Synthesis of Trifluoromethylated Pyrazine-Containing Nitrogen Heterocycles from Trifluoropyruvaldehyde and Ortho-Diamines: Scope and Regiochemistry

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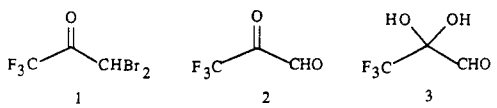
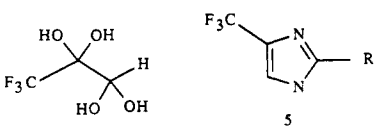
The structures of the reaction products obtained from the condensation of trifluoropyruvaldehyde with a variety of ortho-diamines have been investigated in order to determine the scope of the reaction and also to investigate which of the structural isomers is formed in larger amount in cases in which two products are possible. As a result of intensive ^{13}C, ^{19}F, and ^{1}H NMR studies, as well as X-ray analysis, it has been observed that in aqueous solution, the major product of the reaction is usually derived from reaction of the aldehyde carbonyl of trifluoropyruvaldehyde hydrate (**3**) with the more reactive amino group of the diamine to give an intermediate imine (e.g., **28**), which then dehydrates and cyclizes by reaction of the remaining amino group with the carbonyl adjacent to the trifluoromethyl group.

Since the report of its preparation by bromination of 1,1,1-trifluoroacetone under acidic conditions,[1] 3,3-dibromo-1,1,1-trifluoroacetone (**1**) has been found to undergo hydrolysis with aqueous sodium acetate to yield an aqueous solution of trifluoropyruvaldehyde (**2**), existing principally as the hydrates **3** and **4**.[2,3] Treatment of this aqueous solution with hydroxylamine gives a dioxime,[3] and the addition of aldehydes and ammonia to the solution yields (trifluoromethyl)imidazoles of general structure **5**.[2] The chemistry of trifluoropyruvaldehyde is otherwise largely unexplored.



1 **2** **3**



4 **5**

As part of an ongoing project aimed at the synthesis of trifluoromethylated lumazines as potential riboflavin synthase inhibitors,[4,5] we have investigated the reactions of solutions containing **2**, **3**, and **4** with a variety of ortho-diamines. A major objective of this undertaking, besides defining the scope of the reaction, has been to determine the regiochemistry of the condensation when run on diamines that could lead to structurally isomeric products.

Solutions containing **2**, **3**, and **4** were prepared by hydrolyzing compound **1** in aqueous sodium acetate at 98 °C for 30 min. Methanol or DMF solutions of the ortho-diamines were then added. The results of the condensation reactions are listed in Table I. Since only one structural isomer can be produced in reactions involving the symmetrical diamines **6**, **8**, and **10**, the structures of the products **7**, **9**, and **11** require no special discussion.

Two products, **13** and **14**, were formed in the reaction involving 3, 4-diaminobenzophenone (**12**). The structure of the major isomer **13** was determined by X-ray analysis. The formation of **13** as the major product can be rationalized if it is assumed that the equilibrium between **2** and **3** largely favors **3**, so that the keto function is protected as a hydrate and the aldehyde function of **3** reacts preferentially with the more nucleophilic amino group (see resonance structure **27**) to give intermediate **28**, which is in equilibrium with small amounts of the ketone **29**. The ketone carbonyl of **29** would then react with the less nucleophilic amino group, yielding the observed major product **13**. It is reasonable that the keto function of trifluoropyruvaldehyde would be hydrated to a larger extent than the aldehyde because it is directly attached to the highly electronegative trifluoromethyl group. In an attempt to gain evidence regarding the position of equilibrium between **2** and **3**, the ^{19}F NMR spectrum of a solution obtained after the aqueous sodium acetate hydrolysis of 3,3-dibromo-1,1,1-trifluoroacetone (**1**) was examined. This revealed only one singlet at δ–2.5 upfield from trifluoroacetic acid. In addition, the ^{1}H NMR spectrum of this solution did not display an aldehyde proton signal. These results indicate that the major species actually present in aqueous solution is the unreactive dihydrate **4**. Although **2** and **3** were not observed spectroscopically, their presence is implied by the overall reaction.

Two products, **16** and **17**, also arise from the reaction involving 5,6-diaminouracil (**15**). The assignment of structures to the major and minor isomers is based on two arguments involving ^{13}C NMR data. The α- and β-substituent effects for the trifluoromethyl groups should be consistent when comparing the ^{13}C NMR spectral data for the products **16** and **17**. The ^{13}C NMR chemical shifts for C-6 and C-7 in lumazine (**30**) are δ 141.7 and 150.2, respectively.[6] The corresponding chemical shifts at C-6 and C-7 in the major isomer **16** are at δ 135.00 and 142.99, respectively, so that the α-substituent effect of the trifluoromethyl group is −7.2, while the β-substituent effect is −6.7. In the minor isomer **17**, the signals for C-6 and C-7 appear at δ 135.80 and 144.98, giving an α-substituent effect for the trifluoromethyl group of −5.9 and a β-substituent effect of −5.2. If the structural assignments were

(1) McBee, E. T.; Burton, T. M. *J. Am. Chem. Soc.* **1952**, *74*, 3902.
(2) (a) Baldwin, J. J.; Kasinger, P. A.; Novello, F. C.; Sprague, J. M.; Duggan, D. E. *J. Med. Chem.* **1975**, *18*, 895. (b) Baldwin, J. J.; Christy, M. E.; Denny, G. H.; Habecker, C. N.; Freedman, M. B.; Lyle, P. A.; Ponticello, G. S.; Varga, S. L.; Gross, D. M.; Sweet, C. S. *J. Med. Chem.* **1986**, *29*, 1065.
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(5) Cushman, M.; Wong, W. C.; Bacher, A. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1051.
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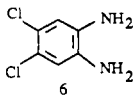
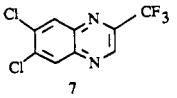
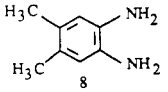
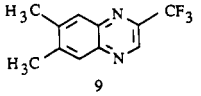
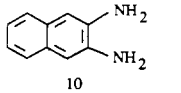
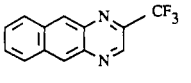
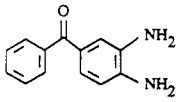
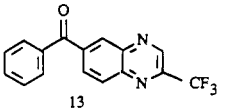
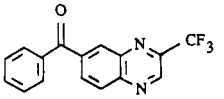
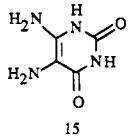
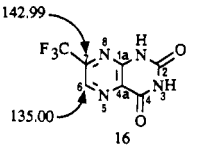
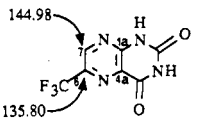
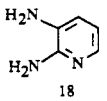
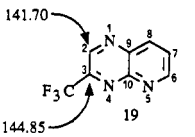
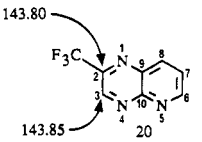
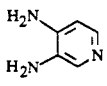
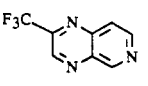
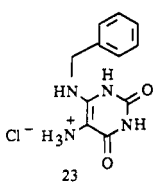
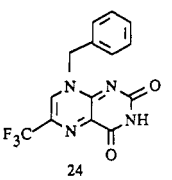
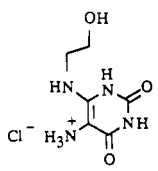
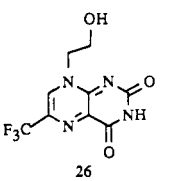
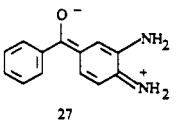
Table I. Reaction of Solutions of Trifluoropyruvaldehyde (2) and Trifluoropyruvaldehyde Hydrate (3) with Ortho-Diamines

reactant	solv (time, temp)	product(s)	% yield
 6	aq MeOH (18 h, 23 °C)	 7	83[a]
 8	aq MeOH (18 h, 23 °C)	 9	57[a]
 10	aq MeOH (18 h, 23 °C)	 11	76[a]
 12	aq MeOH (18 h, 23 °C)	 13	52[a]
		 14	34[a]
 15	DMF 23 °C)	 16	41[b]
		 17	20[b]
 18	aq MeOH (24 h, (23 °C)	 19	74[a]
		 20	4[a]
 21	aq MeOH (6 h, 70 °C)	 22	36[a]
 23	DMF (24 h, 23 °C)	 24	17[a]
 25	DMF (24 h, 23 °C)	 26	26[a]

[a] Yield of product isolated. [b] Yield estimated from the crude yield of the mixture of products **16** and **17** and the ratio, as determined by ^{19}F NMR spectroscopy.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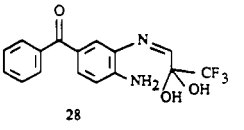
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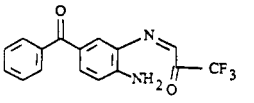
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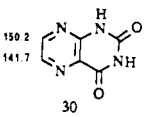
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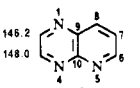
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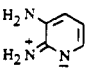
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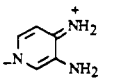
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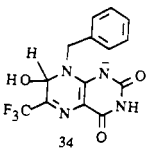
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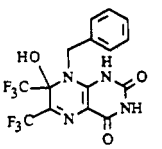
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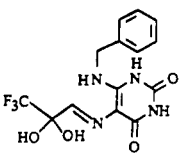
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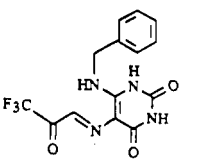
37

reversed, the signals for C-6 and C-7 in 7-(trifluoromethyl)lumazine would appear at δ 144.98 and 135.80, respectively, resulting in an α-substituent effect of −14.4 and a β-substituent effect of +3.3. Also, if the structural assignments were reversed, the C-6 and C-7 signals for 6-(trifluoromethyl)lumazine would be at δ 142.99 and at 135.00, resulting in an α-substituent effect for the trifluoromethyl group of +1.3 and a β-substituent effect of −15.2. Clearly, the reversed assignments are incorrect on the basis of this evidence. In addition, the ^{13}C NMR chemical shifts for C-1a (δ 145–155) in lumazines related to **16** and **17** are downfield from those of C-4a (δ 123–127), and the difference ranges from 20 to 25 ppm.[6] In the ^{13}C NMR spectrum of the major isomer **16**, the C-4a signal appears as a doublet (J = 10.7 Hz) at δ 132.27 due to transoid vicinal three-bond coupling with H-6, while in the minor isomer **17**, the signal for C-1a is a doublet (J = 10.1 Hz) at δ 151.83 due to coupling with H-7. As expected, the signals for C-1a in **16** and C-4a in **17** appear as singlets. Thus, the coupling patterns are also consistent with the assignment of the major isomer as **16** and the minor as **17**. In this example, as with the reaction involving **12**, the aldehyde group of **3** is reacting preferentially with the more reactive 5-amino group of the starting diamine **15**. In the reaction involving 2,3-diaminopyridine (**18**), the assignment of structure **19** to the major isomer and **20** to the minor isomer is based on similar ^{13}C NMR substituent effects and ^{13}C NMR coupling data.

The reaction of 3,4-diaminopyridine (**21**) with **3** gave only one isomer, which is assumed to be derived from reaction of the aldehyde of **3** with the more reactive 3-amino group of **21** (see resonance structure **33**) to give the pyrido[3,4-*b*]pyrazine **22**.

The structure of 8-benzyl-6-(trifluoromethyl)lumazine (**24**) was elucidated mainly on the basis of NOE effects and ^{19}F NMR data. Irradiation of the benzylic protons at δ 5.68 resulted in an NOE of 27.3% for H-7 (δ 8.92), while irradiation of the C-7 proton caused an NOE of 9.1% for the benzylic protons. These NOE effects would not be possible if the trifluoromethyl group were located at C-7. In

aqueous HCl (pH 1), compound **24** shows absorbances at λ_{max} 397 nm (log ϵ 3.91), 265 (4.21), and 202 (4.25), while in aqueous NaOH (pH 13), it displays λ_{max} values at 325 (4.01), 275 (3.96), 253 (4.19), and 215 (4.31). These data are in agreement with structure **24** under acidic conditions, and indicate that **24** undergoes covalent hydration and deprotonation under basic conditions to give anion **34**. A careful titration in phosphate buffer indicated that equal amounts of **24** and **34** are present at pH 7.05. In methanol containing a small amount of HCl, the ^{19}F NMR spectrum of **24** shows a singlet at δ 10.3 downfield from trifluoroacetic acid, while in the presence of a small amount of sodium hydroxide, the signal at δ 10.3 is replaced by one at 9.3, indicating conversion to **34**. This ^{19}F NMR data indicates that the trifluoromethyl group is located at C-6, since if it were at C-7 it would be located on an sp^3-hybridized carbon atom in the anion and should therefore appear upfield from trifluoroacetic acid near δ −4.7, as the C-7 trifluoromethyl group does in the covalently hydrated lumazine **35**.[5]

The structure of **26** has been assigned by comparison of its spectral data with that of **24**. Since the singlet at δ 12.2 downfield from trifluoroacetic acid did not shift in 1 N HCl acid versus 0.25 N NaOH, even though the UV data for **26** were similar to that of **24**, the trifluoromethyl group in **26** must also be located at C-6. There was no evidence for the formation of 7-(trifluoromethyl)lumazines in reactions involving **23** and **25**.

It is of interest that in reactions producing 8-benzyl-6-(trifluoromethyl)lumazine (**24**) and 8-(2-hydroxyethyl)-6-(trifluoromethyl)lumazine (**26**), none of the corresponding 7-trifluoromethyl compounds were isolated. If 8-benzyl-7-(trifluoromethyl)lumazine were formed from **23**, its precursor would be **36**, and compound **36** can be obtained by conducting the reaction between **3** and **23** in a mixture of water and DMF under acidic conditions instead of in DMF. The ^{19}F NMR spectrum of **36** shows a singlet at δ −5.45, upfield from trifluoroacetic acid, indicating that the trifluoromethyl group is attached to an sp^3-hybridized carbon atom. In addition, the ^1H NMR spectrum of **36** shows the signal of the benzyl protons as a doublet due to coupling to the N–H proton, indicating the presence of a secondary amine. The doublet collapsed to a singlet after D_2O exchange. The CIMS spectrum of **36** showed an ion derived from protonation of **37**, which evidently forms in the mass spectrometer probe. When **36** was dissolved in DMF, a large number of decomposition products resulted and the 8-benzyl-7-(trifluoromethyl)lumazine was not formed. This observation may explain why the 6-(trifluoromethyl)lumazines **24** and **26** are isolated in only 17% and 26% yield, respectively, and why the 7-(trifluoromethyl)lumazines are not produced in the reactions involving **23** and **25**.

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt or Mel-Temp apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian FT-80 80-MHz spectrometer in $CDCl_3$, except where noted. The 300-MHz spectra of **16** and **17** were recorded on a GE QE 300 NMR instrument. ^{19}F NMR spectra were obtained on a Perkin-Elmer R-32 instrument operating at 84.6 MHz. ^{19}F NMR chemical shifts are reported relative to trifluoroacetic acid as external standard. ^{13}C NMR spectra were recorded on a Chemagnetics spectrometer operating at 50 MHz. ^1H NOE effects were measured on a Varian XL-200 200-MHz spectrometer. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Analytical thin-layer chromatography was performed on Baker-flex silica gel 1B2-F sheets. Microanalyses were obtained from the Purdue Microanalytical Laboratory. The mass spectra were determined on a Finnigan 4000 spectrometer using an ionization potential of 70 eV. The chemical ionization mass spectra (CIMS) were obtained by using methane, 2-methylpropane, or ammonia as the reagent gas, as noted. High-resolution mass spectra were determined on a Kratos MS50 spectrometer.

6,7-Dichloro-2-(trifluoromethyl)quinoxaline (7). 3,3-Dibromo-1,1,1-trifluoroacetone (**1**, 600 mg, 2.2 mmol) was added to a solution of sodium acetate (720 mg, 8.8 mmol) in water (4 mL). The solution was heated at 98 °C for 30 min. After the solution was cooled to room temperature, a suspension of 4,5-dichloro-*o*-phenylenediamine (**6**, 200 mg, 1.12 mmol) in methanol (4 mL) was added, and the mixture was stirred at room temperature for 18 h. The crude product (300 mg) was filtered and washed with water (10 mL). Sublimation of this solid at 50 °C (0.5 mmHg) gave a white crystalline compound **7** (230 mg, 83%): mp 110–112 °C; UV λ_{max} (methanol) 330 (log ϵ 3.82), 242 (4.56), 209 nm (4.53); IR (KBr) 3060, 3040, 1445, 1430, 1325, 1215, 1160, 1150, 1130, 1095, 1060, 940, 915, 885, 735 cm^{-1}; ^1H NMR (80 MHz) δ 9.16 (s, 1 H), 8.36 (s, 2 H); ^{19}F NMR ($CHCl_3$) δ 11.7 (s, 3 F); CIMS (NH_3 ionizing gas), *m/e* (relative intensity) 270 (M^+ + 3, 8), 268 (M^+ + 1, 12), 250 (10), 248 (31), 69 (100). Anal. Calcd for $C_9H_3Cl_2F_3N_2$: C, 40.45; H, 1.12; Cl, 26.59; F, 21.35; N, 10.49. Found: C, 40.61; H, 0.93; Cl, 26.20; F, 21.09; N, 10.60.

6,7-Dimethyl-2-(trifluoromethyl)quinoxaline (9). 3,3-Dibromo-1,1,1-trifluoroacetone (**1**, 1.00 g, 3.7 mmol) was added to a solution of sodium acetate (1.30 g, 15.8 mmol) in water (6 mL). The solution was heated at 98 °C for 30 min. After the solution was cooled to room temperature, a suspension of 4,5-dimethyl-*o*-phenylenediamine (**8**, 250 mg, 1.8 mmol) in methanol (4 mL) was added, and the mixture was stirred at room temperature for 18 h. The crude product (314 mg) was filtered and washed with water (10 mL). Sublimation of this solid at 40 °C (0.5 mmHg) gave a white crystalline compound **9** (235 mg, 57%): mp 81.5–82.5 °C; UV (methanol) λ_{max} 326 (log ϵ 3.93), 242 (4.50), 206 nm (4.45); IR (KBr) 2900, 1470, 1450, 1330, 1220, 1200, 1150, 1120, 1100, 1060, 1000, 980, 860, 745, 680 cm^{-1}; ^1H NMR (80 MHz) δ 9.06 (s, 1 H), 7.94 (s, 2 H), 2.54 (s, 6 H); ^{19}F NMR ($CHCl_3$) δ 12.3 (s, 3 F); CIMS (CH_4 ionizing gas), *m/e* (relative intensity) 255 (M^+ + 29, 22), 227 (M^+ + 1, 100), 207 (63). Anal. Calcd for $C_{11}H_9F_3N_2$: C, 58.41; H, 3.98; F, 25.22; N, 12.39. Found: C, 58.69; H, 3.92; F, 24.94; N, 12.52.

2-(Trifluoromethyl)benzo[*g*]quinoxaline (11). 3,3-Dibromo-1,1,1-trifluoroacetone (**1**, 600 mg, 2.2 mmol) was added to a solution of sodium acetate (720 mg, 8.8 mmol) in water (4 mL). The solution was heated at 98 °C for 30 min. After the solution was cooled to room temperature, a suspension of naphthalene-2,3-diamine (**10**, 200 mg, 1.2 mmol) in methanol (3 mL) was added, and the mixture was stirred at room temperature for 18 h. The yellow product was filtered and washed with water (10 mL). Recrystallization of the crude product from hexane afforded compound **11** (240 mg, 76%) as yellow crystals: mp 141–143 °C; UV (methanol) λ_{max} 368 (log ϵ 3.73), 352 (3.59), 269 (4.87), 226 nm (4.68); IR (KBr) 3040, 1400, 1350, 1325, 1220, 1180, 1150, 1120, 1050, 950, 900, 860, 730, 670 cm^{-1}; ^1H NMR (80 MHz) δ 9.18 (s, 1 H), 8.81 (s, 2 H), 8.16 (dd, 2 H, *J* = 3 and 6 Hz), 7.66 (dd, 2 H, *J* = 3 and 7 Hz); ^{19}F NMR ($CDCl_3$) δ 11.6 (s, 3 F); CIMS (CH_4 ionizing gas), *m/e* (relative intensity) 227 (M^+ + 29, 12), 249 (M^+ + 1, 100), 229 (29). Anal. Calcd for $C_{13}H_7F_3N_2$: C, 62.90; H, 2.82; F, 22.99; N, 11.29. Found: C, 63.13; H, 2.59; F, 22.67; N, 11.59.

6-Benzoyl-2-(trifluoromethyl)quinoxaline (13). 3,3-Dibromo-1,1,1-trifluoroacetone (**1**, 1.20 g, 4.4 mmol) was added to a solution of sodium acetate (1.80 g, 22 mmol) in water (10 mL). The solution was heated at 98 °C for 30 min. After the solution was cooled to room temperature, a solution of 3,4-diaminobenzophenone (**12**, 500 mg, 2.3 mmol) in methanol (6 mL) was added, and the mixture was stirred at room temperature for 18 h. The light brown product (800 mg) was filtered, washed with water (20 mL), and dried. It was then chromatographed on a silica gel column (150 g, 60–200 mesh, 4.1 × 30 cm), eluting with ethyl acetate–hexane (1:20), to afford isomer **13** (370 mg, 52%) as the less polar compound. The analytical sample was recrystallized from ethyl acetate–hexane: mp 115–116 °C; UV (methanol) λ_{max} 320 (log ϵ 3.67), 251 (4.52), 203 nm (4.52); IR (KBr) 3020, 1650, 1580, 1430, 1330, 1280, 1250, 1220, 1180, 1120, 1060, 950, 920, 870, 820, 770, 710, 680 cm^{-1}; ^1H NMR (80 MHz) δ 9.26 (s, 1 H), 8.56

(s, 1 H), 8.35 (d, 2 H, J = 1 Hz), 7.93–7.52 (m, 5 H); ^{19}F NMR ($CHCl_3$) δ 11.7 (s, 3 F); CIMS (CH_4 ionizing gas), m/e (relative intensity) 303 (M^+ + 1, 100), 283 (40). Anal. Calcd for $C_{16}H_9F_3N_2O$: C, 63.58; H, 2.98; F, 18.87; N, 9.27. Found: C, 63.89; H, 2.86; F, 18.83; N, 9.54.

7-Benzoyl-2-(trifluoromethyl)quinoxaline (14). The more polar compound (239 mg, 34%) from above was recrystallized from ethyl acetate–hexane: mp 108–110 °C; UV (methanol) λ_{max} 320 (log ϵ 3.79), 252 (4.66), 203 nm (4.67); IR (KBr) 3040, 1650, 1585, 1440, 1320, 1270, 1220, 1170, 1140, 1100, 1055, 950, 920, 870, 840, 780, 730, 700, 690 cm^{-1}; ^{1}H NMR (80 MHz) δ 9.23 (s, 1 H), 8.53 (s, 1 H), 8.34 (s, 2 H), 7.91–7.48 (m, 5 H); ^{19}F NMR ($CHCl_3$) δ 11.7 (s, 3 F); CIMS (CH_4 ionizing gas), m/e (relative intensity) 303 (M^+ + 1, 100), 283 (10). Anal. Calcd for $C_{16}H_9F_3N_2O$: C, 63.58; H, 2.98; F, 18.87; N, 9.27. Found: C, 63.93; H, 3.00; F, 19.18; N, 9.12.

7-(Trifluoromethyl)pteridine-2,4(1*H*,3*H*)-dione (16). 3,3-Dibromo-1,1,1-trifluoroacetone (1, 2.82 g, 10.46 mmol) was added to a solution of sodium acetate (3.00 g, 36.5 mmol) in water (20 mL). The solution was heated at 98 °C for 30 min. The solution was cooled to room temperature, diluted with water (10 mL), and extracted with ether (4 × 50 mL). The ether extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum to obtain a yellow liquid. DMF (4 mL) was added, and the solution was added to a suspension of 5,6-diaminopyrimidine-2,4-(1*H*,3*H*)-dione (15, 497 mg, 3.5 mmol) in DMF (4 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated on a rotary evaporator (bath 70 °C) to a volume of 2 mL. The concentrated mixture was applied to a column of alumina (Sigma, neutral, type WN-6, activity grade super 1, 40 g, 2 × 15.5 cm), eluting with water. The fractions containing green fluorescent material under 366-nm UV light were concentrated to yield a mixture of products 16 and 17 (495 mg, 61%) as a yellow solid. The ratio of the products was estimated to be 32:68 by ^{19}F NMR. A small sample of the mixture was separated by preparative HPLC (Econosphere C-18 column, 5 μm, 22 × 250 mm, detecting at 340 nm), eluting with 8% acetonitrile. The major component 16, which eluted second, was recrystallized from water: mp >310 °C; UV (aqueous HCl, pH 1) λ_{max} 331 (log ϵ 3.65), 233 nm (3.88); UV (aqueous NaOH, pH 12) λ_{max} 378 (log ϵ 3.49), 259 nm (4.02); IR (KBr) 3600–2800, 1730, 1690, 1570, 1510, 1440, 1430, 1400, 1360, 1330, 1270, 1240, 1180, 1150, 1080, 1000, 940, 900, 850, 800, 780, 730, 710 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.95–10.55 (br s, 1 H, exchangeable with D_2O), 8.56 (s, 1 H), 3.85–2.75 (br s, 1 H, exchangeable with D_2O); ^{19}F NMR (water) δ 11.00 (s, 3 F); ^{13}C NMR (DMSO-d_6) δ 159.82 (s), 149.79 (s), 149.09 (s), 144.98 (q, J = 35 Hz), 135.88 (s), 128.02 (s), 121.34 (q, J = 275 Hz); FABMS (glycerol + HCl), m/e (relative intensity) 233 (M^+ + 1, 30); high-resolution FABMS (glycerol + HCl) calcd for $C_7H_4F_3N_4O_2$ m/e 233.0286 (M^+ + 1), found 233.0291.

6-(Trifluoromethyl)pteridine-2,4(1*H*,3*H*)-dione (17). The component of the mixture that eluted first during the HPLC above was the minor isomer 17, which was recrystallized from water: mp 260–262 °C; UV (aqueous HCl, pH 1) λ_{max} 325 (log ϵ 3.79), 233 nm (4.01); UV (aqueous NaOH, pH 12) λ_{max} 371 (log ϵ 3.67), 261 nm (4.18); IR (KBr) 3600–2900, 1740, 1700, 1570, 1510, 1430, 1360, 1320, 1290, 1250, 1200, 1170, 1140, 1100, 1000, 930, 850, 780 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.40–11.55 (br s, 1 H, exchangeable with D_2O), 9.09 (s, 1 H), 2.93–3.75 (br s, 1 H, exchangeable with D_2O); ^{19}F NMR (water) δ 12.2 (s, 3 F); ^{13}C NMR (DMSO-d_6) δ 160.01 (s), 151.83 (s), 150.07 (s), 144.98 (s), 135.88 (q, J = 35 Hz), 128.02 (s), 121.34 (q, J = 273 Hz); CIMS (NH_3 ionizing gas), m/e (relative intensity) 250 (M^+ + 18, 100); high-resolution CIMS (NH_3 ionizing gas) calcd for $C_7H_7F_3N_5O_2$ m/e 250.0552 (M^+ + 18), found 250.0547.

3-(Trifluoromethyl)pyrido[2,3-*b*]pyrazine (19). 3,3-Dibromo-1,1,1-trifluoroacetone (1, 1.20 g, 4.4 mmol) was added to a solution of sodium acetate (1.44 g, 17.6 mmol) in water (8 mL). The solution was heated at 98 °C for 30 min. After the solution was cooled to room temperature, a suspension of pyridine-2,3-diamine (18, 250 mg, 2.3 mmol) in methanol (5 mL) was added, and the mixture was stirred at room temperature for 24 h. The brown product 19 (295 mg, 64%) was filtered, washed with water (10 mL), and dried. The filtrate, which contained both 19 and 20, was extracted with $CHCl_3$ (3 × 10 mL). The chloroform extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum to obtain a brown residue that was chromatographed on a silica gel column (15 g, 60-200 mesh, 2 × 12.5 cm), eluting with ethyl acetate–hexane (1:4), to afford the less polar compound 19 (45 mg, 10%, total yield 74%), the more polar compound 20 (20 mg, 4%), and a mixture of 19 and 20 (20 mg). The analytical sample of 19 was recrystallized from hexane–$CHCl_3$: mp 121.5–123 °C; UV (methanol) λ_{max} 317 (log ϵ 4.06), 311 (3.97), 305 (3.95), 265 (3.44), 206 nm (4.29); IR (KBr) 1585, 1540, 1470, 1430, 1380, 1350, 1310, 1195, 1180, 1160, 1130, 1060, 1010, 930, 770, 750, 720 cm^{-1}; ^{1}H NMR (200 MHz) δ 9.27 (m, 1 H), 9.24 (s, 1 H), 8.55 (dd, J = 2 and 8 Hz), 7.85 (dd, 1 H, J = 4 and 8 Hz); ^{19}F NMR ($CDCl_3$) δ 11.8 (s, 3 F); ^{13}C NMR ($CDCl_3$) δ 155.91 (s), 148.56 (s), 144.85 (q, J = 36 Hz), 141.70 (s), 139.39 (s), 139.16 (s), 127.12 (s), 120.27 (q, J = 276 Hz); CIMS (CH_4 ionizing gas), m/e (relative intensity) 228 (M^+ + 29, 8), 200 (M^+ + 1, 100), 180 (12). Anal. Calcd for $C_8H_4F_3N_3$: C, 48.23; H, 2.03; F, 28.64; N, 21.11. Found: C, 47.94; H, 1.89; F, 28.89; N, 20.94.

2-(Trifluoromethyl)pyrido[2,3-*b*]pyrazine (20). The more polar compound 20 from above was recrystallized from hexane: mp 104.5–105.5 °C; UV (methanol) λ_{max} 318 (log ϵ 4.04), 311 (3.95), 305 (3.93), 263 (3.45), 206 nm (4.27); IR (KBr) 3080, 2920, 1600, 1560, 1480, 1470, 1400, 1350, 1340, 1280, 1230, 1080, 1060, 1020, 950, 920, 890, 800, 730, 680 cm^{-1}; ^{1}H NMR (200 MHz) δ 9.35 (s, 1 H), 9.29 (m, 1 H), 8.55 (dd, 1 H, J = 2 and 8 Hz), 7.82 (dd, 1 H, J = 4 and 8 Hz); ^{19}F NMR ($CDCl_3$) δ 12.1 (s, 3 F); ^{13}C NMR ($CDCl_3$) δ 156.66 (s), 151.41 (s), 143.85 (s), 143.80 (q, J = 36 Hz), 138.93 (s), 136.52 (s), 126.69 (s), 120.62 (q, J = 276 Hz); CIMS (NH_3 ionizing gas), m/e (relative intensity) 217 (M^+ + 18, 13), 200 (M^+ + 1, 70), 69 (100). Anal. Calcd for $C_8H_4F_3N_3$: C, 48.23; H, 2.03; F, 28.64; N, 21.11. Found: C, 48.38; H, 1.74; F, 28.53; N, 20.98.

2-(Trifluoromethyl)pyrido[3,4-*b*]pyrazine (22). 3,3-Dibromo-1,1,1-trifluoroacetone (1, 1.20 g, 4.4 mmol) was added to a solution of sodium acetate (1.44 g, 17.6 mmol) in water (8 mL). After the solution was cooled to room temperature, a solution of pyridine-3,4-diamine (21, 218 mg, 2 mmol) in methanol (4 mL) was added, and the mixture was then heated at 70 °C for 6 h. It was then cooled to room temperature and extracted with $CHCl_3$ (3 × 10 mL). The $CHCl_3$ extracts were dried ($MgSO_4$), filtered, and evaporated to give a brown residue. Recrystallization of the product from hexane gave faint yellow crystals of the product 22 (144 mg, 36%): mp 61–62 °C; UV (methanol) 315 (log ϵ 3.34), 230 nm (4.21); IR (KBr) 3040, 1580, 1470, 1440, 1330, 1200, 1180, 1130, 1060, 950, 820, 720, 680 cm^{-1}; ^{1}H NMR (80 MHz) δ 9.69 (d, 1 H, J = 1 Hz), 9.29 (s, 1 H), 8.98 (d, 1 H, J = 6 Hz), 8.08 (dd, J = 1 and 6 Hz); ^{19}F NMR ($CHCl_3$) δ 11.25 (s, 3 F); CIMS (NH_3 ionizing gas) m/e (relative intensity) 217 (M^+ + 18, 1), 200 (M^+ + 1, 6), 69 (100). Anal. Calcd for $C_8H_4F_3N_3$: C, 48.23; H, 2.03; N, 21.11; F, 28.64. Found: C, 48.05; H, 1.69; N, 20.85; F, 28.31.

8-Benzyl-6-(trifluoromethyl)pteridine-2,4(3*H*,8*H*)-dione (24). 3,3-Dibromo-1,1,1-trifluoroacetone (1, 600 mg, 2.2 mmol) was added to a solution of sodium acetate (720 mg, 8.8 mmol) in water (5 mL). The solution was heated at 98 °C for 30 min. The solution was cooled to room temperature, diluted with water (10 mL), and extracted with ether (4 × 50 mL). The ether extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum to obtain a yellow liquid. To this liquid was added DMF (2 mL), and the resulting solution was added to a suspension of 5-amino-4-(benzylamino)uracil hydrochloride[8] (23, 268 mg, 1.0 mmol) in DMF (6 mL). The reaction mixture was stirred at room temperaure for 24 h before the solvent was removed under vacuum (0.5 mmHg). The dark red, semisolid residue was triturated with water (3 mL) at 98 °C for 3 min. The solid was filtered, dried, and chromatographed on a column of silica gel (15 g, 60–200 mesh, 2 × 12.5 cm), eluting with CH_2Cl_2–CH_3CN (4:1). Evaporation of solvent from fractions containing 24 gave this substance as a yellow solid (55 mg, 17%). The analytical sample was recrystallized from $CHCl_3$: mp 226–228 °C; UV (aqueous HCl, pH 1) λ_{max} 397 (log ϵ 3.91), 265 (4.21), 202 nm (4.25); UV (aqueous NaOH, pH 13) λ_{max} 325 (log ϵ 4.01), 275 (3.96), 253 (4.19), 215 nm (4.31); IR (KBr) 3600–2800, 1700, 1620, 1550, 1440, 1400, 1360, 1335, 1260, 1190, 1140, 1020, 800, 750, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200

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MHz) δ 11.50 (s, 1 H), 8.92 (s, 1 H), 7.59–7.37 (m, 5 H), 5.68 (s, 2 H); ^{19}F NMR (Me_2CO) δ 10.8 (s, 3 F); ^{13}C NMR (DMSO-d_6) δ 159.08 (s), 155.04 (s), 152.18 (s), 139.11 (s), 135.47 (s), 13.97 (s), 128.53-128.15 (m, Ar), 126.77 (q, J = 38 Hz), 121.11 (q, J = 270 Hz), 54.55 (s); CIMS (NH_3 ionizing gas), m/e (relative intensity) 340 (M^+ + 18, 71), 323 (M^+ + 1, 90), 250 (100); high-resolution CIMS (i-C_4H_{10} ionizing gas), calcd for $C_{14}H_9F_3N_4O_2$ 322.0677 (M^+), found 322.0678.

8-(2-Hydroxyethyl)-6-(trifluoromethyl)pteridine-2,4-(3*H*,8*H*)-dione (26). 3,3-Dibromo-1,1,1-trifluoroacetone (1, 300 mg, 1.1 mmol) was added to a solution of sodium acetate (360 mg, 4.4 mmol) in water (4 mL). The solution was heated at 98 °C for 30 min. The solution was cooled to room temperature, diluted with water (10 mL), and extracted with ether (3 × 40 mL). The ether extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum to obtain a yellow liquid. DMF (1 mL) was added, and the resulting solution was added to a suspension of 5-amino-4-[(2-hydroxyethyl)amino]uracil hydrochloride[8] (**25**, 110 mg, 0.5 mmol) in DMF (1.5 mL). The reaction mixture was stirred at room temperature for 24 h before it was filtered. The filtrate was evaporated under vacuum (0.5 mmHg). The dark red, semisolid residue was triturated with water (1 mL) at 98 °C for 3 min. The solution was stored at 0 °C overnight before the solid product was filtered. It was then chromatographed on a column of silica gel (15 g, 60–200 mesh, 2 × 12.5 cm), eluting with CH_2Cl_2–CH_3CN (3:1). Evaporation of solvent from fractions containing **26** gave this substance as a yellow solid (35 mg, 26%). The analytical sample was recrystallized from Me_2CO–hexane: mp 226–228 °C dec; UV (aqueous HCl, pH 1) λ_{max} 396 (log ε 3.45), 335 (3.19), 266 nm (4.07); UV (aqueous NaOH, pH 13) λ_{max} 326 (log ε 3.73), 250 (3.95), 219 nm (4.01); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 11.45 (s, 1 H), 8.83 (s, 1 H), 4.94–3.40 (m, 4 H); ^{19}F NMR (water) δ 12.25 (s, 3 F); ^{13}C NMR (DMSO-d_6) δ 159.21 (s), 155.09 (s), 152.16 (s), 138.01 (s), 136.73 (s), 126.26 (q, J = 38 Hz), 121.23 (q, J = 271 Hz), 56.71 (s), 54.85 (s); CIMS (NH_3 ionizing gas), m/e (relative intensity) 294 (M^+ + 18, 62), 277 (M^+ + 1, 26), 250 (100); high-resolution CIMS (NH_3 ionizing gas), calcd for $C_9H_{11}F_3N_5O_3$ m/e 294.0814 (M^+ + 18), found 294.0811.

Compound 36. 3,3-Dibromo-1,1,1-trifluoroacetone (1, 300 mg, 1.1 mmol) was added to a solution of sodium acetate (360 mg, 4.4 mmol) in water (4 mL). The solution was heated at 98 °C for 30 min. After the solution was cooled to room temperature, the pH was adjusted to 1.5 with 2 N HCl. The solution was cooled on an ice–salt bath (−10 °C) and a suspension of 5-amino-4-(benzylamino)uracil hydrochloride (**23**, 78 mg, 0.3 mmol) in DMF (1.5 mL) was added. The mixture was stirred for 30 min. The yellow solid that formed was filtered, washed with cold water (3 mL), and dried to yield compound **36** (45 mg, 75% crude yield): mp 208–210 °C dec; IR (KBr) 3600–2850, 1700, 1610, 1410, 1300, 1180, 1100, 950, 850, 750, 680 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.90 (br s, 1 H, exchangeable with D_2O), 10.55 (s, 1 H, exchangeable with D_2O), 9.05 (s, 1 H), 8.60 (s, 1 H, exchangeable with D_2O), 7.35 (m, 5 H), 4.70 (d, 2 H); ^{19}F NMR (DMSO-d_6) δ −5.45 (s, 3 F); CIMS (i-C_4H_{10} ionizing gas), m/e (relative intensity) 341 (M^+ − 17, 71), 323 (M^+ − 35, 20), 233 (M^+ − 125, 100); high-resolution CIMS (i-C_4H_{10} ionizing gas), calcd for $C_{14}H_{11}F_3N_4O_3$ m/e 340.0783 (M^+ − 18), found 340.0784.

X-ray Analysis of 13. Crystal Data. Compound **13**: $C_{16}H_9F_3N_2O$, fw = 302; monoclinic; a = 12.419 (6) Å, b = 6.911 (4) Å, c = 17.318 (7) Å, β = 116.19 (3)°, V = 1334 (1) Å^3, z = 4, ρ_{calcd} = 1.50 g/cm^3, $F(000)$ = 616, μ(Cu Kα) = 9.68, space group $P2_1/c$ from systematic absences.

Data Collection. Crystallographic data were collected by using Cu Kα X-rays and a monochromater on a Nicolet P3 four-circle diffractometer, with the θ–2θ scan technique out to a 2θ of 116.0°. A variable scan rate was used with a maximum of 29.30°/min, and a minimum of 7.23°/min. The scan range was from 1.2° < $K\alpha_1$ to 1.2° > $K_{\alpha 2}$; the time that backgrounds at both ends of the scan range were counted was equivalent to the scan time. Three standard reflections were measured every 50 reflections.

Structure Analysis. Of the 2086 reflections collected 182 were rejected as systematically absent, leaving 1828 unique reflections, of which 1306 met the condition $F_o > 5\sigma(F_o)$ and were considered observed. The structure was solved by using the MULTAN80 program and refined by SHELX76 to a final R of 0.1315 with the hydrogens fixed in their calculated positions.

The high R value is due to the fact that the three fluorines off C(22) could not be exactly positioned. Attempts to refine the peaks originally assigned as fluorines led to the atomic positions and temperature factors shown in Tables I and II of the supplementary material for the microfilm edition. The final difference map showed two peaks (1.38 and 0.95 e$^-$/Å^3), which were within fluorine bonding distance of C(22).

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Registry No. **1**, 431-67-4; **2**, 91944-47-7; **6**, 5348-42-5; **7**, 115652-57-8; **8**, 3171-45-7; **9**, 115652-58-9; **10**, 771-97-1; **11**, 115652-59-0; **12**, 39070-63-8; **13**, 115652-60-3; **14**, 115652-61-4; **15**, 3240-72-0; **16**, 115652-62-5; **17**, 115652-63-6; **18**, 452-58-4; **19**, 115652-64-7; **20**, 115652-65-8; **21**, 54-96-6; **22**, 115652-66-9; **23**, 107643-81-2; **24**, 115677-98-0; **25**, 17801-78-4; **26**, 115677-99-1; **36**, 115652-67-0.

Supplementary Material Available: Tables of atomic positions, temperature factors, bond lengths, bond angles, and an ORTEP drawing of structure **13** (5 pages). Ordering information is given on any current masthead page.