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A new and efficient synthetic approach to dichlorofluoflavines. Study of the stability of isomeric fluoflavines by HF and B3LYP procedures

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ABSTRACT

The first method for the synthesis of 7,10-dichloro-5,12-dihydroquinoxalino[2,3-*b*]quinoxalines is reported. Treatment of 3,3,6,6-tetrachloro-1,2-cyclohexanedione with diaminomaleonitrile leads to 5,8-dichloro-2,3-dicyanoquinoxaline in near quantitative yields. This compound has been found to be an excellent synthetic equivalent of unavailable 2,3,5,8-tetrachloroquinoxaline. It reacts with *o*-phenylenediamines providing the corresponding dichlorofluoflavines in fair to high yields. These compounds have been identified by NMR spectroscopy and X-ray crystallography. Molecular structures, chemical hardness, $\Delta G^{\neq}_{298}$-values, and relative stabilities of all possible isomeric products have been calculated by HF and B3LYP density functional theory methods.

1. Introduction

The first reference on fluoflavines is Hinsberg and Pollack, who gave the name fluoflavine to the dihydroquinoxalino[2,3-*b*]quinoxaline formed in only 5% yield by reaction of 2,3-dichloroquinoxaline with *o*-phenylenediamine.[1] They formulated its structure as 5,12-dihydro **1** but later it was controversially assigned to be either compound **1** or its 5,11-dihydro isomer[2,3] **2** (Fig. 1). This is understandable considering that NMR studies are particularly difficult, due to the high insolubility of this product, which does not provide fully conclusive spectra if the sample is solved in acidic media. Certain *N*-derivatized fluoflavines were found to be somewhat more soluble than fluoflavine itself. Spectroscopic studies of these compounds were made.[2b] In this case, however, the site where an N-derivatization occurs is not a sure criterion to assume the actual position of both N–H groups in the parent compound.

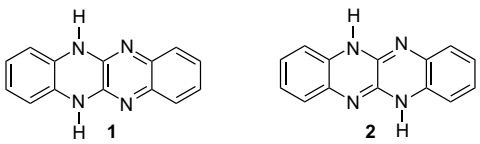

Figure 1. The structures of isomeric fluoflavines.

Over the years different features of the chemistry of fluoflavines, such as synthesis,[1,2a,4] oxidation,[1,4d,5] electrophilic attack,[2b,4i,5a] and electrochemical[2b,6] and photochemical[4k,7] reactions have received considerable attention. Fluoflavines have been described as colorants,[4c,e,8] substances with anthelmintic activity,[4i] and as practical components in confering peculiar properties to polymers[4e,9] and for other uses.[4a,g,m,5a,10] Recently described electronic properties of metal complexes containing this four N-donor system also evidence a notable interest in fluoflavines.[11]

It is clear that the preferred strategy to obtain fluoflavines is based on 2,3-dichloroquinoxaline chemistry.[1,4b,c,i] Some related preparations starting from 2,3-diamino-, 2,3-dihydroxy- or 2,3-diphenoxyquinoxaline instead of 2,3-dichloroquinoxaline have also been described.[2a,4b,e,j] It should be mentioned that certain less general reactions yielding fluoflavines or fluoflavine derivatives, but without participation of quinoxaline intermediates, have also been reported.[4d,f,h,k,l] A survey of the literature shows that there is effective methodology to build the parent compound of the family. However, access to functionalized fluoflavines may be unfeasible or severely limited by unavailability of the required quinoxaline or 1,2-benzenediamine intermediates. This is just the case for the hitherto unknown 7,10-dichlorofluoflavines here reported. The number of chlorinated fluoflavines described is very scanty.[4c,i,m,8,12] However, considering that the synthetic usefulness of chlorophenazines in affording phenazine derivatives is well documented,[13] chlorofluoflavines are of interest in themselves, but also

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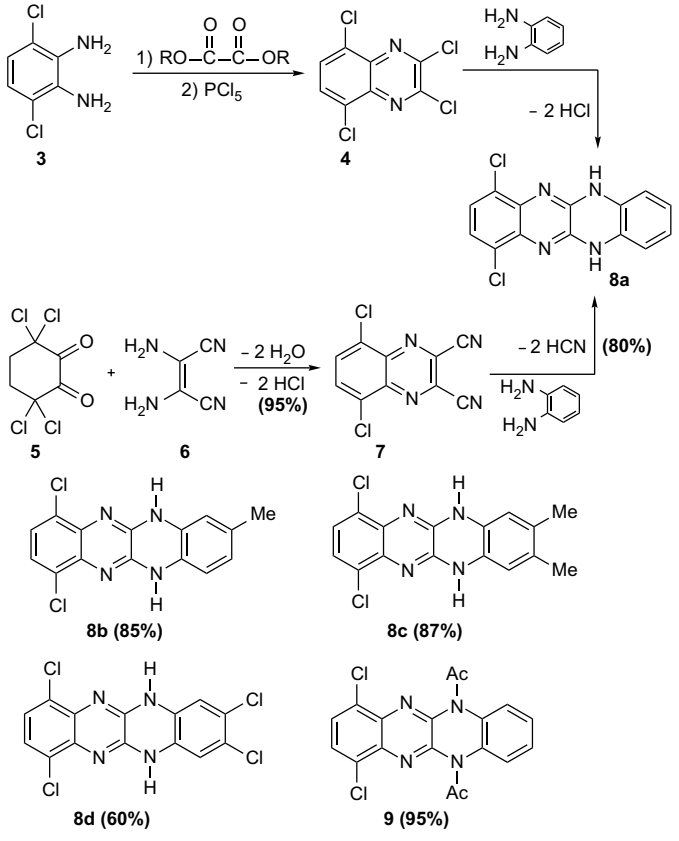
to investigate their potential utility as intermediates to provide further fluoflavine derivatives.

An approach to 7,10-dichlorofluoflavines **8** by the Hinsberg and Pollack route (Scheme 1) appears to be unfeasible. Preparation of 2,3,5,8-tetrachloroquinoxaline **4** following the standard route described for 2,3-dichloroquinoxaline but involving 3,6-dichloro-1,2-phenylenediamine **3** instead of 1,2-phenylenediamine appears to be highly conflictive since **3** is a rare and expensive compound of extremely difficult availability.[14] Its most efficient preparation has been reported in only 15% yield through the synthesis of benzo[*c*][1,2,5]selenadiazole and subsequent chlorination and reduction reactions.[14a]

Recently we developed a new, highly efficient methodology for the synthesis of chlorophenazines[15] starting from 3,3,6,6-tetrachlorocyclohexanedione **5**, which is a cheap and readily available intermediate that can be quantitatively generated by simple chlorination of commercial *trans*-cyclohexanediol. Compound **5** reacts with 1,2-phenylenediamines exhibiting the behavior of an excellent synthetic equivalent of unavailable 3,6-dichloro-1,2-benzoquinone. It also provided an exclusive approach to polychloro-1,2-epoxycyclopentane-1-carboxylic acids and their alkyl esters.[16] Given the interest of these results, we continued working to expand the classes of specifically chlorinated heterocyclic compounds by starting from this profitable reagent. The first outcome of this project is the synthesis of 7,10-dichloro-5,12-dihydroquinoxalino[2,3-*b*]quinoxalines **8** by an expeditious approach that implies the first preparation of 5,8-dichloro-2,3-dicyanoquinoxaline **7** and its use as a key synthetic intermediate.

2. Results and discussion

3,3,6,6-Tetrachloro-1,2-cyclohexanedione **5** was treated with diaminomaleonitrile[17] **6** in the presence of pyridine. The formation of a single product was observed. It was isolated and identified as 5,8-dichloro-2,3-dicyanoquinoxaline **7**, a novel quinoxaline derivative. The yield of this one-pot preparative process was almost quantitative. In the hope of obtaining fluoflavines from **8** we attempted a reaction with 1,2-phenylenediamine in hot pyridine. The formation of a strongly fluorescent product was perceptible after a short time, whereas the total conversion of the starting materials to this product occurred after 6 h. It was isolated as a highly pure yellow powder whose spectral and elemental analyses revealed a dichlorofluoflavine formed in high yield, which was identified as 7,10-dichloro-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline **8a**.



Scheme 1.

Reactions with further 1,2-benzenediamines were also carried out under a similar protocol leading to the corresponding dichlorofluoflavines **8** in fair to high yields. These compounds were also highly fluorescent. These results evidenced that inexpensive and easily available 5,8-dichloro-2,3-dicyanoquinoxaline **7** behaves as an excellent synthetic equivalent of unavailable 2,3,5,8-tetrachloroquinoxaline **4**, providing access to this previously unattainable class of fluoflavine derivatives.

Given that the prepared dichlorofluoflavines exhibit a modest but sufficient solubility in usual spectroscopy solvents, our purpose was to realize a fully reliable characterization of the products formed by a structural study involving a conjunction of tools such as 1D and 2D NMR spectroscopy, single crystal X-ray crystallography, and HF and B3LYP density functional theory methods.

Figure 2 shows the three possible molecular arrangements for any dichlorofluoflavine originated by reaction between 5,8-dichloro-2,3-dicyanoquinoxaline **7** and 1,2-phenylenediamine. First, we focused on determining the relative stabilities of the non-chlorinated isomers (**1**, **2**) as well as the dichlorinated ones (**8a**, **8a′**, **8a″**) by computational methodology. With this purpose, full geometry optimizations were performed at the B3LYP/6-311++G(d,p) level of theory. It was found that 5,12-dihydroquinoxalino[2,3-*b*]quinoxaline **1** is more stable than 5,11-dihydroquinoxalino[2,3-*b*]quinoxaline **2** with relative values of $\Delta G^{\neq}_{298}$=0 and −1.93 kcal/mol, respectively. In the case of dichlorofluoflavines, the lowest stability corresponds to 1,4-dichloro-5,11-dihydroquinoxalino[2,3-*b*]quinoxaline **8a″**, the most stable isomer is 1,4-dichloro-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline **8a′**, whereas stability of 7,10-dichloro-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline **8a** is somewhat lower than that of **8a′** (the relative $\Delta G^{\neq}_{298}$ values for these compounds are 0, −2.76, and −0.77 kcal/mol). Since it has been reported that in most of the cases the chemical hardness (η) is a good indicator for predicting the most stable isomer,[18] the η-values for these isomers were also computed at the B3LYP/6-311++G(d,p) level by using the equation

$$\eta = \frac{I - A}{2} \tag{1}$$

where I is the ionization potential and A the electron affinity of the molecule. To carry out calculations for the positive and negative ions of each isomer, which are necessary to determine the values of I and A in Eq. 1, the respective geometries of the neutral molecules were used. Alternatively, I and A can be approximated in terms of the eigenvalues corresponding to the HOMO and LUMO orbitals,

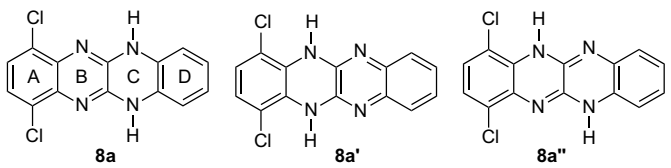


Figure 2. The structurs of isomeric dichlorofluoflavines.

i.e., $I=-E_{HOMO}$, $A=-E_{LUMO}$. The calculated values of η for these isomers were 3.23 eV (**8a**), 3.40 eV (**8a′**), and 3.12 eV (**8a″**). These values confirm that the most energetically stable isomer (**8a′**) is associated with the maximum hardness, while **8a″** exhibiting the minimum hardness has also the largest value of $\Delta G^{\neq}_{298}$. This last structure was clearly discarded by ^{13}C NMR since only 7 resonance signals were recorded instead of 14. However, these spectra were not able to distinguish between structures **8a** and **8a′**. This problem was resolved by ^{15}N HSQC and ^{15}N HMBC experiments, which were found to be in good agreement with arrangement **8a**. Thus, ^{15}N HMBC spectroscopy showed that protonated nitrogens (N5–N12, 117 ppm) correlate with hydrogens H4–H1, whereas non-protonated nitrogens (N6–N11, 239 ppm) correlate with hydrogens H8–H9. This led to the conclusion that the dihydropyrazine system is located in the ring C, whereas pyrazine arrangement pertains to ring B. The ^{15}N HSQC spectrum was consistent with this assumption since protons H5–H12 correlated with N5–N12.

Unfortunately, single crystals suitable for an X-ray diffraction analysis could not be obtained despite intensive effort. Instead, we were successful in an attempt to analyze a diacetylated derivative. The molecular structure found corresponds to **9**, which shows an angular geometry with an interplanar angle of 138.3° (Fig. 3). Selected intramolecular distances and bond angles for this crystal structure are given in Table 1. The optimized geometry of **9** calculated at the HF/6-31G(d) and B3LYP/6-31G(d) levels of theory were in excellent agreement with that found by X-ray analysis and so the computed B3LYP/6-31G(d) interplanar angle was 140.4°. The calculated bond lengths and bond angles are also included in Table 1 for comparison. A perspective of the crystal packing showing hydrogen interactions is shown in Figure 4. As far as we know, this is the first time that a crystallographic molecular structure of a member of the fluoflavines family is reported. Since the optimized geometries of **8a**, **8a′**, and **8a″** were found to be fully planar molecules at all levels of computation, it is worthy of note that formation of product **9** involves a remarkable geometrical change attributable to the loss of conjugation of the nitrogen lone electron pair with both adjacent aromatic systems motivated by a high delocalization at the carbonyl oxygen. It should also be noted that in agreement with the observed in the case of compound **8a**, an ^{15}N HMBC spectrum of **9** clearly showed correlation between acylated nitrogens and H1–H4 protons, whereas nitrogens integrated in the aromatic system correlated with H8–H9 protons. Therefore, any possibility of tautomerism disturbing the initial position of the dihydro system with respect to that where diacetylation occurs could be discarded.

Finally, we will briefly discuss that although **8a** is not the most stable isomer, this was the only compound isolated and identified,

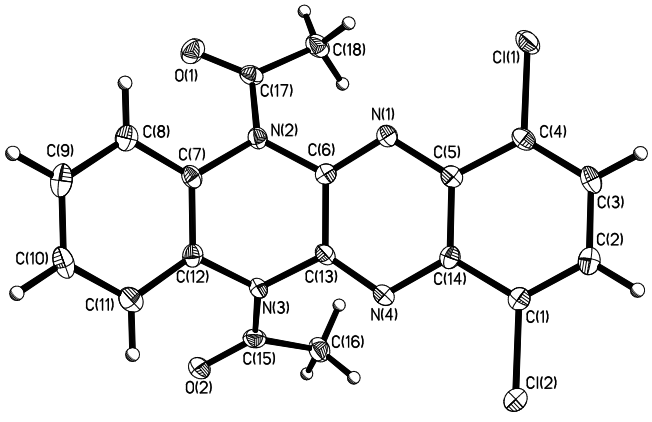


Figure 3. ORTEP of **9**, with thermal ellipsoids shown at 50% probability.

Table 1
Selected bond lengths and bond angles of crystal and calculated structures of **9** and their differences

Bond	Crystal structure (Å)	Calculated structure (Å)[a]	Δ(Å)	Calculated structure (Å)[b]	Δ(Å)
Cl(1)–C(4)	1.729 (2)	1.747	0.018	1.732	−0.003
N(1)–C(5)	1.366 (3)	1.362	0.004	1.361	0.005
N(1)–C(6)	1.302 (3)	1.305	−0.003	1.273	0.029
N(2)–C(6)	1.412 (3)	1.405	0.007	1.397	0.015
N(2)–C(7)	1.439 (3)	1.439	0.000	1.433	0.006
N(3)–C(l2)	1.427 (3)	1.439	−0.012	1.433	−0.006
N(2)–C(17)	1.416 (3)	1.421	−0.005	1.399	0.017
N(3)–C(15)	1.401 (3)	1.421	−0.020	1.399	0.002
O(1)–C(17)	1.209 (3)	1.215	−0.006	1.191	0.018

Bond	Crystal structure (°)	Calculated structure (°)[a]	Δ(°)	Calculated structure (°)[b]	Δ(°)
C(5)–C(4)–Cl(1)	119.40 (16)	119.85	−0.45	120.05	−0.65
C(3)–C(4)–Cl(1)	120.07 (16)	119.75	0.32	119.81	0.26
C(14)–C(1)–Cl(2)	118.53 (16)	119.85	−1.32	120.05	−1.52
C(2)–C(1)–Cl(2)	120.67 (16)	119.75	0.92	119.81	0.86
C(6)–N(1)–C(5)	116.89 (17)	118.13	−1.24	118.48	−1.59
N(1)–C(6)–N(2)	121.36 (18)	121.24	0.12	122.46	−1.10
N(4)–C(13)–N(3)	120.45 (18)	121.24	−0.79	122.46	−2.01
C(6)–N(2)–C(7)	114.45 (17)	114.40	0.05	113.93	0.52
C(13)–N(3)–C(12)	113.56 (17)	114.40	−0.84	113.93	−0.37

[a] Geometry optimized at the B3LYP/6-31G(d) level of theory.
[b] Geometry optimized at the HF/6-31G(d) level of theory.

instead of the more stable **8a′** (the relative values of $\Delta G^{\neq}_{298}$ are −0.77 and −2.76 kcal/mol, and the corresponding hardness 3.23 and 3.40 eV, see above). It is apparent from Scheme 1 that the compound initially formed would be **8a**. To clarify why this isomer does not undergo transformation to **8a′**, the transition states for the intramolecular transformation **8a**→**8a″**→**8a′** have been calculated. The activation energies for this pathway were found to be extremely high, 51.1 and 49.7 kcal/mol at the B3LYP/6-31G(d) level (the corresponding values when correlation energy is not taken into account are even higher, 68.7 and 65.3 kcal/mol at the HF/6-31G(d) level).

In conclusion, a proficient and general method for the synthesis of 7,10-dichlorofluoflavines on the basis of 3,3,6,6-tetrachloro-1,2-cyclohexanedione chemistry is reported. Good yields and easy availability of starting materials are valuable, noteworthy advantages of the method, which allows a privileged access to previously unattainable products.

3. Experimental

3.1. General

NMR spectra were recorded on Bruker Unity 200, 300 or 400 MHz spectrometers. Samples of compounds **8** were prepared by dissolving 6–10 mg of each product in 0.6–0.8 mL $(CD_3)_2SO$. The ^1H and ^{13}C NMR spectra are relative to residual $(CD_2H)S(O)CD_3$ at δ 2.49 ppm and to $(CD_3)_2SO$ at δ 39.5 ppm, respectively. ^1H–^{15}N NMR heteronuclear correlation spectra were recorded using standard techniques. A sample of ^{15}N-formamide referenced to anhydrous liquid ammonia was used as an external standard for ^{15}N chemical shifts. In the HMBC experiment of **8a** the spectral width was set to 2.3 kHz in F2 and to 18.2 kHz in F1, the number of transients was 32 and 1024 time increments were acquired. In the HSQC experiment the spectral width was set to 2.4 kHz in F2 and to 18.3 kHz in F1, the number of transients was 32 and 2048 time increments were acquired. Sample of **9** was prepared by dissolving 30 mg in 0.7 mL $CDCl_3$ and referenced to internal TMS at δ 0.00 ppm for ^1H NMR and to $CDCl_3$ at δ 77.1 ppm for ^{13}C NMR. In the HMBC experiment the spectral width was set to 3.6 kHz in F2 and to

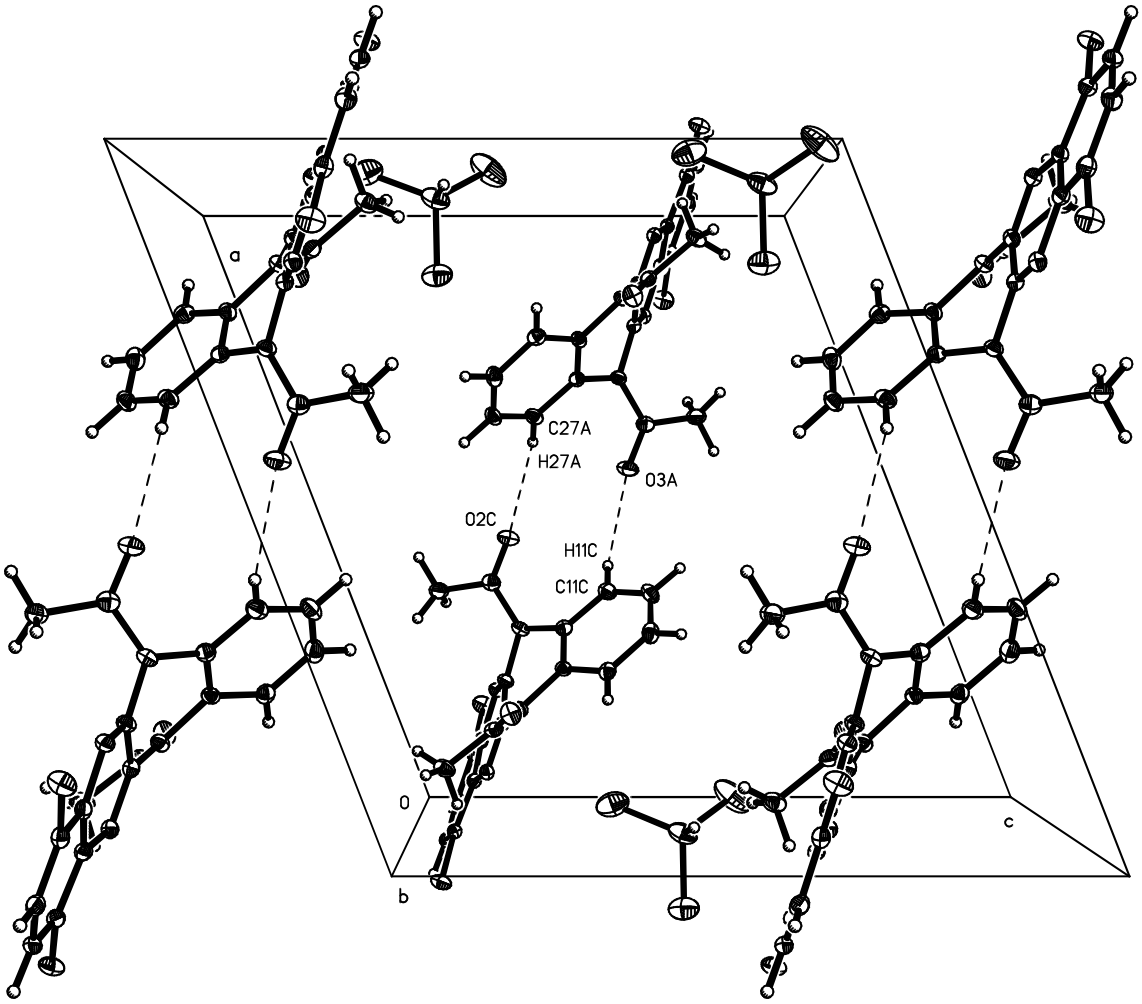


Figure 4. A perspective of the crystal packing of **9**, showing the hydrogen interactions.

16.2 kHz in F1, the number of transients was 48 and 2048 time increments were acquired.

All computations have been performed with the Spartan'06 package program.[19] First, the most stable conformers were determined by using the MMFF molecular mechanics method.[20] Next, these conformers were used as input for ab initio molecular orbital and density functional theory calculations of geometry optimizations at the Hartree–Fock and B3LYP levels of theory with the 6-31G(d) and 6-311++G(d,p) base sets. There were no significant differences between the results obtained with the different base sets. Frequency calculations were performed at the same level of theory as the geometry optimizations to characterize the stationary points as local minima (equilibrium structures). Activation energies were obtained as the difference between the total molecular energy of the transition state and that of the ground state.

3.2. Preparation of 5,8-dichloro-2,3-dicyanoquinoxaline (7)

A solution of 3,3,6,6-tetrachlorocyclohexanedione **5** (20 mmol) in dimethylformamide (20 mL) was added dropwise to a warmed solution (60 °C) of diaminomaleonitrile **6** (24 mmol) in dimethylformamide (80 mL). The solution was stirred at this temperature for 8 h. Pyridine (40 mmol) was added and the reaction mixture was stirred at 80 °C for 2 h and cooled to room temperature. Addition of cold brine (500 mL) provoked the formation of a brown solid precipitate that was separated by filtration and crystallized from chloroform giving brown prisms mp 265–267 °C (dec). Yield 95%. (Found: C 48.36; H 0.80; N 22.28. $C_{10}H_2Cl_2N_4$ requires: C 48.23; H 0.81; N 22.50.) ^{1}H NMR δ (DMSO-d_6, 200 MHz): 8.39 (s, 2H); ^{13}C NMR δ (DMSO-d_6, 200 MHz): 114.13 (C), 131.55 (C), 132.58 (C), 134.63 (CH), 138.22 (C); MS m/z (%): 250 (M^++2, 70), 248 (M^+, 100), 196 (6), 146 (34), 144 (50), 109 (20), 74 (17); IR (Nujol): 1586, 1540, 1314, 1302, 1209, 1196, 1123, 947, 854, 699, 608 cm^{-1}.

3.3. Preparation of fluoflavines (8)

A mixture of 5,8-dichloro-2,3-dicyanoquinoxaline **7** (1.2 mmol), the appropriate *o*-phenylenediamine (3.6 mmol), and pyridine (20 mL) was refluxed for 6 h (16 h in the case of product **8d**). After cooling, the reaction mixture was poured into 200 mL of cold brine and the solid precipitate formed was collected by filtration and purified by column chromatography (silica gel/ethyl acetate–hexane 2:1).

3.4. 7,10-Dichloro-5,12-dihydroquinoxalino[2,3-*b*] quinoxaline (8a)

Yield 80%; yellow powder (ethyl acetate–hexane); mp 256–259 °C (dec). (Found: C 55.83; H 2.63; N 18.22. $C_{14}H_8Cl_2N_4$ requires: C 55.47; H 2.66; N 18.48.) ^{1}H NMR δ (DMSO-d_6, 300 MHz): 6.56–6.63 (m, 4H), 7.05 (s, 2H), 10.46 (br s, 2H); ^{13}C NMR δ (DMSO-d_6, 400 MHz): 113.86 (CH), 122.24 (CH), 123.93 (CH), 125.78 (C), 129.02

(C), 137.06 (CCl), 144.87 (C); MS *m*/*z* (%): 304 (M^++2, 70), 302 (M^+, 100), 232 (M^+−2 Cl, 5), 231 (55), 151 (3), 102 (4); IR (Nujol): 3395, 1622, 1587, 1539, 1175, 970, 800, 745 cm^{-1}.

3.5. 7,10-Dichloro-2-methyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (8b)

Yield 85%; yellow powder (ethyl acetate–hexane); mp 215–217 °C (dec). (Found: C 57.11; H 3.24; N 17.49. $C_{15}H_{10}Cl_2N_4$ requires: C 56.80; H 3.18; N 17.66.) ^{1}H NMR δ (DMSO-d_6, 400 MHz): 2.11 (s, 3H), 6.47–6.53 (m, 3H), 7.11 (s, 2H), 10.44 (br s, 1H), 10.46 (br s, 1H); ^{13}C NMR δ (DMSO-d_6, 400 MHz): 20.37 (CH_3), 114.00 (CH), 114.56 (CH), 123.09 (CH), 124.20 (CH), 124.36 (CH), 125.89 (C), 125.98 (C), 126.86 (C), 129.11 (C), 131.80 (C), 137.27 (CCl), 137.47 (CCl), 145.37 (C), 145.41 (C); MS *m*/*z* (%): 318 (M^++2, 68), 316 (M^+, 100), 281 (M^+−Cl, 10), 245 (31), 114 (23), 103 (28), 89 (41), 76 (41), 52 (41); IR (Nujol): 3418, 1628, 1589, 1539, 1186, 975, 944, 799 cm^{-1}.

3.6. 7,10-Dichloro-2,3-dimethyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (8c)

Yield 87%; yellow powder (ethyl acetate–hexane); mp 268–270 °C (dec). (Found: C 57.89; H 3.71; N 17.14. $C_{16}H_{12}Cl_2N_4$ requires: C 58.02; H 3.65; N 16.92.) ^{1}H NMR δ (DMSO-d_6, 300 MHz): 1.98 (s, 6H), 6.39 (s, 2H), 7.05 (s, 2H), 10.41 (br s, 2H); ^{13}C NMR δ (DMSO-d_6, 300 MHz): 18.73 (CH_3), 115.26 (CH), 124.18 (CH), 125.86 (C), 126.84 (C), 130.23 (C), 137.44 (CCl), 145.47 (C); MS *m*/*z* (%): 332 (M^++2, 70), 330 (M^+, 100), 315 (M^+−CH_3, 14), 317 (8), 259 (6), 165 (10); IR (Nujol): 3409, 1619, 1588, 1538, 1179, 962, 874, 798 cm^{-1}.

3.7. 2,3,7,10-Tetrachloro-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (8d)

Yield 60%; yellow powder (ethyl acetate–hexane); mp 282–284 °C (dec). (Found: C 45.44; H 1.61; N 15.30. $C_{14}H_6Cl_4N_4$ requires: C 45.20; H 1.63; N 15.06.) ^{1}H NMR δ (DMSO-d_6, 400 MHz): 6.70 (s, 2H), 7.18 (s, 2H), 10.70 (br s, 2H); ^{13}C NMR δ (DMSO-d_6, 300 MHz): 114.41 (CH), 123.37 (C), 124.46 (CH), 126.15 (C), 129.7 (C), 136.67 (C), 144.00 (C); MS *m*/*z* (%): 374 (M^++4, 49), 372 (M^++2, 100), 370 (M^+, 79), 301 (27), 299 (38), 265 (7), 186 (18), 149 (19), 57 (23); IR (Nujol): 3364, 1645, 1580, 1520, 1181, 952, 881, 799 cm^{-1}.

3.8. Preparation of 5,12-diacetyl-7,10-dichloro-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (9)

7,10-Dichloro-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline **5a** (1.4 mmol) was treated with acetic anhydride (15 mL) at reflux temperature for 16 h and the resulting reaction mixture was concentrated to dryness yielding a crude material that was recrystallized from methanol–chloroform to give brown prisms mp 232–235 °C (dec). Yield 95%. (Found: C 56.12; H 3.16; N 14.32. $C_{18}H_{12}Cl_2N_4O_2$ requires: C 55.83; H 3.12; N 14.47.) ^{1}H NMR δ ($CDCl_3$, 400 MHz): 2.71 (s, 6H), 7.30–7.35 (m, 2H), 7.74 (s, 2H), 7.92–7.96 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 400 MHz): 25.13 (CH_3), 125.27 (CH), 126.38 (CH), 129.43 (CH), 131.03 (C), 131.08 (C), 136.47 (C), 144.38 (C), 168.71 (CO); MS *m*/*z* (%): 344 (M^+−C_2H_2O, 6), 304 (53), 302 (M^+−$2C_2H_2O$, 100), 266 (9), 231 (30), 102 (10); IR (Nujol): 1692, 1344, 1298, 1256, 1234, 1188, 1016, 762, 670 cm^{-1}.

Crystal data. $C_{18.5}H_{12.5}Cl_{3.5}N_4O_2$, M_r=446.90, monoclinic, space group *Cc*, *a*=15.6451(8), *b*=17.5842(8), *c*=14.5831(7) Å, β=111.283(2)°, *V*=3738.3(3) $Å^3$ at −100 K; *Z*=8, D_x=1.588 g/cm^3, *F*(000)=1816, μ=0.59/mm. *Data collection*. A pale yellow prism 0.30×0.29×0.26 mm was mounted in inert oil on a glass fibre and transferred to the cold gas stream of the diffractometer (Bruker SMART APEX CCD). Of 21,503 measured reflections, 8424 were unique (R_{int}=0.0196) and were used for all calculations. *Structure refinement*. The structures were refined anisotropically against F^2 (program SHELXL-97, G.M. Sheldrick, University of Göttingen). The methyl group was refined as a rigid group, other H with a riding model. This structure is refined in *Cc*. The final wR_2 value was 0.0842 for all reflections, 510 parameters and 2 restraints, with R_1 0.0333 for reflections with $I>2\sigma(I)$; max $\Delta\rho$ 0.695 e/$Å^3$, *S* 1.05.

The program PLATON suggests the higher symmetry *C*2/*c* as default with ADDSYM, but ADDSYM EXACT does not find it, which suggests 'almost but not quite' *C*2/*c*. We did not manage to refine it successfully in *C*2/*c*. When all the atoms are anisotropic, with normal anisotropic displacement parameters, and all hydrogens are fixed the R_1=0.1698 and wR_2=0.4151 and no residual electron density is higher than 0.5 e/$Å^3$.

Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC 711405.

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Supplementary data

X-ray structural data of compound **9**; NMR spectra of compounds **7**, **8a**, and **9**; optimized geometries and energies for compounds **8a**, **8a′**, **8a″**, and **9**, as well as transition state structures for **8a**→**8a″** and **8a″**→**8a′**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.059.

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