)pterin (8c). Recrystallization from absolute ethanol gave 813 mg (70%) of a cream-colored microcrystalline solid: mp 327–328 °C; NMR ($CDCl_3$) δ 1.35 (s, 9 H), 1.36 (s, 9 H), 8.38 (br, 1 H), 8.81 (br, 1 H), 12.20 (br, 1 H); IR (KBr) 3020–3340 (br), 2230, 1690, 1615 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.38; H, 6.42; N, 21.40. Found: C, 62.23; H, 6.51; N, 21.31.

2-Pivaloyl-6-[(methoxymethyl)ethynyl]pterin (8d). Recrystallization from absolute ethanol gave 627 mg (56%) of cream-colored microcrystals: mp 225–226 °C; NMR ($CDCl_3$) δ 1.36 (s, 9 H), 3.49 (s, 3 H), 4.39 (s, 2 H), 8.45 (br, 1 H), 8.86 (s, 1 H), 12.45 (br, 1 H); IR (KBr) 3040–3300 (br), 1680, 1620 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}N_5O_3$: C, 57.14; H, 5.39; N, 22.22. Found: C, 56.89; H, 5.47; N, 22.11.

General Procedure for Preparation of the Pterins 5a–d by Hydrolysis of the Corresponding 2-Pivaloylpterins 8a–d. The 2-pivaloylpterin (0.4 mmol) was heated 6–8 h under reflux with 1.5 N NaOH in 95% ethanol. The progress of the hydrolysis was monitored by TLC. The solvent was removed by evaporation under reduced pressure, and the residual solid was dissolved in water (10 mL). Acidification with acetic acid, cooling to 2 °C for 18 h, and filtering gave a solid, which was washed sequentially with water, ethanol, and ether and dried at 80 °C in vacuo.

Compounds **5a–d** obtained by the above procedure were identical in every respect with the compounds prepared as described above by hydrolysis of the appropriate 2,4-diaminopteridines **4a–d**. Observed yields were as follows: **5a**, 97 mg (92%); **5b**, 84 mg (86%); **5c**, 82 mg (85%); **5d**, 81 mg (88%).

Registry No. **1**, 25911-65-3; **2**, 17231-51-5; **3a**, 108472-96-4; **3b**, 108472-97-5; **3c**, 108472-98-6; **3d**, 108472-99-7; **4a**, 108473-00-3; **4b**, 108473-01-4; **4c**, 108473-02-5; **4d**, 108473-03-6; **5a**, 108473-04-7; **5b**, 108473-05-8; **5c**, 108473-06-9; **5d**, 108473-07-0; **6**, 64507-68-2; **7**, 108473-08-1; **8a**, 108473-09-2; **8b**, 108473-10-5; **8c**, 108473-11-6; **8d**, 108473-12-7; PhC≡CH, 536-74-3; $CH_3(CH_2)_3C{\equiv}CH$, 693-02-7; $(CH_3)_3CC{\equiv}CH$, 917-92-0; $CH_3OCH_2C{\equiv}CH$, 627-41-8; guanidine hydrochloride, 50-01-1.

First Synthesis of Sulfoxides and Sulfones in the 3*H*-Phenothiazin-3-one and 5*H*-Benzo[*a*]phenothiazin-5-one Ring Systems. Addition Reactions with Nucleophiles

Yves Girard,* Pierre Hamel,* Michel Thérien, James P. Springer,† and Jordan Hirshfield†

Merck Frosst Canada Inc., Pointe Claire-Dorval, Quebec, Canada H9R 4P8, and Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

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We report the first synthesis of sulfoxides and sulfones in the 3*H*-phenothiazin-3-one and 5*H*-benzo[*a*]-phenothiazin-5-one ring systems. The pronounced reactivity of the parent compounds **2a**, **2b**, **4a**, and **4b** does not allow their isolation, but they can be conveniently trapped, as various types of adducts, with nucleophiles such as water, alcohols, and amines. The monoadduct **16b** of 3-oxo-3*H*-phenothiazine 5,5-dioxide with *n*-propylamine rearranges into a derivative of the novel oxazolo[5,4-*c*]phenothiazine ring system (**17**).

Introduction

The scope of interest in phenothiazine derivatives covers a wide assortment of areas. Complexes such as Methylene Blue are well-known as dyes, bacteriological stains, or redox indicators, while other types of derivatives have been reported as antioxidants,[1] antiseptics,[2] insecticides,[3] anthelmintics,[4] etc.

† Rahway, NJ.

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