for providing access to the LSIMS instrumentation. This study was supported by NIH Grant ES 02728 (S.D.N.), a stipend from the Netherlands Organization for the Enhancement of Pure Science, and a Fulbright grant (J.H. N.M.).

Registry No. **1a**, 111189-86-7; **1b**, 111265-75-9; **1c**, 111265-76-0; **1d**, 111265-77-1; **2a**, 111189-87-8; **2b**, 111265-78-2; **3a**, 111189-88-9; **3b**, 111408-40-3; 2'-dG, 961-07-9; 2-BA, 14925-39-4.

Pteridines. 53. A Convenient Synthetic Approach to 10-Deazaaminopterin and 10-Deazafolic Acid[1]

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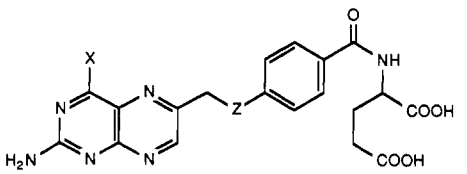
An unambiguous approach to the preparation of 10-deazaaminopterin is described which involves, as its key step, a palladium-catalyzed reaction of 2-amino-3-cyano-5-bromopyrazine with *tert*-butyl 4-ethynylbenzoate. A similar strategy utilizing 2-pivaloyl-6-chloropterin leads to a key intermediate for the preparation of 10-deazafolic acid.

Since its introduction into the clinic in 1953, methotrexate (MTX, 1) has become one of the most widely used chemotherapeutic agents, useful either alone or in combination therapy for the treatment of acute lymphocytic leukemia, choriocarcinoma, breast carcinoma, head and neck cancer, oat cell carcinoma, mycosis fungoides, and osteogenic sarcoma.[2] MTX acts by inhibition of dihydrofolate reductase, the enzyme responsible for the reduction of dihydrofolic acid to tetrahydrofolic acid. The latter is a precursor to a series of enzyme cofactors critical for a variety of one-carbon transfer reactions, which in turn are essential for the biosynthesis of purines and pyrimidines and hence DNA.[3-5] Unfortunately, the cytotoxicity resulting from a blockade of the biosynthesis of these crucial coenzymes is nonspecific, and rapidly proliferating normal cells as well as cancer cells are affected. As a consequence, MTX therapy is underscored by many serious side effects and, with higher doses, extreme toxicity. Intensive research programs over the past decade have been aimed at modifying the MTX structure in such a way as to increase its selectivity of action. Among the most promising of such MTX analogues are 10-deazaaminopterin (**2**)[6-12] and its 10-ethyl derivative (**3**).[8,9,13] The latter appears to be exceptionally promising; its substantially greater activity compared with MTX itself against a variety of murine tumors is attributed to a more favorable membrane transport and to a greater degree of polyglutamation in tumor as contrasted to normal cells. An exhaustive review of the biological and biochemical properties of these and other deaza analogues of MTX has recently appeared.[14]



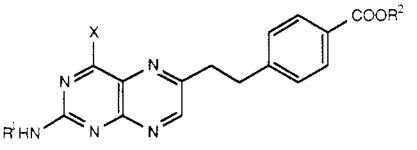
1. X = NH_2, Z = NCH_3
2. X = NH_2, Z = CH_2
3. X = NH_2, Z = $CHCH_2CH_3$
4. X = OH, Z = CH_2

In light of the promising activity of **2** and its 10-substituted analogues, considerable effort has been devoted to the development of alternative syntheses. The principal strategies that have been utilized thus far for the synthesis of **2** are the following: (1) A Boon–Leigh condensation of 2,4-diamino-5-nitro-6-chloropyrimidine with an appropriate α-amino ketone (usually protected) to give a 6-substituted aminopyrimidine, which is then reductively cyclized following appropriate deprotection of the carbonyl group.[7,9,15] (2) Wittig condensation of the triphenylphosponium ylide derived from 2,4-diamino-6-(bromomethyl)pteridine with diethyl *N*-(4-formylbenzoyl)-L-glutamate followed by catalytic reduction, oxidation of the intermediate 5,6,7,8-tetrahydro derivative, and final saponification.[10,11] (3) Condensation of 2,4,5,6-tetraaminopyrimidine with an α-bromoaldehyde already substituted with the eventual C-6 substituent.[7,8,12] This latter synthesis suffers from the inherent regiochemical ambiguity of such cyclization procedures, which has been discussed extensively elsewhere.[16]

(1) For the previous paper in this series, see: Taylor, E. C.; Ray, P. S. *Synth. Commun.*, in press.
(2) Bertino, J. R. In *Cancer and Chemotherapy*; Crooke, S. T., Prestayko, A. W., Eds.; Academic: New York, 1981; p 359.
(3) (a) Rosowsky, A.; Freisheim, J. H.; Moran, R. G.; Solan, V. C.; Bader, H.; Wright, J. E.; Radicke-Smith, M. *J. Med. Chem.* **1986**, *29*, 655 and references cited therein. (b) Rosowsky, A.; Bader, H.; Radicke-Smith, M.; Cucchi, C. A.; Wick, M. M.; Freisheim, J. H. *J. Med. Chem.* **1986**, *29*, 1703.
(4) Krumdieck, C. L.; Tamura, T.; Eto, I. In *Vitam. Horm.* (N.Y.) **1983**, *40*, 45.
(5) Covey, J. M. *Life Sci.* **1980**, *26*, 665.
(6) DeGraw, J. I.; Kisliuk, R. L.; Gaumont, Y.; Baugh, C. M.; Nair, M. G. *J. Med. Chem.* **1974**, *17*, 552.
(7) DeGraw, J. I.; Brown, V. H.; Kisliuk, R. L.; Sirotnak, F. M. In *Chemistry and Biology of Pteridines*; Kisliuk, R. L., Brown, G. M., Eds.; Elsevier: New York, 1979; p 225.
(8) DeGraw, J. I.; Brown, V. H.; Tagawa, H.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. *J. Med. Chem.* **1982**, *25*, 1227.
(9) Nair, M. G. *J. Org. Chem.* **1985**, *50*, 1879.
(10) Piper, J. R.; Montgomery, J. A. *J. Med. Chem.* **1980**, *23*, 320.
(11) Piper, J. R.; Montgomery, J. A., U.S. Pat. 4 172 200, October 23, 1979.
(12) DeGraw, J. I.; Sirotnak, F. M., U.S. Pat. 4 639 319, January 18, 1983.
(13) DeGraw, J. I.; Christie, P. H.; Tagawa, H.; Kisliuk, R. L.; Gaumont, Y.; Schmid, F. A.; Sirotnak, F. M. *J. Med. Chem.* **1986**, *29*, 1056.
(14) Montgomery, J. A.; Piper, J. R. In *Folate Antagonists as Therapeutic Agents*; Sirotnak, F. M., Burchall, J. J., Ensininger, W. B., Montgomery, J. A., Eds.; Academic: New York, 1984; Vol. 1, p 219.
(15) DeGraw, J. I.; Brown, V. H.; Kisliuk, R. L.; Gaumont, Y. *J. Med. Chem.* **1971**, *14*, 866.

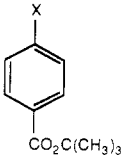
0022-3263/88/1953-0035$01.50/0

We describe in this paper an alternative and unambiguous synthetic route to 10-deazaaminopterin (**2**). This new strategy is based upon a general procedure recently developed in our laboratory for the preparation of 6-alkynylpteridine derivatives,[17] which utilizes a palladium-catalyzed coupling reaction between an appropriate halogenated heterocycle and a monosubstituted acetylene. Thus, 2-amino-3-cyano-5-bromopyrazine condensed smoothly with phenylacetylene, 1-hexyne, 3,3-dimethyl-1-butyne, and methyl propargyl ether to give the corresponding 2-amino-3-cyano-5-alkynylpyrazines, which were then cyclized with guanidine to the appropriate 2,4-diamino-6-alkynylpteridines. Alternatively, palladium-catalyzed coupling of 6-chloro-2-pivaloylpterin with the above acetylenes gave the corresponding 6-alkynyl derivatives, which were then hydrolyzed to the target 6-alkynylpterins. We have now utilized the above procedures for the preparation of 4-amino-4-deoxy-10-deazapteroic acid (**5**; a known precursor to 10-deazaaminopterin (**2**) (loc. cit.)) and 2-pivaloyl-10-deazapteroic acid (**6**; a precursor of 10-deazapteroic acid[18] and 10-deazafolic acid (**4**)[19]).

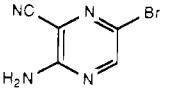


5, X = NH_2, $R^1 = R^2 = H$
6, X = OH, $R^1 = COC(CH_3)_3$, $R^2 = H$
7, X = NH_2, $R^1 = H$, $R^2 = C(CH_3)_3$
8, X = OH, $R^1 = COC(CH_3)_3$, $R^2 = C(CH_3)_3$
9, X = OH, $R^1 = COCH_3$, $R^2 = H$

As our monosubstituted acetylene, we chose *tert*-butyl 4-ethynylbenzoate (**12**) because of both its lipophilic character, which insures improved solubility of the resulting pteridine derivatives in organic solvents, and its ease of removal (with gaseous HCl in nitromethane). This material was prepared in good overall yield (54%) from 4-bromobenzoyl chloride by reaction with *tert*-butyl alcohol in pyridine to give **10**, followed by a palladium-catalyzed coupling reaction with (trimethylsilyl)acetylene to yield **11**. Final removal of the trimethylsilyl grouping with anhydrous potassium carbonate in methanol gave **12**.

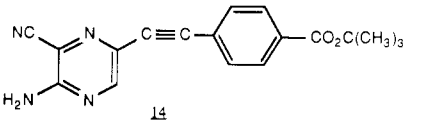


10, X = Br
11, X = C≡CTMS
12, X = C≡CH

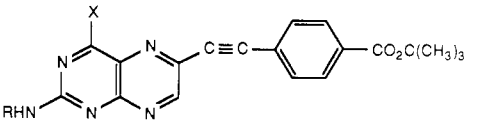


13

Reaction of acetylene **12** with 2-amino-3-cyano-5-bromopyrazine (**13**)[17] in acetonitrile containing a large excess of triethylamine and a catalytic amount of the palladium dichloride–triphenylphosphine complex (prepared in situ) and cuprous iodide[20] gave the coupled product **14**. Pyrimidine ring annulation with guanidine in refluxing *tert*-butyl alcohol gave the pteridine **15** in 87% yield. Catalytic hydrogenation of the triple bond gave the *tert*-butyl ester of 4-amino-4-deoxy-10-deazapteroic acid (**7**, 72% yield), and the *tert*-butyl ester was then smoothly cleaved with gaseous HCl in nitromethane. This sequence of reactions provided a simple and unequivocal synthesis of 4-amino-4-deoxy-10-deazapteroic acid (**5**, 87% yield). The conversion of this compound to 10-deazaaminopterin (**2**) by peptide coupling with diethyl L-glutamate followed by saponification has been described elsewhere.[6-9,12]

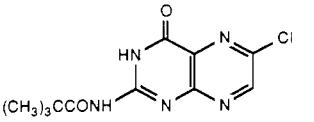


14

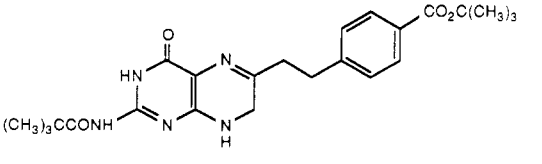


15, X = NH_2, R = H
16, X = OH, R = $COC(CH_3)_3$

Using similar methodology, we have also prepared a precursor to 10-deazafolic acid (**4**). Coupling of *tert*-butyl 4-ethynylbenzoate (**12**) with 2-pivaloyl-6-chloropterin (**17**)[17] in refluxing acetonitrile/triethylamine in the presence of catalytic amounts of the palladium acetate/tri-*o*-tolylphosphine complex (prepared in situ) and cuprous iodide gave the 6-ethynyl derivative **16**. Under these conditions, the reaction did not go to completion (TLC); even after heating at 100 °C in a sealed tube for 16 h, 30% of starting material was recovered. The coupled product (54% yield) was then hydrogenated over 10% Pd/C in dichloromethane/methanol (1:10) at atmospheric pressure and at room temperature. Even under these mild conditions, however, the product of reduction proved to be the 7,8-dihydropterin **18**. However, oxidation to the pterin **8** was readily achieved by bubbling oxygen through a solution of **18** in dichloromethane. Selective removal of the *tert*-butyl ester in the presence of the 2-pivaloyl group was accomplished with gaseous HCl in nitromethane, thus providing the 2-pivaloyl derivative of 10-deazapteroic acid (**6**).



17



18

The 2-acetyl derivative (**9**) of 10-deazapteroic acid has been previously described, and it has been converted to 10-deazafolic acid by peptide coupling with diethyl L-glutamate followed by saponification and hydrolysis of the 2-acetyl group.[19] The advantages of solubilizing pterins by pivaloylation rather than acetylation have already been stressed, and the facile removal of the 2-pivaloyl group

(16) Taylor, E. C. In *Chemistry and Biology of Pteridines*; Blair, J. A., Ed.; Walter de Gruyter: New York, 1983; p 23.
(17) Taylor, E. C.; Ray, P. S. *J. Org. Chem.* **1987**, *52*, 3997.
(18) DeGraw, J. I.; Tsakotellis, P.; Kisliuk, R. L.; Gaumont, Y. *J. Heterocycl. Chem.* **1971**, *8*, 105.
(19) Struck, R.; Shealy, Y. F.; Montgomery, J. A. *J. Med. Chem.* **1971**, *14*, 693.
(20) See: Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

under either mildly basic or aqueous acidic conditions has been previously described.[1,17] Thus, 2-pivaloyl-10-deazapteroic acid should prove to be a particularly useful alternative to the 2-acetyl derivative for conversion to 10-deazafolic acid.

Experimental Section

***tert*-Butyl 4-Bromobenzoate (10).** A solution of 4-bromobenzoyl chloride (11 g, 0.05 mol) in anhydrous dichloromethane (30 mL) was added dropwise to a stirred mixture of dry *tert*-butyl alcohol (7.4 g, 0.1 mol), dry pyridine (7.9 g, 0.1 mol), and dichloromethane (50 mL). The mixture was stirred at room temperature under nitrogen for two days and then extracted with water (2 × 100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residual oil was distilled to give 10 g (78%) of a colorless oil: bp 91–92 °C (1.2 mmHg); NMR ($CDCl_3$) δ 1.59 (s, 9 H), 7.53 (d, 2 H, J = 8.7 Hz), 7.85 (d, 2 H, J = 8.7 Hz); IR (neat) 1710 cm^{-1}. Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.09; Br, 31.08. Found: C, 51.41; H, 5.36; Br, 30.83.

***tert*-Butyl 4-Ethynylbenzoate (12).** A mixture containing *tert*-butyl 4-bromobenzoate (5.14 g, 0.02 mol), palladium acetate (45 mg, 0.2 mmol), triphenylphosphine (105 mg, 0.4 mmol), (trimethylsilyl)acetylene (4.3 mL, 0.03 mol), and triethylamine (30 mL) was heated in a sealed tube at 100 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and extracted with water. The organic solution was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel with a mixture of 10% ethyl acetate in hexanes as eluent to give *tert*-butyl 4-[(trimethylsilyl)ethynyl]benzoate (11) as a dark oil: NMR ($CDCl_3$) δ 0.26 (s, 9 H), 1.59 (s, 9 H), 7.49 (d, 2 H, J = 8.23 Hz), 7.91 (d, 2 H, J = 8.23 Hz). This material was dissolved in anhydrous methanol (30 mL), and anhydrous potassium carbonate (300 mg) was added to the mixture, which was then stirred at room temperature under nitrogen for 3 h. The reaction mixture was diluted with dichloromethane, extracted with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was distilled to give 2.83 g (70% over two steps) as a colorless solid: bp 60–70 °C, 0.1 mmHg; mp 71–72 °C; NMR ($CDCl_3$) δ 1.62 (s, 9 H), 3.23 (s, 1 H), 7.55 (d, 2 H, J = 8.11 Hz), 7.96 (d, 2 H, J = 8.11 Hz); IR (KBr) 2100, 1700, 1600 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.86; H, 6.79.

***tert*-Butyl 4-[(2-Amino-3-cyanopyrazin-5-yl)ethynyl]benzoate (14).** A mixture of 2-amino-3-cyano-5-bromopyrazine[17] (1.1 g, 5.527 mmol), palladium chloride (50 mg, 0.282 mmol), triphenylphosphine (150 mg, 0.572 mmol), copper(I) iodide (54 mg, 0.283 mmol), triethylamine (2 mL), and *tert*-butyl 4-ethynylbenzoate (1.2 g, 5.940 mmol) in acetonitrile (30 mL) was heated under reflux under a nitrogen atmosphere for 18 h. The solvent was removed by evaporation under reduced pressure, and the residue was chromatographed twice on silica gel with 1% methanol in chloroform as eluent. The fractions containing the product (R_f 0.5 in 5% methanol in dichloromethane on silica gel) were combined, the solvent was removed in vacuo, and the residual solid was recrystallized from benzene to give 844 mg (48%) of yellow microcrystals: mp 214–215 °C; NMR ($CDCl_3$) δ 1.62 (s, 9 H), 5.49 (br, 2 H), 7.62 (d, 2 H, J = 8.2 Hz), 8.10 (d, 2 H, J = 8.2 Hz), 8.44 (s, 1 H); IR (KBr) 3420, 3340, 3240, 2240, 1715, 1645 cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.50; H, 5.00; N, 17.50. Found: C, 67.22; H, 5.07; N, 17.41.

***tert*-Butyl 4-[(2,4-Diaminopteridin-6-yl)ethynyl]benzoate (15).** Sodium (21 mg, 0.913 mmol) was dissolved in dry *tert*-butyl alcohol (10 mL) under nitrogen, guanidine hydrochloride (85 mg, 0.900 mmol) was added with stirring, and after 5 min, *tert*-butyl 4-[(2-amino-3-cyanopyrazin-5-yl)ethynyl]benzoate (100 mg, 0.312 mmol) was added. The mixture was heated under reflux for 8 h under nitrogen and cooled to room temperature, and the suspended solid was collected by filtration, washed well with water followed by cold ethanol, and dried at 80 °C in vacuo. Recrystallization from ethyl acetate gave 96 mg (87%) of a bright yellow microcrystalline powder: mp >300 °C; NMR (Me_2SO-d_6) δ 1.55 (s, 9 H), 7.0 (br, 2 H), 7.72 (d, 2 H, J = 8.3 Hz), 7.85 (br, 2 H), 7.96 (d, 2 H, J = 8.3 Hz), 8.86 (s, 1 H); IR (KBr) 3460 (br), 3340 (br), 3160 (br), 1715, 1640 cm^{-1}. Anal. Calcd for $C_{19}H_{18}N_6O_2$: C, 62.98; H, 4.97; N, 23.20. Found: C, 62.89; H, 5.03; N, 23.17.

***tert*-Butyl 4-[(2,4-Diaminopteridin-6-yl)ethyl]benzoate (7).** A mixture of *tert*-butyl 4-[(2,4-diaminopteridin-6-yl)ethynyl]benzoate (30 mg, 0.828 mmol) and 10% palladium-on-charcoal (10 mg) in DMF (5 mL) was hydrogenated under 1 atm of hydrogen at room temperature for 12 h. The reaction mixture was filtered through Celite and diluted with water (30 mL). The mixture was extracted with ethyl acetate (2 × 30 mL) and dried over anhydrous sodium sulfate, and solvent was removed under reduced pressure. Recrystallization of the residue from ethanol gave 22 mg (72%) of a yellow microcrystalline solid: mp >300 °C; NMR ($CDCl_3$) δ 1.60 (s, 9 H), 3.17 (m, 4 H), 7.22 (d, 2 H, J = 8.12 Hz), 7.91 (d, 2 H, J = 8.12 Hz), 8.57 (s, 1 H); HRMS calcd for $C_{19}H_{22}N_6O_2$ m/z 366.1804, found m/z 366.1792.

4-[(2,4-Diaminopteridin-6-yl)ethyl]benzoic Acid (5). *tert*-Butyl 4-[(2,4-diaminopteridin-6-yl)ethyl]benzoate (15 mg) was added to 15 mL of nitromethane, which had been saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at 0 °C for 15 min and then at 20 °C for 0.5 h. The mixture was diluted with anhydrous ether, and the solid was collected by filtration to give 11 mg (87%) of a yellow powder: mp >300 °C. The NMR spectrum (in TFA-d) of this material was identical in every respect with the spectrum of 5 reported by Nair.[9]

***tert*-Butyl 4-[[2-(Pivaloylamino)-4(3*H*)-oxopteridin-6-yl]ethynyl]benzoate (16).** A mixture of 2-pivaloyl-6-chloropterin[17] (1.0 g, 3.552 mmol), palladium acetate (100 mg, 0.445 mmol), tri-*o*-tolylphosphine (271 mg, 0.890 mmol), copper(I) iodide (84 mg, 0.445 mmol), triethylamine (5 mL), and *tert*-butyl 4-ethynylbenzoate (720 mg, 3.564 mmol) in acetonitrile (20 mL) was heated at 100 °C in a sealed tube for 16 h. The solvent was removed by evaporation under reduced pressure, and the residue was chromatographed on silica gel, eluting with 1% methanol in chloroform. The fractions containing the product were combined, and the solvent was removed in vacuo. The residue was subjected to radial chromatography on silica plates with the above solvent mixture as eluent. The solid obtained after evaporation of the solvent was recrystallized from a mixture of chloroform/ethanol to give 857 mg (54%) of a cream-colored microcrystalline powder: mp >300 °C; NMR ($CDCl_3$) δ 1.37 (s, 9 H), 1.62 (s, 9 H), 7.67 (d, 2 H, J = 8.2 Hz), 8.03 (d, 2 H, J = 8.2 Hz), 8.42 (br s, 1 H), 8.99 (s, 1 H), 12.45 (br s, 1 H); IR (KBr) 3060–3300 (br), 2210 (w), 1710, 1680, 1610 cm^{-1}. Anal. Calcd for $C_{24}H_{25}N_5O_4 \cdot 0.75H_2O$: C, 62.50; H, 5.75; N, 15.18. Found: C, 62.79; H, 5.55; N, 15.24. HRMS calcd for $C_{24}H_{25}N_5O_4$ m/z 447.1906, found m/z 447.1916.

***tert*-Butyl 4-[[2-(Pivaloylamino)-4(3*H*)-oxopteridin-6-yl]ethyl]benzoate (8).** A mixture of *tert*-butyl 4-[[2-(pivaloylamino)-4(3*H*)-oxopteridin-6-yl]ethynyl]benzoate (100 mg) and 10% palladium-on-charcoal (20 mg) in 10% dichloromethane in methanol (30 mL) was hydrogenated at 1 atm at room temperature for 45 min. The reaction was filtered through a pad of Celite, and the solvent was removed by evaporation under reduced pressure. The crude solid was suspended in ethanol, and the mixture was heated under reflux for 5 min. The insoluble material was collected by filtration, dissolved in 5% methanol in dichloromethane, and left stirring at room temperature, with oxygen bubbling through the solution, until no starting material remained by TLC (3 days). The solvent was removed in vacuo, and the residue was subjected to radial chromatography on silica gel plates, eluting with 2% methanol in chloroform. The residue obtained after removal of the solvent was triturated with carbon tetrachloride to give 72 mg (72%) of a colorless microcrystalline solid: mp 237–238 °C; NMR ($CDCl_3$) δ 1.34 (s, 9 H), 1.58 (s, 9 H), 3.21 (m, 2 H), 3.32 (m, 2 H), 7.20 (d, 2 H, J = 8.11 Hz), 7.88 (d, 2 H, J = 8.11 Hz), 8.46 (br, 1 H), 8.51 (s, 1 H), 12.38 (br, 1 H); IR (KBr) 3060–3300 (br), 1710, 1680, 1620 cm^{-1}; HRMS calcd for $C_{24}H_{29}N_5O_4$ m/z 451.2219, found m/z 451.2221.

4-[[2-(Pivaloylamino)-4(3*H*)-oxopteridin-6-yl]ethyl]benzoic Acid (6). *tert*-Butyl 4-[[2-(pivaloylamino)-4(3*H*)-oxopteridin-6-yl]ethyl]benzoate (30 mg) was added to nitromethane (20 mL), which had been saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at 0 °C for 10 min and then at room temperature for 30 min. The mixture was diluted with anhydrous ether, and the solid was collected by filtration and dried in vacuo at 80 °C to give 22 mg (83%) of a cream-colored solid: mp >300 °C; NMR (Me_2SO-d_6) δ 1.24 (s,

9 H), 3.18 (m, 2 H), 3.21 (m, 2 H), 7.35 (d, 2 H, J = 8.08 Hz), 7.82 (d, 2 H, J = 8.08 Hz), 8.76 (s, 1 H), 11.48 (br, 2 H); HRMS calcd for $C_{20}H_{21}N_5O_4$ m/z 395.1593, found m/z 395.1576.

Acknowledgment. We are deeply indebted to Dr. George S. K. Wong, who pioneered the palladium coupling procedure in our group for the attachment of carbon side chains to related heterocycles and who also provided us with the above procedure for the preparation of *tert*-butyl 4-ethynylbenzoate.

Registry No. **2**, 52454-37-2; **4**, 33963-89-2; **5**, 33047-42-6; **6**, 111323-82-1; **7**, 111292-00-3; **8**, 111292-02-5; **10**, 59247-47-1; **11**, 111291-96-4; **12**, 111291-97-5; **13**, 17231-51-5; **14**, 111291-98-6; **15**, 111291-99-7; **16**, 111292-01-4; **17**, 108473-08-1; 4-bromobenzoyl chloride, 586-75-4; (trimethylsilyl)acetylene, 1066-54-2; guanidine hydrochloride, 50-01-1.

3-Allyl-4-aryl-1,3,4-oxa(and thia)diazolidine-2,5-diones and Thio Analogues via a Facile Polyhetero-Claisen Rearrangement

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The attempted preparation of 2-(allyloxy)-4-aryl-1,3,4-oxa(and thia)diazolin-5(4*H*)-ones and thio analogues **4** by treatment of allyl 2-aryl-2-(chlorocarbonyl)hydrazinecarboxylates and thio analogues **3** with base at 15–25 °C gave instead 3-allyl-4-aryl-1,3,4-oxa(and thia)diazolidine-2,5-diones and thio analogues **5**. The inability to detect **4** indicates that these compounds undergo Claisen rearrangement in an extremely facile fashion.

Introduction

Prior to this investigation, disubstituted-1,3,4-oxadiazolidine-2,5-diones have been prepared by two methods. Hurd and Cesark[1] found that pyrolysis of 2-carbethoxy-1,2-dialkylhydrazinecarbonyl chlorides, at 140–180 °C, provides disubstituted diazasuccinic anhydrides in quantitative yields.

Henderson and Zweig[2] reported that diphenyldiazasuccinic anhydride could be prepared in 35% yield by the copper(II)-catalyzed pyrolysis of the corresponding hydrazinecarbonyl chloride.

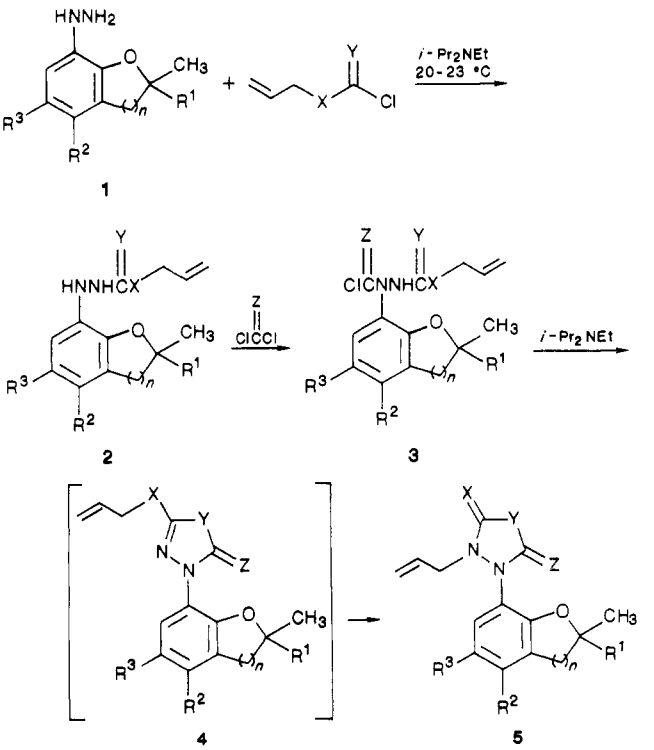
In an attempt to prepare 2-allyloxy analogues and thio derivatives of the broad-spectrum insecticide 4-(2,3-dihydro-2,2,4-trimethylbenzofuran-7-yl)-2-methoxy-1,3,4-oxadiazol-5(4*H*)-one,[3] several arylhydrazines **1** were converted into allyl 2-aryl-2-(chlorocarbonyl)hydrazinecarboxylates and thio analogues **3** (Scheme I). However, when the **3** compounds were subjected to dehydrochlorination conditions, e.g., diisopropylethylamine, 15–25 °C, the desired **4** compounds were not isolated as they readily underwent Claisen rearrangement to give 3-allyl-4-aryl-1,3,4-oxa(and thia)diazolidine-2,5-diones ("diazasuccinic anhydrides") **5** and thiono analogues. These results are discussed in the present paper.

Results

7-Hydrazino-2,3-dihydro-2,2-dimethylbenzofuran[3] (**1a**), 8-hydrazino-3,4-dihydro-2,5-dimethylbenzopyran[4] (**1c**), 7-hydrazino-2,3-dihydro-2,2,4-trimethylbenzofuran[3] (**1b**), and 8-hydrazino-5-chloro-3,4-dihydro-2,6-dimethylbenzopyran[4] (**1d**) reacted readily with allyl chloro(and thiol and dithio)-formate in the presence of diisopropylethylamine (Hünig's base) as acceptor for hydrogen chloride to give the respective allyl hydrazinecarboxylates ("carbazates"), thio and dithio derivatives **2** in good yields (Table I).

All **2** compounds reacted readily with phosgene at 0–20 °C in solution (THF, toluene, ethyl acetate) to give chlorocarbonylated allyl carbazates **3a–c** in essentially quantitative yields. Thiophosgene reacted analogously with **2d** to give **3e**. With the exception of **3a**, which melted at

Scheme I[a]



[a] (**a**) $R^1 = CH_3$, $R^2 = R^3 = H$, X = Y = Z = O, n = 1; (**b**) $R^1 = R^2 = CH_3$, $R^3 = H$, X = S, Y = Z = O, n = 1; (**c**) $R^1 = R^3 = H$, $R^2 = CH_3$, X = Y = Z = O, n = 2; (**d**) $R^1 = H$, $R^2 = Cl$, $R^3 = CH_3$, X = Y = S, Z = O, n = 2; (**e**) $R^1 = H$, $R^2 = Cl$, $R^3 = CH_3$, X = Y = Z = S, n = 2.

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(1) Hurd, C. D.; Cesark, F. F. *J. Am. Chem. Soc.* **1967**, *89*, 1417.
(2) Henderson, W. A.; Zweig, A. *J. Chem. Soc., Chem. Commun.* **1972**, 169.
(3) Pilgram, K. H.; Skiles, R. D. U.S. Pat. 4 406 910, 1983; 4 467 104, 1984 (to Shell Oil Company).

0022-3263/88/1953-0038$01.50/0