washed (water, then methanol) by centrifugation, and dried overnight under high vacuum to give 65 mg (65%) of **1**, identical with an authentic sample.

Registry No.—**1**, 119-44-8; **2**, 529-69-1; **4**, 19994-56-0; **5**, 54632-07-4; **6**, 54632-08-5; **7**, 42770-07-0; **8**, 54632-09-6; **9**, 54632-10-9; **10**, 54632-11-0; **11**, 54632-12-1; **12**, 26212-13-5; **13**, 54632-13-2; **14**, 54632-14-3; **15**, 54632-15-4; **16**, 54632-16-5; **17**, 54632-17-6; **18**, 54632-18-7; **19**, 17231-50-4; **20**, 26212-23-7; **21**, 42346-89-4; **22**, 54632-19-8; **23**, 54632-20-1; **24**, 31010-60-3; **25**, 42346-93-0; **26**, 54632-21-2; **30**, 26212-17-9; 2-trifluoroacetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone, 54632-22-3; 2-acetamido-3-carbamoyl-5-methyl-6(1*H*)-pyrazinone, 54632-23-4.

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Pteridines. XXXVIII. Synthesis of Some 2,4-Diamino-6-Substituted Methylpteridines. A New Route to Pteroic Acid[1,2]

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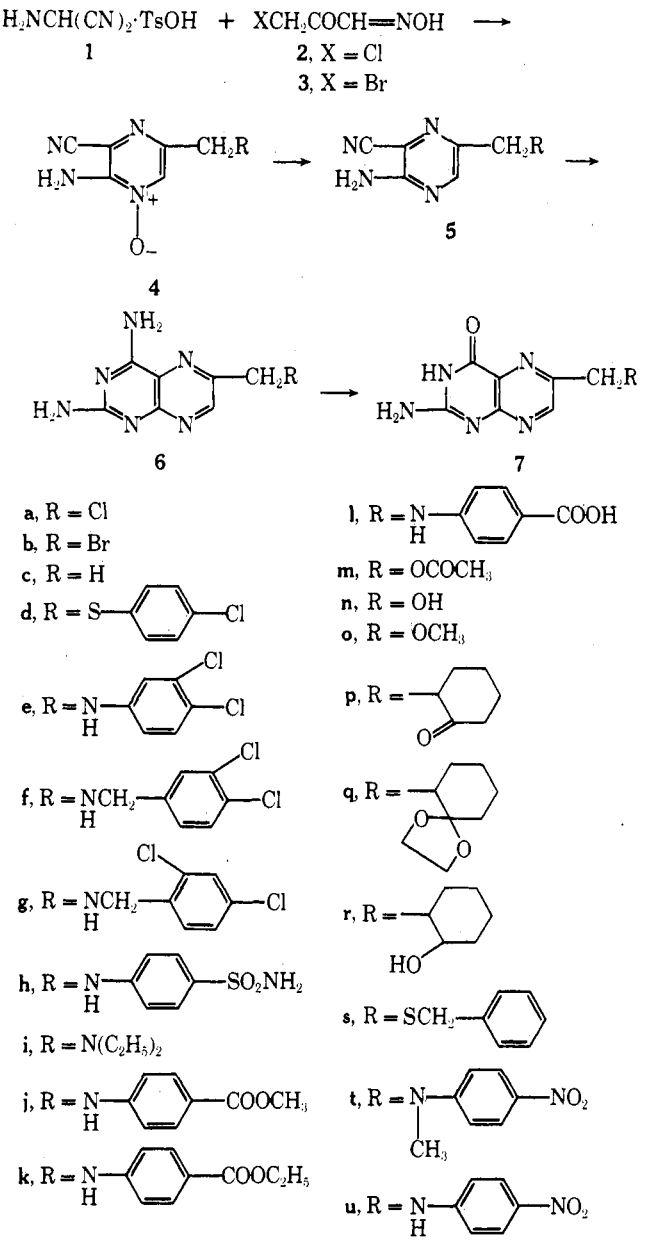
A versatile, flexible route to a variety of 6-substituted 2,4-diaminopteridines (**6**) and 6-substituted pterins (**7**) is described which involves the reaction of 2-amino-3-cyano-5-chloromethylpyrazine (**5**) with nucleophiles, followed by ring closure with guanidine (to give **6**), and final acid hydrolysis (to give **7**). Among the compounds conveniently prepared by this unequivocal route are 2,4-diamino-6-hydroxymethylpteridine, 6-hydroxymethylpterin, and pteroic acid. A three-component, one-pot (TCOP) condensation of aminomalononitrile tosylate, β-bromopyruvaldoxime, and added nucleophile has been developed which leads directly, in moderate yield but high purity, to 2-amino-3-cyano-5-substituted pyrazine 1-oxides (**4**).

Previous papers in this series have described a new, general, and unequivocal synthesis of 6- and/or 7-substituted pteridines from pyrazine 1-oxide intermediates, prepared by the condensation of α-aminonitriles with α-ketoaldoximes or α-oximino aldehydes.[3-5] The synthesis of 2,4-diaminopteridines substituted in position 6 with olefinic substituents suitable for final elaboration into multifunctional side chains characteristic of some of the naturally occurring pterins (i.e., biopterin, neopterin, urothion, etc.) involved (a) the preliminary formation of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**4a**) by the condensation of aminomalononitrile tosylate (**1**) with β-chloropyruvaldoxime (**2**), (b) deoxygenation with phosphorus trichloride to 2-amino-3-cyano-5-chloromethylpyrazine (**5a**), (c) elaboration of the olefinic side chain by means of the Wittig reaction, and (d) terminal closure of the pyrimidine ring by cyclization with guanidine.[5] The present paper describes a number of nucleophilic displacement reactions on the chloromethyl substituent in **5a**, and the elaboration of the resulting substituted methylpyrazines to a variety of new 2,4-diaminopteridines and pterins. This paper also describes new and unequivocal syntheses of pteroic acid and of 6-hydroxymethylpterin, and a convenient three-component, one-pot (TCOP) synthesis of 2-amino-3-cyano-5-substituted methylpyrazine 1-oxides.

Although the primary chloro substituent in **5a** is reactive toward nucleophiles (we have previously described its displacement by methoxide ion and by triphenylphosphine[5]), conditions must be chosen with care because of the ease of nucleophilic addition to the 3-cyano grouping. Displacement by sodium 4-chlorothiophenolate occurred smoothly in methanol solution in high yield, without concomitant addition to the extremely reactive nitrile grouping, to give **5d**. Reaction of **5a** with aromatic amines, however, proved to be more critical, and optimum reaction conditions involved the use of acetonitrile as solvent, although DMSO at higher temperatures could also be employed. Thus, reaction of **5a** with 3,4-dichloroaniline, ethyl 4-aminobenzoate, or sulfanilamide in the presence of potassium carbonate led to the formation in high yield of the pyrazines **5e, 5k,** and **5h,** respectively. Reaction of **5a** with 3,4-dichloro- and 2,4-dichlorobenzylamine, and with diethylamine, all occurred smoothly in 2-propanol solution to give the pyrazines **5f, 5g,** and **5i,** respectively. Cyclization of these pyrazine *o*-aminonitriles to the corresponding 2,4-diaminopteridines (**6**) proceeded in the normal manner with guanidine in methanol in the presence of sodium methoxide.

The conversion of 2,4-diaminopteridines to pterins [2-amino-4(3*H*)-pteridinones] by selective hydrolysis of the 4-amino group has been exploited previously.[4,6-8] Thus, alkaline hydrolysis of **6k** gave pteroic acid (**7**), identical in every respect with an authentic sample.[9] This synthesis of pteroic acid is a five-step process utilizing readily available starting materials and involving crystalline intermediates

Scheme I



at all steps prior to the final cyclization to the penultimate 2,4-diaminopteridine, and it is completely unequivocal in that *only* the 6-substituted derivative is obtained. Extensions of this procedure to the preparation of related 6-substituted pteridines such as folic acid, aminopterin, and methotrexate will be described in forthcoming publications.

Condensation of 2-amino-3-cyano-5-chloromethylpyrazine (**5a**) with potassium acetate in 2-propanol resulted in smooth displacement of the primary halogen atom by an acetoxy group to give 2-amino-3-cyano-5-acetoxymethylpyrazine (**5m**). Cyclization of this latter compound with guanidine in the presence of sodium methoxide then gave 2,4-diamino-6-hydroxymethylpteridine (**6n**), which has recently been shown to be a valuable intermediate, via its conversion to 2,4-diamino-6-bromomethylpteridine, for the preparation of aminopterin and homologs.[10] Compound **6n** was previously prepared as a potential inhibitor of folic acid biosynthesis by Baugh and Shaw[8] by the classical Isay-type condensation of 2,4,5,6-tetraaminopyrimidine with dihydroxyacetone, but not only is this procedure intrinsically equivocal, but it leads to the simultaneous formation of 2,4-diamino-6-methylpteridine, which apparently cannot be separated from **6n**.[10] Since acid hydrolysis of **6n** readily gives 6-hydroxymethylpterin (**7n**),[8] this simple sequence of reactions makes this latter naturally occurring pteridine and biogenetic precursor to folic acid readily available in pure form.

The reaction of **5a** with enamines was briefly studied as a potential route to pteridine derivatives, functionalized at C-6 with hydroxyalkyl groups, which are of considerable interest as potential biopterin antagonists. Thus, the condensation of **5a** with 1-pyrrolidino-1-cyclohexene in refluxing THF, followed by in situ acid hydrolysis, led to 2-amino-3-cyano-5-(2-oxocyclohexylmethyl)pyrazine (**5p**), which was reduced with sodium borohydride to the corresponding cyclohexanol derivative **5r**. The ethylene ketal **5q** was prepared from **5p** by ketalization with ethylene glycol and acid. The pyrazine intermediates **5q** and **5r** were converted into the corresponding 2,4-diaminopteridines **6q** and **6r** by condensation with guanidine; acid hydrolysis of the former then gave 2,4-diamino-6-(2-oxocyclohexylmethyl)pteridine (**6p**). One may thus anticipate that the reaction of **5a** with cyclic as well as acyclic enamines should provide ready access to a diversity of related pteridines substituted at position 6 by multifunctional carbon substituents.

In an earlier publication we had described the preparation of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**4a**) by condensation of β-chloropyruvaldoxime with aminomalononitrile in 2-propanol.[5] We had noted at the time that the use of methanol as solvent led to appreciable quantities of the 5-methoxymethylpyrazine 1-oxide **4o**. However, a subsequent observation that the conversion of **4a** to **4o** required 48 hr of reflux in methanol clearly indicated that the formation of **4o** in the above condensation reaction must have involved nucleophilic displacement of chlorine by methanol at some stage prior to ring closure to **4a**. This incidental observation suggests that condensation of a β-halopyruvaldoxime with aminomalononitrile in *the presence of an added nucleophile* should lead directly to 2-amino-3-cyano-5-substituted methylpyrazine 1-oxides (a three-component, one-pot or TCOP condensation). We have briefly explored this concept with some success. For example, a TCOP reaction involving aminomalononitrile tosylate, β-bromopyruvaldoxime (**3**), and benzyl mercaptan in 2-propanol solution led in moderate yield to pure 2-amino-3-cyano-5-(benzylthiomethyl)pyrazine 1-oxide (**4s**), which could be deoxygenated with phosphorus trichloride to **5s**, identical with an authentic sample prepared by the reaction of benzyl mercaptan with **5a**. In similar fashion, the pyrazine 1-oxides **4t** and **4u** were prepared by TCOP reactions. There appears to be a subtle dependence, however, upon a combination of nucleophilicity and basicity in the added nucleophile for success in these TCOP reactions. For example, potassium acetate, 4-chlorothiophenol, 2-nitro-4-chloroaniline, and 3,4-dichloroaniline all failed to give satisfactory TCOP reactions, apparently because they were either insufficiently nucleophilic (**4a** was isolated from each of these reaction mixtures), or too basic (leading to the tosyl salt of the added nucleophile). An attempted TCOP reaction utilizing triphenylphosphine as the added nucleophile led to reductive debromination and the formation of 2-amino-3-cyano-5-methylpyrazine 1-oxide (**4c**). This initially surprising result is, however, consistent with previous observations that α-bromocarbonyl compounds are reductively debrominated with triphenylphosphine in protic solvents.[11,12] Since 2-amino-3-cyano-5-bromomethylpyrazine 1-oxide (**4b**) reacts normally with triphenylphosphine in 2-propanol to give the phosphonium salt **4** [R = $^{+}P(C_6H_5)_3Br^{-}$], it seems reasonable to assume that the

formation of **4c** in the above TCOP reaction involves initial in situ formation of pyruvaldoxime from β-bromopyruvaldoxime (**3**) and triphenylphosphine, but attempts to confirm this by examination of the reaction of these two compounds in the absence of aminomalononitrile tosylate (**1**) were frustrated by extensive decomposition. As expected on the basis of earlier findings,[12] substitution of β-chloropyruvaldoxime (**2**) for **3** in the above TCOP reaction led to the phosphonium salt **4** (R = $^{+}P(C_6H_5)_3Cl^{-}$).

All of the pyrazine 1-oxides prepared by the TCOP procedure were deoxygenated to the respective pyrazines **5s, 5t,** and **5u,** which were then condensed with guanidine in the usual manner to give the 2,4-diaminopteridines **6s, 6t,** and **6u.**

The conversions described above are summarized in Scheme I.

Experimental Section[13]

2-Amino-3-cyano-5-(4-chlorophenylthiomethyl)pyrazine (5d). A mixture of 4.0 g of 2-amino-3-cyano-5-chloromethylpyrazine,[5] 3.5 g of 4-chlorothiophenol, and 1.3 g of sodium methoxide in 120 ml of methanol was stirred overnight at room temperature and then poured into 200 ml of ice water. The precipitated solid was collected by filtration and then heated under reflux with 50 ml of methanol for 30 min. Cooling and filtering then gave 6.1 g (94%) of **5d** as a colorless, microcrystalline solid, mp 161–162°. The analytical sample, mp 162–163°, was prepared by recrystallization from methanol.

Anal. Calcd for $C_{12}H_9N_4SCl$: C, 52.08; H, 3.26; N, 20.25; S, 11.57; Cl, 12.84. Found: C, 51.89; H, 3.20; N, 20.29; S, 11.21; Cl, 13.14.

2-Amino-3-cyano-5-(3,4-dichloroanilinomethyl)pyrazine (5e). A mixture of 1.68 g of 2-amino-3-cyano-5-chloromethylpyrazine, 8.10 g of 3,4-dichloroaniline, and 1.38 g of potassium carbonate in 50 ml of acetonitrile was stirred for 24 hr at room temperature. The precipitated product (contaminated by potassium salts) was collected by vacuum filtration and washed with a little cold acetonitrile. The product was then stirred with 50 ml of ether to remove excess aniline, collected again by filtration, washed with ether, and dried. Recrystallization of the product from ethyl acetate (charcoal) then gave 2.15 g (73%) of **5e** as a bright yellow powder, mp 198–199° dec. The analytical sample, mp 200–201° dec, was prepared by recrystallization from methanol.

Anal. Calcd for $C_{12}H_9N_5Cl_2$: C, 48.98; H, 3.06; N, 23.81; Cl, 24.15. Found: C, 48.78; H, 3.31; N, 24.04; Cl, 23.91.

2-Amino-3-cyano-5-(3,4-dichlorobenzylaminomethyl)pyrazine (5f). To 0.34 g of 2-amino-3-cyano-5-chloromethylpyrazine in 50 ml of 2-propanol was added 1.76 g of 3,4-dichlorobenzylamine. The reaction mixture was stirred for 24 hr at room temperature, after which time the light yellow precipitate which had separated was collected by filtration and dried, yield 0.54 g. To this crude product was added 50 ml of water, the pH was adjusted to 11 with 0.5 *N* NaOH, and the resulting precipitate was again collected by filtration. The yellow powder was added to a column of silica gel, and the column was then eluted with chloroform–ethyl acetate (1:3). The first two materials to be eluted from the column were the unreacted amine and the dialkylated amine (identified by NMR); the fractions containing **5f** then followed. Evaporation of the eluates gave 0.21 g (34%) of **5f.** Recrystallization from ethyl acetate gave a light yellow microcrystalline powder, mp 135–137°.

Anal. Calcd for $C_{13}H_{11}N_5Cl_2$: C, 50.67; H, 3.60; N, 22.73. Found: C, 50.74; H, 3.70; N, 22.50.

2-Amino-3-cyano-5-(2,4-dichlorobenzylaminomethyl)pyrazine (5g). This compound was prepared in 44% yield from 2-amino-3-cyano-5-chloromethylpyrazine and 2,4-dichlorobenzylamine as described above for the preparation of **5f,** mp (from diisopropyl ether) 136–138°.

Anal. Calcd for $C_{13}H_{11}N_5Cl_2$: C, 50.67; H, 3.60; N, 22.73. Found: C, 50.75; H, 3.58; N, 22.88.

2-Amino-3-cyano-5-(sulfanilamidomethyl)pyrazine (5h). A mixture of 0.84 g of 2-amino-3-cyano-5-chloromethylpyrazine, 4.30 g of sulfanilamide, and 0.69 g of potassium carbonate in 40 ml of acetonitrile was stirred for 24 hr at room temperature. Filtration then gave 0.71 g (47%) of an orange-yellow microcrystalline solid which was recrystallized from acetonitrile, mp 190–192°.

Anal. Calcd for $C_{12}H_{12}N_6O_2S$: C, 47.36; H, 3.97; N, 27.62. Found: C, 47.20; N, 3.94; N, 27.88.

2-Amino-3-cyano-5-(*N,N*-diethylaminomethyl)pyrazine (5i). A mixture of 1.68 g of 2-amino-3-cyano-5-chloromethylpyrazine, 1.63 g of diethylamine, and 50 ml of 2-propanol was stirred for 1.5 hr, during which time a mild exothermic reaction took place and then subsided. The reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in water with addition of a few drops of 6 *N* HCl. The resulting acid solution was extracted with two 10-ml portions of ethyl acetate, and the pH was adjusted to 10 by addition of 40% NaOH. This basic solution was then extracted with three 15-ml portions of ethyl acetate, the ethyl acetate (from the latter extraction) was evaporated under reduced pressure, and the residual yellow plates were recrystallized from petroleum ether (bp 60–70°) to give 1.42 g (69%) of pale yellow, shining platelets, mp 90–92°.

Anal. Calcd for $C_{10}H_{15}N_5$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.69; H, 7.17; N, 33.77.

2-Amino-3-cyano-5-(4-carbethoxyanilinomethyl)pyrazine (5k). Under the same conditions as described for the preparation of **5e,** 2-amino-3-cyano-5-chloromethylpyrazine and ethyl 4-aminobenzoate were condensed in DMSO to give **5k** (64% yield) as a pale yellow crystalline solid, mp 184–185° (from ethanol).

Anal. Calcd for $C_{15}H_{15}N_5O_2$: C, 60.59; H, 5.09; N, 23.56. Found: C, 60.88; H, 5.08; N, 23.85.

2-Amino-3-cyano-5-acetoxymethylpyrazine (5m). A mixture of 10.0 g of 2-amino-3-cyano-5-chloromethylpyrazine and 8.9 g of potassium acetate in 400 ml of 2-propanol was stirred at 80–90° for 3 hr and then evaporated to dryness under reduced pressure. Trituration of the residue for 30 min in 100 ml of water followed by filtration gave a light gray solid which was dissolved in hot methanol, treated with Norite, and then evaporated to a small volume. Cooling then gave 8.3 g (73%) of **5m** as a colorless, crystalline solid, mp 140–141°.

Anal. Calcd for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found. C, 49.90; H, 4.14; N, 29.17.

2-Amino-3-cyano-5-(2-oxocyclohexylmethyl)pyrazine (5p). A solution of 5.0 g of 2-amino-3-cyano-5-chloromethylpyrazine and 4.9 g of 1-pyrrolidino-1-cyclohexene in 500 ml of tetrahydrofuran was heated under reflux overnight. Water (5 ml) was then added and refluxing was continued for an additional 1.5 hr. The reaction mixture was then evaporated to dryness under reduced pressure, the residue was dissolved in 800 ml of chloroform, and the resulting solution was washed with 100 ml of water. The chloroform solution was then evaporated to dryness, the residue was triturated with a small amount of cold methanol, and the colorless, microcrystalline solid was collected by filtration to give 5.1 g (74%) of **5p,** mp 171–172°. The analytical sample was prepared by recrystallization from methanol without change in the melting point.

Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.49; H, 6.07; N, 24.50.

2-Amino-3-cyano-5-(2-ethylenedioxycyclohexylmethyl)pyrazine (5q). A mixture of 2.6 g of 2-amino-3-cyano-5-(2-oxocyclohexylmethyl)pyrazine and 0.8 g of ethylene glycol in 70 ml of benzene containing 0.05 g of *p*-toluenesulfonic acid was heated under reflux for 3 hr. Excess solvent was removed by evaporation under reduced pressure, the solid residue was suspended in 50 ml of methanol and stirred at room temperature for 30 min, and the resulting solid was collected by filtration and recrystallized from methanol to give 2.0 g (65%) of fine colorless needles of **5q,** mp 169–170°.

Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.29; H, 6.61; N, 20.43. Found: C, 61.38; H, 6.69; N, 20.56.

2-Amino-3-cyano-5-(2-hydroxycyclohexylmethyl)pyrazine (5r). To a suspension of 2.0 g of 2-amino-3-cyano-5-(2-oxocyclohexylmethyl)pyrazine in 50 ml of cold methanol was added 0.17 g of sodium borohydride, and the resulting suspension was stirred for 10 min at 0° and then for an additional 30 min at room temperature. By this time the reaction mixture had become homogeneous. It was then evaporated under reduced pressure to dryness, and the residue was slurried for 10 min with 10 ml of 0.5 *N* HCl. The precipitated solid was collected by filtration, washed thoroughly with water, and recrystallized from methanol to give 1.4 g (70%) of light yellow crystals of **5r,** mp 151–155°. The NMR spectrum of this product (DMSO-d_6) indicated that a mixture of cis and trans isomers (~2:1) was formed in the reduction. No attempt was made to separate or further characterize this mixture, which was preserved in the subsequent guanidine cyclization to **6r** (vide infra).

Anal. Calcd for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 62.05; H, 6.98; N, 24.20.

2-Amino-3-cyano-5-(benzylthiomethyl)pyrazine 1-Oxide (4s). To a solution of 3.32 g of β-bromopyruvaldoxime and 2.48 g of benzyl mercaptan in 30 ml of 2-propanol was added 5.04 g of ami-

nomalononitrile tosylate, and the mixture was stirred at room temperature for 24 hr. The light yellow precipitate which had separated was collected by filtration (3.02 g, 55%) and recrystallized from ethanol to give a yellow, microcrystalline solid, mp 135–136° dec.

Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.41; H, 4.70; N, 20.76.

2-Amino-3-cyano-5-(*N*-methyl-4-nitroanilinomethyl)pyrazine 1-Oxide (4t). This compound was prepared in 56% yield from β-bromopyruvaldoxime, aminomalononitrile tosylate, and *N*-methyl-*p*-nitroaniline as described above for the preparation of **4s**, mp (from ethanol) 213–214° dec.

Anal. Calcd for $C_{13}H_{12}N_6O_3$: C, 52.00; H, 4.03; N, 27.99. Found: C, 51.84; H, 4.28; N, 28.15.

2-Amino-3-cyano-5-(*p*-nitroanilinomethyl)pyrazine 1-Oxide (4u). This compound was prepared in 29% yield from β-bromopyruvaldoxime, aminomalononitrile tosylate, and *p*-nitroaniline as described above for the preparation of **4s**, except that the initial precipitate proved to be the tosyl salt of **4u**. The free base was obtained as yellow needles, mp 143° dec, by suspending the salt in dilute sodium hydroxide, filtering, and recrystallizing the collected solid from methanol.

Anal. Calcd for $C_{12}H_{10}N_6O_3$: C, 50.35; H, 3.52; N, 29.36. Found: C, 50.36; H, 3.67; N, 29.31.

2-Amino-3-cyano-5-(benzylthiomethyl)pyrazine (5s). To a solution of 0.82 g of 2-amino-3-cyano-5-(benzylthiomethyl)pyrazine 1-oxide in 20 ml of tetrahydrofuran, cooled in an ice bath, was added 0.8 ml of phosphorus trichloride. The ice bath was then removed and the reaction mixture was allowed to warm to room temperature, with stirring, over a period of 45 min and then evaporated to a small volume under reduced pressure. The residual crystals were collected by filtration, washed with 10 ml of cold water, and recrystallized from benzene to give 0.49 g (64%) of light yellow platelets, mp 143–145° dec.

Anal. Calcd for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.88; H, 4.76; N, 21.41.

2-Amino-3-cyano-5-(*N*-methyl-*p*-nitroanilinomethyl]pyrazine (5t). This compound was prepared in 93% yield by deoxygenation of 2-amino-3-cyano-5-(*N*-methyl-*p*-nitroanilinomethyl)pyrazine 1-oxide with phosphorus trichloride as described above for the preparation of **5s**, mp (from methanol) 193–194° dec.

Anal. Calcd for $C_{13}H_{12}N_6O_2$: C, 54.93; H, 4.25; N, 29.56. Found: C, 54.74; H, 4.01; N, 29.73.

2-Amino-3-cyano-5-(*p*-nitroanilinomethyl)pyrazine (5u). This compound was prepared in 95% yield by deoxygenation of 2-amino-3-cyano-5-(*p*-nitroanilinomethyl)pyrazine 1-oxide with phosphorus trichloride as described above for the preparation of **5s**, mp (from acetonitrile) 238–239° dec.

Anal. Calcd for $C_{12}H_{10}N_6O_2$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.53; H, 3.78; N, 31.40.

2-Amino-3-cyano-5-methylpyrazine 1-Oxide (4c). A mixture of 1.66 g of β-bromopyruvaldoxime, 2.62 g of triphenylphosphine, and 2.53 g of aminomalononitrile tosylate in 20 ml of 2-propanol was stirred at room temperature for 5 hr. The yellow precipitate which had separated was collected by filtration (0.87 g, 57%) and recrystallized from ethanol to give pure **4c**, mp 186–187° (lit.[4] mp 187–188°), identical with an authentic sample.

2,4-Diamino-6-(4-chlorophenylthiomethyl)pteridine (6d). To a methanolic solution of guanidine (prepared by adding 2.7 g of guanidine hydrochloride to 200 ml of dry methanol containing 3.5 g of sodium methoxide, and removal of the precipitated sodium chloride by filtration) was added 5.0 g of 2-amino-3-cyano-5-(4-chlorophenylthiomethyl)pyrazine, and the resulting mixture was heated under reflux for 24 hr. The precipitate which had formed was collected by filtration and extracted for 30 min with hot methanol. Filtration then gave 5.3 g (93%) of **6d** as a pale yellow, microcrystalline solid, mp 286–287° dec.

Anal. Calcd for $C_{13}H_{11}N_6SCl$: C, 48.98; H, 3.46; N, 26.37; S, 10.05; Cl, 11.15. Found: C, 48.89; H, 3.57; N, 26.58; S, 9.99; Cl, 11.33.

The following compounds were similarly prepared from the appropriate 2-amino-3-cyanopyrazine precursor and guanidine.

2,4-Diamino-6-(3,4-dichloroanilinomethyl)pteridine (6e), 76% yield, mp (from DMF) 294–295° dec.

Anal. Calcd for $C_{13}H_{11}N_7Cl_2$: C, 46.43; H, 3.28; N, 29.17; Cl, 21.13. Found: C, 46.58; H, 3.47; N, 29.34; Cl, 20.99.

2,4-Diamino-6-(benzylthiomethyl)pteridine (6s), 85% yield, mp (from methanol) 152–154° dec.

Anal. Calcd for $C_{14}H_{14}N_6S$: C, 56.17; H, 5.05; N, 28.07. Found: C, 56.21; H, 4.76; N, 27.85.

2,4-Diamino-6-(*N*-methyl-4-nitroanilinomethyl)pteridine (6t), 85% yield, mp (from DMF) >350° dec.

Anal. Calcd for $C_{14}H_{14}N_8O_2$: C, 51.53; H, 4.32; N, 34.34. Found: C, 50.40; H, 4.38; N, 34.92.

2,4-Diamino-6-(3,4-dichlorobenzylaminomethyl)pteridine (6f), 66% yield, mp (from methanol–acetonitrile) 263–264° dec.

Anal. Calcd for $C_{14}H_{13}N_7Cl_2$: C, 48.01; H, 3.74; N, 28.00. Found: C, 47.94; H, 3.78; N, 28.08.

2,4-Diamino-6-(2,4-dichlorobenzylaminomethyl)pteridine (6g), 80% yield, mp (from methanol) 264–265° dec.

Anal. Calcd for $C_{14}H_{13}N_7Cl_2$: C, 48.01; H, 3.74; N, 28.00. Found: C, 47.92; H, 3.84; N, 28.00.

2,4-Diamino-6-(sulfanilamidomethyl)pteridine (6h), 87% yield, mp (after extraction of impurities with hot acetonitrile) >300° dec.

Anal. Calcd for $C_{13}H_{14}N_8O_2S$: C, 45.08; H, 4.07; N, 32.35. Found: C, 44.97; H, 4.21; N, 32.12.

2,4-Diamino-6-(*N,N*-diethylaminomethyl)pteridine (6i), 68% yield, mp (from ethanol) 271–272° dec.

Anal. Calcd for $C_{11}H_{17}N_7$: C, 53.42; H, 6.93; N, 39.65. Found: C, 53.40; H, 7.09; N, 39.64.

2,4-Diamino-6-(4-carbomethoxyanilinomethyl)pteridine (6j),[14] 66% yield, mp (from methanol–THF) 258–259° dec.

Anal. Calcd for $C_{15}H_{15}N_7O_2$: C, 55.38; H, 4.62; N, 30.15. Found: C, 55.49; H, 4.66; N, 30.25.

2,4-Diamino-6-(4-carbethoxyanilinomethyl)pteridine (6k),[15] 85% yield, mp (by extraction of impurities with hot methanol) 284–286° dec (lit.[16] mp 277° dec).

2,4-Diamino-6-hydroxymethylpteridine (6n), 84% yield, mp (from water) 333–334° dec.

Anal. Calcd for $C_7H_8N_6O$: C, 43.73; H, 4.20; N, 43.73. Found: C, 43.98; H, 4.12; N, 43.74.

2,4-Diamino-6-(2-ethylenedioxycyclohexylmethyl)pteridine (6q), 89% yield, mp (from methanol) 275–276° dec.

Anal. Calcd for $C_{15}H_{20}N_6O_2$: C, 56.95; H, 6.37; N, 26.57. Found: C, 57.04; H, 6.38; N, 26.30.

2,4-Diamino-6-(2-hydroxycyclohexylmethyl)pteridine (6r), 52% yield, mp (from methanol) 287–288° dec.

Anal. Calcd for $C_{13}H_{18}N_6O$: C, 56.92; H, 6.61; N, 30.64. Found: C, 56.89; H, 6.67; N, 30.84.

2-Amino-6-(4-carboxyanilinomethyl)-4(3*H*)-pteridinone (Pteroic Acid, 7l). A suspension of 0.5 g of 2,4-diamino-6-(4-carbethoxyanilinomethyl)pteridine in 160 ml of 0.2 *N* NaOH was heated under gentle reflux for 1.5 hr under an atmosphere of nitrogen. The resulting clear, colorless solution was cooled to 0° and the pH adjusted to 3–4 with dilute hydrochloric acid. The precipitate which separated was collected by centrifugation and suspended in 1 l. of boiling water and 1 *N* NaOH was added slowly until complete solution had been achieved (10 ml). The resulting solution was treated with Norite and filtered, and the pH of the filtrate was slowly adjusted to 3–4. The resulting fine yellow solid was collected by filtration and washed with water, methanol, and then ether, yield, 0.4 g (83%), mp >400°.

Anal. Calcd for $C_{14}H_{12}N_6O_3$: C, 53.84; H, 3.87; N, 26.91. Found: C, 54.04; H, 3.80; N, 27.11.

2,4-Diamino-6-(2-oxocyclohexylmethyl)pteridine (6p). To a solution of 1.0 g of 2,4-diamino-6-(2-ethylenedioxycyclohexylmethyl)pteridine in 1 ml of trifluoroacetic acid was added, under ice–salt bath cooling and stirring, 0.2 ml of concentrated H_2SO_4. The solution was stirred for 15 min at 0–5° and poured into ice water and the resulting slurry was stirred for an additional 15 min. The solid which was collected by filtration was triturated for 30 min with 50 ml of 2 *N* NaOH and filtered, and the collected solid was digested with 50 ml of refluxing methanol. Filtration then gave 0.7 g (81%) of **6p** as a yellow, microcrystalline solid, mp 282–283° dec. The analytical sample was recrystallized from a large volume of methanol without change in the melting point.

Anal. Calcd for $C_{13}H_{16}N_6O$: C, 57.34; H, 5.92; N, 30.86. Found: C, 57.09; H, 5.79; N, 30.70.

Registry No.—1, 5098-14-6; **3**, 37150-52-0; **4c**, 19994-56-0; **4s**, 54798-18-4; **4t**, 54798-19-5; **4u**, 54798-20-8; **5d**, 54798-21-9; **5e**, 54798-22-0; **5f**, 54798-23-1; **5g**, 54798-24-2; **5h**, 54798-25-3; **5i**, 54798-26-4; **5k**, 54798-27-5; **5m**, 54798-28-6; **5n**, 54798-29-7; **5p**, 54798-30-0; **5q**, 54798-31-1; *cis*-**5r**, 54798-32-2; *trans*-**5r**, 54798-33-3; **5s**, 54798-34-4; **5t**, 54832-63-2; **5u**, 54798-35-5; **6d**, 54798-36-6; **6e**, 54798-37-7; **6f**, 54798-38-8; **6g**, 54798-39-9; **6h**, 54798-40-2; **6i**, 54798-41-3; **6j**, 54798-42-4; **6k**, 23853-08-9; **6n**, 945-24-4; **6p**, 54798-43-5; **6q**, 54798-44-6; **6r**, 54798-45-7; **6s**, 54798-46-8; **6t**, 54798-47-9; **7l**, 119-24-4; 2-amino-3-cyano-5-chloromethylpyra-

zine, 40127-91-1; 4-chlorothiophenol, 106-54-7; 3,4-dichloroaniline, 95-76-1; 3,4-dichlorobenzylamine, 102-49-8; 2,4-dichlorobenzylamine, 95-00-1; sulfanilamide, 63-74-1; diethylamine, 109-89-7; ethyl 4-aminobenzoate, 94-09-7; potassium acetate, 127-08-2; 1-pyrrolidino-1-cyclohexene, 1125-99-1; ethylene glycol, 107-21-1; benzyl mercaptan, 100-53-8; *N*-methyl-*p*-nitroaniline, 100-15-2; *p*-nitroaniline, 100-01-6; guanidine, 113-00-8.

References and Notes

(1) For the previous paper in this series, see E. C. Taylor and P. A. Jacobi, *J. Am. Chem. Soc.*, submitted for publication.
(2) This work was supported by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.
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(13) All compounds were fully characterized by ir and NMR spectroscopy, and were shown to be homogeneous (except where otherwise noted) by TLC. Ir spectra were recorded on a Perkin-Elmer Model 237-B spectrophotometer, and NMR spectra on a Varian A-60A spectrophotometer using TMS as an internal standard in $DCCl_3$ and DMSO-d_6, and as an external standard in D_2O and TFA. All melting points are uncorrected and were determined on a Thomas-Hoover capillary apparatus.
(14) Prepared by cyclization of **5k** with guanidine in methanol in the presence of sodium methoxide; the methyl ester is formed by transesterification.
(15) Prepared by cyclization of **5k** with guanidine in ethanol in the presence of sodium ethoxide.
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Thallium in Organic Synthesis. XL. Preparation and Synthetic Utility of Diarylthallium Trifluoroacetates[1,2]

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Two methods are described for the preparation of diarylthallium trifluoroacetates: (1) the "disproportionation" of arylthallium ditrifluoroacetates by heating in acetone, and (2) the reaction of arylmagnesium bromides with thallium(III) trifluoroacetate (TTFA) to give diarylthallium bromides, conversion of the latter to diarylthallium hydroxides, and, finally, treatment with trifluoroacetic acid (TFA). Although it has been widely believed that diarylthallium(III) compounds are chemically inert, it is shown that these diarylthallium trifluoroacetates are useful, versatile intermediates for the synthesis of unsymmetrical biphenyls (by irradiation in benzene), aryl iodides (by heating with iodine in chloroform), and phenols (by reaction with lead tetraacetate–triphenylphosphine in TFA solution, followed by alkaline hydrolysis of the resulting aryl trifluoroacetates).

Diarylthallium(III) derivatives have been known for over 50 years, but the reported chemistry of these compounds is prosaic, perhaps as a result of a widespread belief that they are "amongst the most stable and least reactive organometallic compounds known".[3] We report that this reputed lack of reactivity is a myth, and that diarylthallium trifluoroacetates are useful and versatile intermediates for the preparation of unsymmetrical biphenyls, aryl iodides, and phenols.

Preparation of Diarylthallium Trifluoroacetates. Literature methods for the preparation of diarylthallium compounds involve the reaction of thallium(III) halides with arylboronic acids, with diarylmercury compounds, or with Grignard reagents.[4a-c] Two new methods for their preparation are described below.

Thallation of aromatic substrates with thallium(III) trifluoroacetate (TTFA) is now a well-known process[5a,b] in which the position taken by thallium with respect to substituents already present can often be controlled by a combination of kinetic, thermodynamic, and chelation factors.[6] We have reported previously on the "disproportionation" of the resulting arylthallium ditrifluoroacetates to give diarylthallium trifluoroacetates upon treatment with triethyl phosphite.[7] It was found in the course of this work that attempted recrystallization of the arylthallium ditrifluoroacetates from water or from acetone resulted in partial "disproportionation". We have now found that heating arylthallium ditrifluoroacetates in acetone for 1 hr, followed by addition of water, results in smooth conversion to diarylthallium trifluoroacetates in good to excellent yield (method A). This simple procedure thus supplements the triethyl phosphite "disproportionation" method utilized previously.[7] Representative compounds prepared by method A are listed, along with yield and melting point, in Table I.

Table I
Representative Diarylthallium Trifluoroacetates by Method A[a]

$$ArTl(OCOCF_3)_2 \xrightarrow[\text{water}]{\text{acetone}} Ar_2TlOCOF_3$$

$Ar_2TlOCOF_3$ registry no.	Ar	Yield, %	Mp, °C[b]
27675-18-9	4-$CH_3C_6H_4$	99	289–291
27675-21-4	3,4-$(CH_3)_2C_6H_3$	93	274–276
27675-19-0	2,4-$(CH_3)_2C_6H_3$	93	278–280
27675-20-3	2,5-$(CH_3)_2C_6H_3$	64	243–245
27675-22-5	2,4,6-$(CH_3)_3C_6H_2$	99	214–216
55073-42-2	2-Dibenzylfuranyl	47	286–287

[a] Melting points and elemental analyses were determined after one recrystallization of the diarylthallium trifluoroacetate from ethyl acetate. Satisfactory C, H analyses were reported for each compound listed in the table. [b] All of the compounds melted with decomposition.