Synthesis of Bis(trifluoromethylated) Pyrazine-containing Nitrogen Heterocycles from Hexafluorobiacetyl and *ortho*-Diamines. Stabilization of the Covalent Dihydrates of Pteridines and Pyrido[3,4-*b*]pyrazines by Trifluoromethyl Groups

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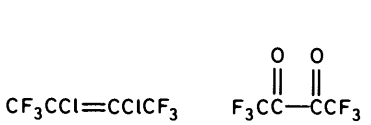
An investigation of the structures of the reaction products derived from perfluorobutane-2,3-dione (PFBD) and a variety of *ortho*-diamines has been undertaken with the aim of determining the extent to which trifluoromethyl groups stabilize covalently bound hydrates. The substituted quinoxalines as well as the pyrido[2,3-*b*]pyrazine (**25**) and the lumazines (**27**), (**29**), and (**31**) were all found to exist as completely dehydrated aromatic species. Depending on the reaction conditions, both the aromatic form (**33**) and the stable, neutral covalent dihydrate form (**34**) could be obtained from the reaction of PFBD with 4,5-diamino-6-hydroxypyrimidinium sulphate (**32**). The pyrido[3,4-*b*]pyrazine system (**36**) as well as the pteridine (**38**) were also found to exist as stable, neutral covalent dihydrates in which the pyrazine ring is selectively hydrated.

Since the report of its preparation from the chromic acid oxidation of 2,3-dichloro-1,1,1,4,4,4-hexafluorobut-2-ene (**1**) by Moore and Clark in 1965, perfluorobutane-2,3-dione (**2**) (PFBD) has proved to be a highly reactive compound which is prone to unusual chemistry.[1] For example, instead of the 'normal' reaction to afford perfluorobutane, PFBD reacts with sulphur tetrafluoride to give the spirosulphurane (**3**),[2] and its reaction with three-co-ordinate phosphorus compounds has yielded a variety of substituted dioxaphospholenes of general structure (**4**) which have been studied extensively in relation to the stereochemical problems posed by phosphoranes.[3] Radical anions result from the reduction of compound (**2**) with a platinum electrode, alkali metal t-butoxides in Me_2SO, iodide, bromide, or alkali metals such as sodium, lithium, potassium, or caesium.[4] The photodecomposition of PFBD produces carbon monoxide and perfluoroethane,[5] and the competing 1,2- and 1,4-photochemical additions of PFBD to 1,2-difluoroethylene have also been reported.[6] A diastereoisomeric mixture of dioxanes (**5**) results from the reaction of PFBD with ethylene glycol dimethanesulphonate in the presence of fluoride ion.[7]

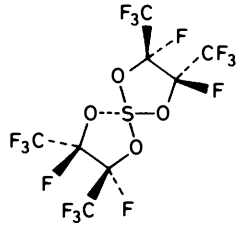
Although the preparation of 2,3-bis(trifluoromethyl)quinoxaline (**7**) (Table) from the reaction of PFBD with *o*-phenylenediamine (**6**) was briefly mentioned (no yield reported) in the publication describing the original PFBD preparation, the potential utility of this reaction in the preparation of an array of fluorinated nitrogen heterocyclic compounds containing the pyrazine moiety has not been previously explored.

A variety of aromatic nitrogen heterocyclic systems, including pteridines,[8] naphthyridines,[9] quinazolines,[10] 1,3-*x*-triazanaphthalenes,[11] pyrazinopyridines,[12] and pyrimido[5,4-*e*]-*as*-triazines[13] are known to exist in aqueous solution partially as unstable, covalently bound hydrates derived from the addition of water across C=N bonds.[14] The protonated forms of these hydrates are known to be significantly more stable than the neutral species, which readily dehydrate to form aromatic substances.[14] The initial carbinolamine adducts formed from the reaction of α-fluoro ketones with primary amines are unusually stable toward dehydration because of the high electronegativity of fluorine.[15] The possibility therefore exists that the reaction of PFBD with *ortho*-diamines might be expected to provide novel covalently bound hydrates (carbinolamines) of sufficient stability to allow isolation and characterization of the neutral species. On the other hand, it may also be argued that the greater steric bulk of a trifluoromethyl group relative to hydrogen would destabilize the covalent hydrate form and accelerate dehydration to generate the aromatic species. Indeed, the insertion of a methyl group at the site where nucleophilic attack (by ^-OH or H_2O) occurs during hydration of the aromatic forms greatly hinders the addition of water, and this 'blocking effect' of a methyl group has been utilized to diagnose the location of covalent hydration in a variety of aromatic nitrogen heterocyclic systems.[14a] A major objective of the present study was therefore to determine which types of reaction products derived from PFBD and *ortho*-diamines would exist as stable, covalently bound hydrates and which would aromatize by dehydration. It has already been demonstrated that electronegative substituents located in the 4-position of certain pteridines stabilize the covalent hydrate forms of these systems to the extent that they may be isolated as relatively stable solids.[16–21] The factors which may be utilized



(**1**)

(**2**)



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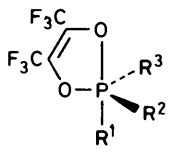

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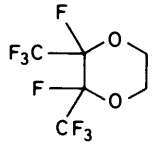
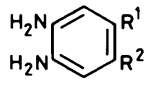
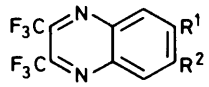
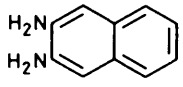
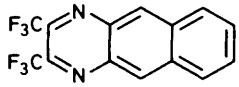
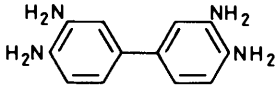
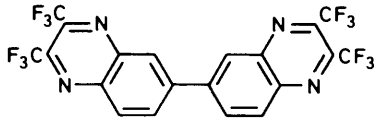
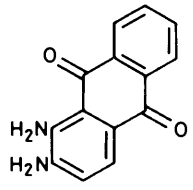
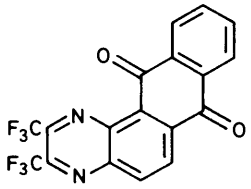
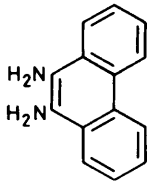
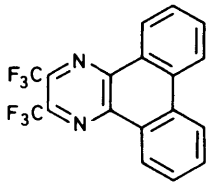


(**5**)

Table. The reaction of perfluorobutane-2,3-dione with *ortho*-diamines

Reactant	Product	% Yield isolated
		
(6) $R^1 = R^2 = H$	(7) $R^1 = R^2 = H$	21
(8) $R^1 = R^2 = Me$	(9) $R^1 = R^2 = Me$	71
(10) $R^1 = COH, R^2 = H$	(11) $R^1 = CO_2H, R^2 = H$	33
(12) $R^1 = R^2 = Cl$	(13) $R^1 = R^2 = Cl$	74
14 $R^1 = Bz, R^2 = H$	(15) $R^1 = Bz, R^2 = H$	78
 (16)	 (17)	54
 (18)	 (19)	35
 (20)	 (21)	76
 (22)	 (23)	57

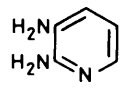
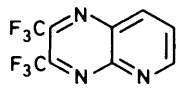
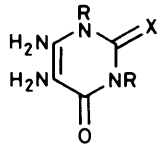
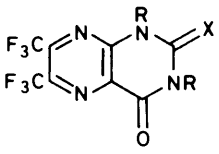
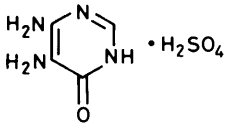
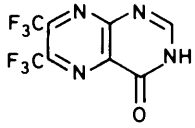
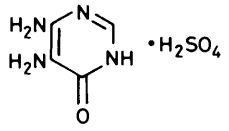
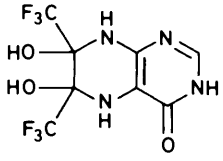
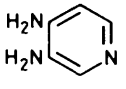
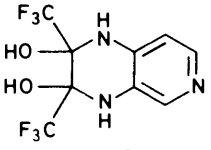
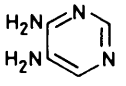
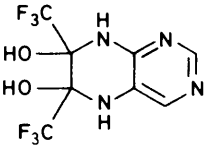
to stabilize the unstable covalent hydrate forms of aromatic nitrogen heterocyclic systems are of interest because of the important roles these substances play in certain biochemical transformations and also in natural product chemistry.[14a,d]†

Results and Discussion

The PFBD (2) used in this investigation was prepared by the chromic acid oxidation of the alkene (1) according to the original procedure[1a] as modified by Ramirez *et al.*[3a] This gave acceptable yields of PFBD, δ_F 3.20 (CF_3CO_2H = 0), accompanied by small amounts of an impurity which produced a singlet at δ 0.87 in the ^{19}F n.m.r. spectrum of the product. This impurity was identified as trifluoroacetyl chloride on the basis of its known formation during the oxidation of the starting material (1)[1b] and the fact that trifluoroacetyl chloride has previously been reported to display a singlet δ 0.7 p.p.m. downfield from trifluoroacetic acid in the ^{19}F n.m.r. spectra of mixtures containing both compounds.[23] No impurities were detected by ^{19}F n.m.r. spectroscopy in PFBD obtained by heating DMF solutions of the diastereoisomeric mixture of cyclic sulphates (39) which was obtained as a by-product during the chromic acid oxidation of compound (1).[1b] However, from the practical standpoint, the small amount of trifluoroacetyl chloride present in the 'impure' PFDB did not pose a problem during reactions with *ortho*-diamines, as similar results were

† A covalent hydrate or a closely related species derived from 6,7-dimethyl-8-ribityl-lumazine has been postulated as an intermediate in the biosynthesis of riboflavin.[22]

Table (cont.)

 (24)	 (25)	66
 (26) R = Me, X = O (28) R = H, X = O (30) R = H, X = S	 (27) R = Me, X = O (29) R = H, X = O (31) R = H, X = S	67 36 85
 (32)*a*	 (33)	90
 (32)*b*	 (34)	47
 (35)	 (36)	20
 (37)	 (38)	9

[a] The reaction was run in DMF. [b] The reaction was performed in a mixture of DMF and 5% aq. $NaHCO_3$.

obtained with samples derived from either source. PFBD, which boils at 20 °C, may be conveniently used and stored in DMF solution.

The results are summarized in the Table. The substituted quinoxalines (**7**), (**9**), (**11**), (**13**), (**15**), (**17**), (**19**), (**21**), and (**23**), as well as the pyrazine (**25**) and the lumazines (**27**), (**29**), and (**31**) were all found to exist as dehydrated aromatic species. These substances all displayed ^{19}F n.m.r. spectra in which the trifluoromethyl groups either appeared as two quartets (J 12 Hz) or as a singlet or a symmetrical multiplet in the region δ 10.3—15.2 p.p.m. downfield from CF_3CO_2H, which is consistent with their attachment to sp^2 hybridized carbon atoms. The u.v. spectra were all in agreement with molecules containing completely aromatic pyrazine rings. The electron impact mass spectra of these substances all had characteristic peaks at m/z 69 and at $M^+ - 69$, corresponding to the loss of trifluoromethyl cation and radical, respectively, from the parent radical cation.[24] The chemical ionization mass spectra consistently indicated the loss of HF from the $(M^+ + 1)$ ion. All of the compounds prepared in this study produced an intense band located between 1 145 and 1 190 cm^{-1} in the i.r. spectra, which is attributed to an asymmetric CF_3 stretching mode.[25]

In order to estimate the effect which two trifluoromethyl groups at C-6 and C-7 have on the acidity of the pteridine-

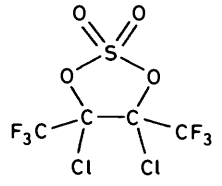
2,4(1*H*,3*H*)-dione system, the pK_a of 6,7-dimethyl-lumazine was compared with that of 6,7-bis(trifluoromethyl)lumazine (**29**). The u.v. spectrum of the anion derived from compound (**29**) displays a maximum at 282 nm, while the anion of 6,7-dimethyl-lumazine absorbs at 272 nm. The neutral molecules are transparent in this region. Spectrophotometric titration of both substances in trisodium citrate–disodium phosphate buffer (20mM) with hydrochloric acid revealed pK_a values of 8.34 and 6.08 for 6,7-dimethyl-lumazine and 6,7-bis(trifluoromethyl)-lumazine, respectively. A pK_a value of 8.40 ± 0.08 was previously recorded for 6,7-dimethyl-lumazine.[26]

The outcome of the reaction between 4,5-diamino-6-hydroxy-pyrimidinium sulphate (**32**) and PFBD was found to depend on the reaction conditions. When the reaction was conducted under anhydrous conditions in DMF, the aromatic species (**33**) was isolated. Utilization of a mixture of DMF and aqueous $NaHCO_3$ led to the covalent dihydrate (**34**), which was isolated as a stable solid. However, treatment of a methanol solution of (**33**) with a large excess of aqueous $NaHCO_3$ at room temperature for 4 days did not result in its conversion into compound (**34**) as evidenced by u.v. spectroscopy. The trifluoromethyl groups of (**34**) appeared in its ^{19}F n.m.r. spectrum as a multiplet at δ_F −1.10 to −1.60 p.p.m. upfield from CF_3CO_2H, supporting their attachment to sp^3 hybridized carbon atoms. In comparison to the u.v. spectrum of (**33**), which displayed maxima at 355 and 251 nm, the spectrum of compound (**34**) showed shorter wavelength maxima at 272 and 212 nm. The covalent attachment of the water in (**34**) was also confirmed by the f.a.b. mass spectrum, which clearly indicated a molecular weight of 320. The reaction mixture that afforded the dihydrate (**34**) also yielded compound (**40**), which is probably derived from ring-opening and hydrolysis of an alternative covalent monohydrate (**41**) formed by addition of water across the C=N bond in the 1,2-position of (**33**).

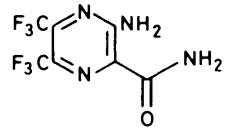
The reaction of pyridine-3,4-diamine (**35**) with PFBD also led to a covalently dihydrated pyrido[3,4-*b*]pyrazine (**36**) as a stable solid material. The dihydrate (**36**) proved to be exceptionally stable during mass spectrometry. The f.a.b. and c.i. mass spectra both showed peaks corresponding to the (M^+ + 1) ion, and even during e.i. mass spectrometry at 70 eV the molecular ion was stable enough for a high resolution mass measurement.[27]

A third example of the stabilization of covalent dihydrates by trifluoromethyl groups was provided by the reaction of pyrimidine-4,5-diamine (**37**) with PFBD, which afforded compound (**38**). The e.i.m.s. of this substance, which displayed an apparent 'molecular ion' at *m/z* 268 (M^+ − 36), is derived from the completely dehydrated aromatic species. The complete loss of water from covalently bound dihydrates during electron impact mass spectrometry is not unexpected and is thought to be largely due to thermal dehydration and partly due to electron impact-induced dehydration.[27] However, the covalently dihydrated pteridine structure of (**38**) was clearly demonstrated by f.a.b. mass spectroscopy, which indicated an (M^+ + 1) ion at *m/z* 305. In common with compounds (**34**) and (**36**), the ^{19}F spectrum of (**38**) showed signals relatively close to the CF_3CO_2H standard. The u.v. spectrum of the product (**38**) was similar to that of the starting material (**37**).

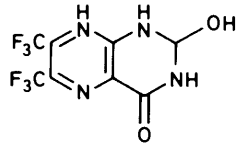
Diastereoisomers are of course possible for the covalently bound dihydrates (**34**), (**36**), and (**38**). The signals for the two trifluoromethyl groups of these substances appear in their ^{19}F n.m.r. spectra as a complex, symmetrical multiplet which displays second-order coupling. However, the fact that these symmetrical multiplets closely resemble those observed for the two trifluoromethyl groups in certain of the aromatic pyrazines in which the signals also appear close together is suggestive that only one of the two possible diastereoisomers of (**34**), (**36**), and (**38**) has been isolated. Also, the presence of only one isomer is evident by t.l.c. However, on the basis of the available evidence it is not apparent which of the two possible diastereoisomers is present. This situation is similar to that previously encountered in the other known pyrazine dihydrates.[17]



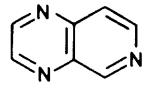
(**39**)



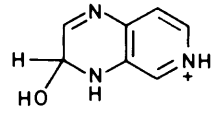
(**40**)



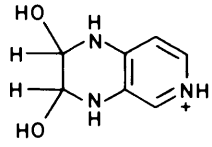
(**41**)



(**42**)



(**43**)

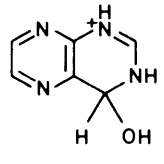


(**44**)

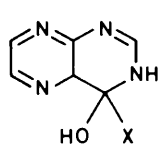
The stable aromatic trifluoromethylated quinoxalines prepared in this study might not be expected to exist as covalent hydrates since quinoxalines in general do not undergo any covalent hydration, even in aqueous acid. A similar argument can be made for compounds (**25**), (**27**), (**29**), and (**31**) since no covalent hydration has been detected in related systems.[28,29] In these cases, the electronegative trifluoromethyl groups do not provide enough stabilization of the intermediate carbinolamines so that they can be isolated as stable substances, and the competing dehydration pathway to form aromatic substances predominates.

The case of compounds (**33**) and (**34**) is of interest because although pteridine forms unstable covalent hydrates which have been detected in aqueous solution,[8] 4-hydroxypteridine is known not to undergo this reaction.[29,30] This was the only case detected in which the two trifluoromethyl groups enabled the isolation of a stable dihydrate of a system which is otherwise devoid of covalent hydration in aqueous solution.

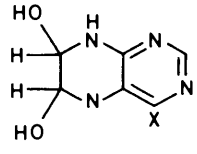
Pyrido[3,4-*b*]pyrazine (1,4,6-triazanaphthalene) (**42**) has been formed in 1M-H_2SO_4 initially as the protonated monohydrate (**43**) and later as the dihydrate (**44**).[31,32] The ratio of the monohydrated to the neutral aromatic species in aqueous solution at equilibrium is 1:10 000.[33] The two trifluoromethyl groups in compound (**36**) result in the formation of a stable neutral dihydrate. None of the monohydrate corresponding to structure (**43**) was detected in the reaction product derived from PFBD and the diamine (**35**).



(**45**)



(**46**)



(**47**)

Acidification of aqueous solutions of pteridine results in the rapid formation of the 3,4-hydrated species (**45**).[34] In this case, the ratio of the neutral hydrate to the neutral aromatic compound at equilibrium is 1:3.45.[34] However, the introduction of electronegative substituents in the 4-position results in formation of stable neutral 3,4-monohydrates (**46**) and 5,6,7,8-dihydrates (**47**), with the ratio being determined by the nature of the substituent (X = CO_2Et, CO_2H, $CONH_2$, CN, CF_3).[16-21] A trifluoromethyl group located at C-4 has been found to sterically hinder attack of water molecules on C-4, so that the pyrazine ring is initially dihydrated to form compound (**47**) (X = CF_3). However, the electronegativity of the CF_3 group stabilizes the 3,4-hydrate so that it is eventually formed as the thermodynamically more stable product (**46**).[18,21] It is therefore not surprising that the introduction of two trifluoromethyl groups into the pyrazine ring of compound (**38**) leads to the isolation of the 5,6,7,8-dihydrated species, which is the initial product and probably also the thermodynamically more stable hydrate formed in the condensation of pyrimidine-5,6-diamine (**37**) with PFBD.

It can be expected that the concept of covalent hydrate stabilization by trifluoromethyl groups will eventually be utilized in the design of riboflavin synthase inhibitors.[22] It has also already been emphasized that many of the physical properties of covalent hydrates recorded in the literature refer to partially hydrated and thus poorly defined equilibrium mixtures and that these measurements should be replaced by values for pure, stable substances.[14a]

Experimental

All reactions were performed under a nitrogen atmosphere. DMF was removed from the reaction mixtures under reduced pressure at ambient temperature overnight. DMF solutions of perfluorobutane-2,3-dione were stored at 8 °C in the dark prior to use. M.p.s were determined on a Thomas-Hoover Unimelt or on a Wagner and Munz apparatus. ^1H N.m.r. spectra were recorded on Varian FT-80 80 MHz or Varian T-60 60 MHz spectrometers using $CDCl_3$ as the solvent, except where noted. Chemical shifts are reported in p.p.m. relative to internal Me_4Si. ^{19}F N.m.r. spectra were determined on a JEOL C 60 HL spectrometer operating at 56.45 MHz or on a Perkin-Elmer instrument at 84.6 MHz using $CDCl_3$ as the solvent, except where noted. Chemical shifts are reported in p.p.m. relative to external CF_3CO_2H. ^{13}C N.m.r. spectra were recorded on a JEOL JNM FX 60 instrument. I.r. spectra were recorded on Beckman IR-33 or on Perkin-Elmer 157G and 257 spectrometers. Microanalyses were performed by the Purdue and Munich Technical University Microanalytical Laboratories. The electron impact mass spectra (e.i.m.s.) were obtained on either a Finnegan 4000 or a MAT CH-5 spectrometer operating with an ionization potential of 70 eV. Chemical ionization mass spectra (c.i.m.s.) were obtained on a Finnegan 4000 instrument using methane as the reagent gas. Fast atom bombardment mass spectra (f.a.b.m.s.) were run on a Kratos MS50 spectrometer at room temperature using glycerol matrix. High resolution mass spectra were also determined on the Kratos MS50 spectrometer. U.v. spectra were determined on a Zeiss PM6 or on a Cary 17 spectrophotometer.

2,3-*Bis*(*trifluoromethyl*)*quinoxaline* (**7**).—A solution of perfluorobutane-2,3-dione (370 mg, 1.19 mmol) in DMF (2 ml) was added to a solution of *o*-phenylenediamine (**6**) (110 mg, 1 mmol) in DMF (1 ml) at room temperature. After 1.5 h the DMF was evaporated and the semi-solid residue was crystallized by dissolving it in hot EtOH (5 ml) and then diluting the solution with water (5 ml). The resulting white solid (55 mg, 21%) was filtered off; m.p. 117—118 °C (lit.,[1a] m.p. 117—118 °C); $\lambda_{max.}$(MeOH) 315 (ε 4 675) and 237 nm (47 865); $\nu_{max.}$(KBr) 1 570, 1 490, 1 475, 1 425, 1 345, 1 285, 1 210, 1 190, 1 165, 1 140, 1 105, 1 005, 785, and 750 cm^{-1}; δ_H 8.45—7.97 (m, 4 H); δ_F 12.83 (s, 6 F); *m/z* (e.i.m.s.; relative intensity) 266 (M^+, 41), 197 (33), 102 (24), 76 (31), 75 (13), and 69 (100) (Found: M^+, 266.0279. Calc. for $C_{10}H_4F_6N_2$: *M*, 266.0279).

6,7-*Dimethyl*-2,3-*bis*(*trifluoromethyl*)*quinoxaline* (**9**).—A solution of perfluorobutane-2,3-dione (194 mg, 1 mmol) in DMF (1.18 ml) was added to a stirred solution of 4,5-dimethyl-*o*-phenylenediamine (136 mg, 1 mmol) in DMF (1 ml) at 0 °C. The reaction was stirred at 0 °C for 2 h 15 min and then evaporated at room temperature (0.5 mmHg). The brown, solid residue was recrystallized by dissolution in hot EtOH (1.5 ml) and then dilution of the hot solution with water (1.4 ml), to yield a white solid (0.21 g, 71%); m.p. 129—130 °C; $\lambda_{max.}$(EtOH) 325 (ε 5 640) and 247 nm (44 600); $\nu_{max.}$(KBr) 1 485, 1 460, 1 425, 1 355, 1 295, 1 240, 1 220, 1 185, 1 160, 1 110, 1 000, 880, 790, and 760 cm^{-1}; δ_H 8.03 (s, 2 H) and 2.58 (s, 6 H); δ_C 145.3 (s), 128.5 (d, *J* 58 Hz), 120.5 (q, *J* 277 Hz), 20.6 (q, *J* 1.6 Hz); δ_F 12.20 (s, 6 F); *m/z* (e.i.m.s.; relative intensity) 294 (M^+, 100), 279 (20), 275 (19), 274 (65), 225 (10), 104 (12), 103 (21), 77 (18), and 69 (16) (Found: C, 49.05; H, 2.8; N, 9.6. $C_{12}H_8F_6N_2$ requires C, 48.99; H, 2.74; N, 9.50%).

2,3-*Bis*(*trifluoromethyl*)*quinoxaline*-6-*carboxylic Acid*. (**11**).—A solution of perfluorobutane-2,3-dione (388 mg, 2 mmol) in DMF (4.1 ml) was added to a solution of 3,4-diaminobenzoic acid (0.30 g, 2 mmol) in DMF (2 ml) at room temperature. The reaction mixture was stirred for 2.5 h and then evaporated at room temperature (0.5 mmHg). The solid residue was recrystallized by dissolution in boiling EtOH (7 ml), removal of the insoluble material by filtration, and dilution of the filtrate with water (20 ml), to give solid material (206 mg, 33%). The analytical sample was sublimed at 120 °C (0.5 mmHg); m.p. 183—184 °C, $\lambda_{max.}$(EtOH) 340 (ε 4 680) and 257 nm (12 000); $\nu_{max.}$(KBr) 1 710, 1 410, 1 350, 1 290, 1 220, 1 190, and 1 000 cm^{-1}; δ_H[$(CD_3)_2SO$] 9.08 (d, 1 H, *J* 1.6 Hz), 8.85 (dd, 1 H, *J* 1.6, 8.8 Hz), 8.62 (d, 1 H, *J* 8.8 Hz), and 8.03 (br s, 1 H, exchangeable with D_2O); δ_F[$(CD_3)_2SO$] 10.30 (s, 6 F); *m/z* (e.i.m.s.; relative intensity) 310 (M^+, 100), 293 (71), 291 (11), 265 (21), 241 (14), and 69 (19) (Found: C, 42.45; H, 1.45; N, 8.95. $C_{11}H_4F_6N_2O_2$ requires C, 42.60, H, 1.30; N, 9.03%).

6,7-*Dichloro*-2,3-*bis*(*trifluoromethyl*)*quinoxaline* (**13**).—A solution of perfluorobutane-2,3-dione (80 mg, 0.412 mmol) in DMF (0.5 ml) was added to a solution of 4,5-dichloro-*o*-phenylenediamine (**12**) (50 mg, 0.28 mmol) in DMF (1 ml) at room temperature. After 18 h, the solvent was evaporated and the brown, solid residue was subjected to silica gel (6 g) column chromatography, eluting with $CHCl_3$–hexane (1:1). Concentration of the eluant afforded a white, crystalline solid (70 mg, 74%). The analytical sample was sublimed at 40 °C (0.2 mmHg); m.p. 75—77 °C; $\lambda_{max.}$(MeOH) 342 (ε 6 455), 330 (6 165), 246 (52 480), and 211 nm (33 155); $\nu_{max.}$($CHCl_3$) 2 980, 1 440, 1 400, 1 350, 1 330, 1 275, 1 150, 1 100, 1 080, 990, 965, and 870 cm^{-1}; δ_H 8.44 (s, 2 H); δ_F 15.10 (s, 6 F); *m/z* (e.i.m.s.; relative intensity) 339 [(M^+ + 5), 10], 335 [(M^+ + 3), 65], 335 [(M^+ + 1), 100], 317 (35), 315 (53), 235 (55), and 192 (72) (Found: C, 35.45; H, 0.4; Cl, 21.3; F, 34.2; N, 8.4. $C_{10}H_2Cl_2F_6N_2$ requires C, 35.82; H, 0.60; Cl, 21.19; F, 34.03%).

6-*Benzoyl*-2,3-*bis*(*trifluoromethyl*)*quinoxaline* (**15**).—A solution of perfluorobutane-2,3-dione (80 mg, 0.41 mmol) in DMF (0.5 ml) was added to a solution of 3,4-diaminobenzophenone (**14**) (51 mg, 0.24 mmol) in DMF (1 ml) at room temperature. After 19 h, the solvent was evaporated and the grey, solid residue was recrystallized from hexane to afford the product

(**15**) as a colourless solid (70 mg, 78%); m.p. 112—112.5 °C; $\lambda_{max.}$(MeOH) 251 nm (ε 26 915); $\nu_{max.}$($CHCl_3$) 1 660, 1 590, 1 335, 1 275, 1 150, 1 135, 1 110, 1 080, 990, and 880 cm^{-1}; δ_H 8.61—8.35 (m, 3 H) and 7.94—7.42 (m, 5 H); δ_F 15.20 (s, 6 F); *m/z* (c.i.m.s.; relative intensity) 371 [(M^+ + 1), 100] and 351 (46) (Found: C, 55.05; H, 1.95; F, 30.75; N, 7.85. $C_{17}H_8F_6N_2O$ requires C, 55.14; H, 2.16; F, 30.81; N, 7.57%).

2,3-*Bis*(*trifluoromethyl*)*benzo*[g]*quinoxaline* (**17**).—A solution of perfluorobutane-2,3-dione (194 mg, 1 mmol) in DMF (2.1 ml) was added dropwise to a stirred solution of naphthalene-2,3-diamine (**16**) (158 mg, 1 mmol) in DMF (1 ml) at 0 °C. The reaction was allowed to proceed for 2 h at 0 °C. The solvent was evaporated at room temperature (0.5 mmHg) and the solid residue was recrystallized by addition to hot EtOH (20 ml). A small amount of insoluble material was removed by filtration, and the filtrate was concentrated to a volume of 5 ml. This resulted in the crystallization of orange needles (170 mg, 54%), which displayed an orange fluorescence when irradiated at 366 nm; m.p. 186—187 °C; $\lambda_{max.}$(EtOH) 365 (ε 970), 276 (33 900), and 227 nm (17 500); $\nu_{max.}$(KBr) 1 420, 1 380, 1 365, 1 330, 1 295, 1 220, 1 205, 1 160, 1 090, 1 010, 900, and 762 cm^{-1}; δ_H 8.70 (s, 2 H), 8.17 (m, 2 H), and 7.70 (m, 2 H); δ_F 12.66 (s, 6 F); *m/z* (e.i.m.s.; relative intensity) 316 (M^+, 100), 247 (11), 152 (29), 126 (10), and 69 (5) (Found: C, 52.95; H, 1.85; N, 9.05. $C_{14}H_6F_6N_2$ requires C, 53.18; H, 1.91; N, 8.86%).

2,2',3,3'-*Tetrakis*(*trifluoromethyl*)-6,6'-*biquinoxalinyl* (**19**).—A solution of perfluorobutane-2,3-dione (388 mg, 2 mmol) in DMF (4.1 ml) was added to benzidine-3,3'-diamine (**18**) (214 mg, 1 mmol). The solution was stirred at room temperature for 2 h after which time the solvent was evaporated at room temperature (0.5 mmHg). The residue was triturated with boiling EtOH and the insoluble brown powder was removed by filtration. The filtrate was concentrated to a volume of 5 ml and the solid product (188 mg, 35%) was filtered off; m.p. 157—158 °C; $\lambda_{max.}$(EtOH) 345 (ε 18 900) and 270 nm (45 000); $\nu_{max.}$(KBr) 1 615, 1 490, 1 430, 1 348, 1 290, 1 215, 1 169, 1 101, 1 008, 846, and 750 cm^{-1}; δ_H 8.92 (br s, 2 H), 8.68 (br s, 4 H); δ_F 13.33 (s, 12 F); *m/z* (e.i.m.s.; relative intensity) 530 (M^+, 100), 461 (13), 298 (8), and 69 (42) (Found: C, 45.35; H, 1.2; N, 10.7. $C_{20}H_6F_6N_4$ requires C, 45.30; H, 1.14; N, 10.57%).

2,3-*Bis*(*trifluoromethyl*)*naphtho*[2,3-f]*quinoxaline*-7,12-*dione* (**21**).—A solution of perfluorobutane-2,3-dione (80 mg, 0.41 mmol) was added to a solution of 1,2-diaminoanthraquinone (**20**) (49 mg, 0.21 mmol) at room temperature. The mixture was stirred for 12 h, after which time the solvent was evaporated and the brown, solid residue was purified on a silica gel (6 g) column, eluting with $CHCl_3$–hexane (1:1) to give orange crystals of the dione (**21**) (62 mg, 76%). The analytical sample was recrystallized from CCl_4; m.p. 229—230.5 °C; $\lambda_{max.}$(MeCN) 247 (ε 58 885), 206 nm (31 620); $\nu_{max.}$($CHCl_3$) 1 670, 1 585, 1 335, 1 275, 1 150, 1 100, 990, and 965 cm^{-1}; δ_H 8.93 (d, 1 H, *J* 9 Hz), 8.62 (d, 1 H, *J* 9 Hz), 8.42—8.21 (m, 2 H), and 7.99—7.74 (m, 2 H); δ_F (THF) 14.30—13.60 (m, 6 F); *m/z* (c.i.m.s.; relative intensity) 397 [(M^+ + 1), 100], 379 (23), and 377 (21) (Found: C, 54.35; H, 1.25; F, 28.6; N, 6.95. $C_{18}H_6F_6N_2O_2$ requires C, 54.55; H, 1.52; F, 28.79; N, 7.07%).

2,3-*Bis*(*trifluoromethyl*)*dibenzo*[f,h]*quinoxaline* (**23**).—A solution of perfluorobutane-2,3-dione (80 mg, 0.41 mmol) in DMF (0.5 ml) was added to a suspension of phenanthrene-9,10-diamine (50 mg, 0.24 mmol) in DMF (1 ml). After 12 h at room temperature, the stirred reaction mixture was heated at 50 °C for 3 h. Evaporation of the solvent yielded a yellow solid, which was purified by silica gel (6 g) column chromatography, eluting with $CHCl_3$–hexane (1:2). This afforded white crystals (50 mg, 57%). The analytical sample was recrystallized from hexane, m.p. 202—203 °C; $\lambda_{max.}$(dioxane) 296 (ε 15 490) and 258 nm (58 885); $\nu_{max.}$($CHCl_3$) 2 990, 1 600, 1 540, 1 445, 1 350, 1 330, 1 305, 1 270, 1 150, 1 120, 1 105, and 1 020 cm^{-1}; δ_H 9.27—9.15 (m, 2 H), 8.69—8.57 (m, 2 H), and 8.01—7.67 (m, 4 H); δ_F(THF) 14.70 (s, 6 F); *m/z* (c.i.m.s.; relative intensity) 367 [(M^+ + 1), 100] and 347 (88) (Found: C, 59.2; H, 1.95; F, 30.9; N, 7.6. $C_{18}H_8F_6N_2$ requires C, 59.02; H, 2.19; F, 31.15; N, 7.65%).

2,3-*Bis*(*trifluoromethyl*)*pyrido*[2,3-b]*pyrazine* (**25**).—A solution of perfluorobutane-2,3-dione (160 mg, 0.82 mmol) in DMF (1 ml) was added to a solution of pyridine-2,3-diamine (50 mg, 0.46 mmol) in DMF (0.5 ml) at room temperature. The solution was heated at 50 °C for 4 h and the solvent was then evaporated. The oily residue was subjected to silica gel (6 g) column chromatography, eluting with $CHCl_3$, which gave yellow crystals of the product (**25**) (81 mg, 66%). The analytical sample was recrystallized from hexane; m.p. 72.5—75 °C; $\lambda_{max.}$(MeOH) 316 (ε 6 605), 309 (5 130), 303 (5 130), and 215 nm (13 805); $\nu_{max.}$($CHCl_3$) 2 980, 2 960, 1 595, 1 545, 1 450, 1 390, 1 350, 1 320, 1 270, 1 150, 1 120, 1 080, and 980 cm^{-1}; δ_H 9.45 (dd, 1 H, *J* 4,2 Hz), 8.68 (dd, 1 H, *J* 8,2 Hz), and 7.99 (dd, 1 H, *J* 8,4 Hz); δ_F 15.20—14.60 (m, 6 F); *m/z* (c.i.m.s.; relative intensity) 268 [(M^+ + 1), 100], 248 (36), and 192 (40) (Found: C, 40.4; H, 0.9; F, 42.5; N, 15.5. $C_9H_3F_6N_3$ requires C, 40.45; H, 1.12; F, 42.70; N, 15.73%).

1,3-*Dimethyl*-6,7-*bis*(*trifluoromethyl*)*pteridine*-2,4(1H,3H)-*dione* (**27**).—A solution of perfluorobutane-2,3-dione (388 mg, 2 mmol) in DMF (4.85 ml) was added to a stirred suspension of 5,6-diamino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione hydrate (**26**) (188 mg, 1 mmol) in DMF (1 ml). The reaction mixture was stirred at room temperature for 3 h prior to evaporation of the solvent at room temperature (0.5 mmHg). The oily residue was triturated with water (1.5 ml) and the solid precipitate of compound (**27**) (219 mg, 67%) was filtered off. The analytical sample was recrystallized twice from aqueous acetone and sublimed at 135 °C (0.5 mmHg), m.p. 172—173 °C; $\lambda_{max.}$ (H_2O; pH 5.2) 335 (ε 5 833) and 250 nm (16 250); $\nu_{max.}$(KBr) 1 744, 1 685, 1 582, 1 381, 1 300, 1 251, 1 190, 1 180, 1 160, 755, and 730 cm^{-1}; δ_H [$(CD_3)_2CO$] 3.70 (s, 3 H) and 3.47 (s, 3 H); δ_F [$(CD_3)_2CO$] 11.97 (q, 3 F, *J* 12 Hz) and 10.36 (q, 3 F, *J* 12 Hz); *m/z* (e.i.m.s.; relative intensity) 328 (M^+, 100), 309 (12), 299 (17), 272 (11), 271 (12), 243 (42), 216 (33), 196 (11), and 69 (15) (Found: C, 36.6; H, 1.8; N, 16.95%; M^+, 328.0397. $C_{10}H_6F_6N_4O_2$ requires C, 36.60; H, 1.84; N, 17.07%; *M*, 328.0395).

6,7-*Bis*(*trifluoromethyl*)*pteridine*-2,4(1H,3H)-*dione* (**29**).—5,6-Diaminopyrimidine-2,4(1*H*,3*H*)-dione (**28**) (230 mg, 1.62 mmol) was suspended in DMF (4 ml) and a solution of perfluorobutane-2,3-dione (310 mg, 1.60 mmol) in DMF (1.9 ml) was added at room temperature. After 2 h 40 min, the reaction mixture was concentrated on a rotary evaporator (bath 75 °C) to a volume of 1.5 ml. The concentrated mixture was applied to a column of alumina (Merck, activity II-III, 20 g, 1.4 × 24 cm) and the column was eluted with water. The fractions containing green fluorescent material when irradiated at 366 nm were concentrated to yield the product (**29**) (176 mg, 37%) as a hygroscopic solid, m.p. > 300 °C; $\lambda_{max.}$ (H_2O + NaOH, pH 12) 380 (ε 4 794) and 270 nm (19 328); $\lambda_{max.}$ (H_2O + HCl, pH 1) 330 (ε 6 185) and 240 nm (11 906); $\nu_{max.}$(KBr) 3 660—3 300, 1 680, 1 640, 1 566, 1 505, 1 369, 1 290, 1 170, 1 117, 992, and 835 cm^{-1}; δ_F (DMF) 13.16 (q, 3 F, *J* 12 Hz) and 10.76 (q, 3 F, *J* 12 Hz); *m/z* (e.i.m.s.; relative intensity) 300 (M^+, 1.5), 257 (1.2), 97 (8), 71 (10), 69 (13), 60 (80), 57 (21), 55 (18), 45 (73), 44 (43), and 43 (100) (Found: C, 28.9; H, 1.3; N,

16.45. $C_8H_2F_6N_4O_2 \cdot 1.8H_2O$ requires C, 28.89; H, 1.70; N, 16.85%).

1,2-*Dihydro*-2-*thioxo*-6,7-*bis*(*trifluoromethyl*)*pteridin*-4(3H)-*one* (**31**).—A solution of perfluorobutane-2,3-dione (80 mg, 0.41 mmol) in DMF (0.5 ml) was added to a suspension of 4,5-diamino-2,3-dihydro-2-thioxopyrimidin-6(1*H*)-one (**30**) (42 mg, 0.27 mmol) in DMF (1 ml). The solid material dissolved after several min. The solution was stirred at room temperature for 12 h before the solvent was evaporated. The brown residue was purified by silica gel (2 g) column chromatography, eluting with EtOAc–hexane (1:3; 50 ml). This gave the product (**31**) as a yellow solid (71 mg, 85%). The analytical sample was recrystallized from $CHCl_3$, m.p. 230—231 °C; $\lambda_{max.}$(MeOH) 337 (ε 29 510) and 238 nm (15 345); $\nu_{max.}$(KBr) 3 210, 3 140, 1 700, 1 575, 1 530, 1 460, 1 360, 1 320, 1 275, 1 220, 1 175, 1 155, 1 115, 1 105, 975, 745, and 725 cm^{-1}; δ_H [$(CD_3)_2SO$] 8.02 (s, 1 H, exchangeable with D_2O) and 7.27 (br s, 1 H, exchangeable with D_2O); δ_F(MeOH) 14.28 (q, 3 F, *J* 13 Hz) and 12.58 (q, 3 F, *J* 13 Hz); *m/z* (c.i.m.s.; relative intensity) 317 [(M^+ + 1), 100] and 297 (28) (Found: C, 30.5; H, 0.65; F, 35.9; N, 18.1; S, 10.25. $C_8H_2F_6N_4OS$ requires C, 30.38; H, 0.63; F, 36.08; N, 17.72; S, 10.13%).

6,7-*Bis*(*trifluoromethyl*)*pteridine*-4-(3H)-*one* (**33**).—A solution of perfluorobutane-2,3-dione (80 mg, 0.41 mmol) in DMF (0.5 ml) was added to a suspension of 4,5-diamino-6-hydroxypyrimidinium sulphate (**32**) (50 mg, 0.22 mmol) in DMF (1 ml) at room temperature. The reaction mixture was stirred for 12 h, after which it was filtered and the filtrate evaporated. The residue was subjected to silica gel (2 g) column chromatography, eluting with EtOAc–hexane (1:1; 60 ml) to yield the product (**33**) (57 mg, 90%) as a white solid. The analytical sample was recrystallized from EtOH, m.p. > 275 °C; $\lambda_{max.}$(MeOH) 355 (ε 4 265) and 251 nm (10 715); $\nu_{max.}$(KBr) 3 240, 3 080, 2 910, 2 850, 1 725, 1 600, 1 560, 1 550, 1 530, 1 465, 1 460, 1 370, 1 310, 1 290, 1 220, 1 205, 1 170, 1 150, 1 130, 1 085, 965, and 735 cm^{-1}; δ_H [$(CD_3)_2SO$] 8.64 (s, 1 H) and 7.89 (br s, 1 H, exchangeable with D_2O); δ_F(MeOH) 13.94 (q, 3 F, *J* 12 Hz) and 12.56 (q, 3 F, *J* 12 Hz); *m/z* (c.i.m.s.; relative intensity) 285 [(M^+ + 1), 100] and 265 (25) (Found: C, 33.25; H, 0.5; N, 19.0. $C_8H_2F_6N_4O \cdot 0.3H_2O$ requires C, 33.19; H, 0.91; N, 19.35%).

6,7-*Dihydroxy*-6,7-*bis*(*trifluoromethyl*)-5,6,7,8-*tetrahydropteridin*-4(3H)-*one* (**34**).—A solution of perfluorobutane-2,3-dione (160 mg, 0.82 mmol) in DMF (1 ml) was added to an ice-cold solution of 4,5-diaminopyrimidinium sulphate (**32**) (100 mg, 0.45 mmol) in 5% aqueous $NaHCO_3$ (2 ml). After the mixture had been stirred at room temperature for 21 h, the crude product (114 mg) was filtered off and washed with water. Recrystallization from acetone gave the product (**34**) as a white, crystalline solid (68 mg, 47%), which was dried *in vacuo* at 77 °C, m.p. > 270 °C; $\lambda_{max.}$(MeOH) 272 (ε 8 315) and 212 nm (19 055); $\nu_{max.}$(KBr) 3 300, 3 220, 1 670, 1 655, 1 650, 1 640, 1 635, 1 620, 1 610, 1 605, 1 280, 1 200, 1 145, and 1 080 cm^{-1}; δ_H [$(CD_3)_2SO$] 9.14 (br s, 1 H), 7.90 (s, 1 H), 7.63 (s, 1 H), 7.25 (s, 2 H), and 4.83 (s, 1 H); δ_F (MeOH) −1.10—−1.60 (m, 6 F); *m/z* (f.a.b.m.s.; relative intensity) 321 [(M^+ + 1), 100] (Found: C, 30.25; H, 1.55; N, 17.3. $C_8H_6F_6N_4O_3$ requires C, 30.01; H, 1.89; N, 17.50%).

2,3-*Bis*(*trifluoromethyl*)-1,2,3,4-*tetrahydropyrido*[3,4-b]-*pyrazine*-2,3-*diol* (**36**).—A solution of perfluorobutane-2,3-dione (320 mg, 1.65 mmol) in DMF (2 ml) was added to a suspension of pyridine-3,4-diamine (100 mg, 0.92 mmol) in DMF (1 ml). After the mixture had been stirred at room temperature for 19 h, the solvent was evaporated and the residue was triturated with EtOAc. The yellow solid (160 mg) was filtered off. Recrystallization of the crude product from MeCN afforded compound (**36**) as a white solid (55 mg, 20%), m.p. 200—203 °C (decomp.); $\lambda_{max.}$(MeOH) 291 (ε 3 090), 251 (2 345), and 213 nm (14 790); $\nu_{max.}$(KBr) 3 380, 3 210, 3 130, 3 070, 2 980, 2 940, 1 635, 1 625, 1 560, 1 545, 1 380, 1 295, 1 260, 1 240, 1 210, 1 180, 1 145, 1 120, 1 110, 1 060, 990, 940, 890, 790, 725, and 680 cm^{-1}; δ_H [$(CD_3)_2SO$] 9.51 (s, 1 H), 8.18—7.88 (m, 5 H), and 7.08 (d, 1 H, *J* 6 Hz); δ_H [$(CD_3)_2SO + D_2O$] 7.99 (d, 1 H, *J* 6 Hz), 7.95 (s, 1 H), and 7.08 (d, 1 H, *J* 6 Hz); δ_H(MeOH) −1.06—−1.49 (m, 6 F); *m/z* (c.i.m.s; relative intensity) 304 [(M^+ + 1), 25], 286 (44), 268 (100), and 248 (43); *m/z* (f.a.b.m.s; relative intensity) 304 [(M^+ + 1), 100]; (Found: 303.0445. $C_9H_7F_6N_3O_2$ requires 303.0443).

6,7-*Bis*(*trifluoromethyl*)-5,6,7,8-*tetrahydropteridine*-6,7-*diol* (**38**).—A solution of perfluorobutane-2,3-dione (388 mg, 2 mmol) in DMF (4.1 ml) was added to a solution of pyrimidine-4,5-diamine (**37**) (0.22 g, 2 mmol) at room temperature. The solution was stirred for 3 h and then evaporated. The residue was dissolved in the minimum of hot EtOH and the solution was diluted with water (4 ml). The blue powder was removed by suction filtration. The filtrate was evaporated and the amorphous residue crystallized on trituration with a mixture of acetone and ligroin (10 + 5 ml, respectively) to give the product (**38**) as a white solid (54 mg, 9%), m.p. > 250 °C; $\lambda_{max.}$ (water; pH 5.2) 295 (ε 6 119) and 250 nm (4 478); $\nu_{max.}$(KBr) 3 700—2 500, 1 645, 1 565, 1 310, 1 285, 1 220, 1 175, 1 135, 1 050, 960, and 920 cm^{-1}; δ_H [$(CD_3)_2SO$] 8.55 (s, 1 H), 8.06 (s, 1 H), 7.86 (s, 1 H), 7.45 (s, 1 H), and 7.38 (s, 2 H); δ_H [$(CD_3)_2SO + D_2O$] 8.06 (s, 1 H) and 7.86 (s, 1 H); δ_F 0.60—0.00 (m, 6 F); *m/z* (e.i.m.s; relative intensity) 268 (M^+ − 36), 249 (13), 241 (48), 214 (41), 199 (10), 145 (13), 93 (14), 78 (10), and 69 (32); *m/z* (f.a.b.m.s; relative intensity) 305 [(M^+ + 1), 100] (Found: C, 29.9; H, 2.0; N, 17.6. $C_8H_6F_6N_4O_2 \cdot 0.75H_2O$ requires C, 30.25; H, 2.38; N, 17.64%).

2-*Carbamoyl*-5,6-*bis*(*trifluoromethyl*)*pyrazine*-3-*amine* (**40**).—When the mother-liquor of crude product (**34**) was allowed to stand, compound (**40**) (24 mg, 20%) crystallized; m.p. 162—165 °C; $\lambda_{max.}$(MeOH) 353 (ε 5 250), 257 (14 790), and 203 nm (4 365); $\nu_{max.}$(KBr) 3 440, 3 390, 3 280, 3 200, 1 680, 1 610, 1 580, 1 430, 1 355, 1 275, 1 235, 1 205, 1 145, 1 120, 1 040, 970, 805, 735, 710, 660, and 615 cm^{-1}; δ_F(MeOH) 15.00 (q, 3 F, *J* 12 Hz) and 11.92 (q, 3 F, *J* 12 Hz); *m/z* (c.i.m.s; relative intensity) 275 [(M^+ + 1), 95] and 255 (100) (Found: C, 30.3; H, 1.3; N, 19.85. $C_7H_4F_6N_4 \cdot \frac{1}{2}H_2O$ requires C, 30.27; H, 1.60; N, 20.17%).

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