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Tetrahedron
Tetrahedron 60 (2004) 6747–6755

An efficient method for the synthesis of 1-chlorophenazines based on the selective cathodic reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione☆

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Received 6 April 2004; revised 7 June 2004; accepted 16 June 2004

Available online 2 July 2004

Dedicated to Professor José Vicente on the occasion of his 60th birthday

Abstract—An efficient method for the synthesis of 1-chlorophenazines has been established. It is based on the use of 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **4** as a synthetic equivalent of 3-chloro-1,2-benzoquinone **3**. The intermediate **4** was prepared in near quantitative yield by electroreductive monodechlorination of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**, which is an inexpensive and easily available starting material. Efficient reactions of **4** with primary 1,2-phenylenediamines provided the corresponding 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines **6**, which were directly aromatized by treatment with 2,6-lutidine to give the title compounds in high yields. X-ray crystallographic structures for 1,1,4-trichloro-1,2,3,4-tetrahydro-6-methylphenazine **6f**, 8-benzoyl-1,1,4-trichloro-1,2,3,4-tetrahydrophenazine **6ea**, and 1,7-dichlorophenazine **10db** have been determined.

1. Introduction

Phenazines show properties with a wide range of significant applications.[1] One special interest lies in the biological activity of certain naturally occurring phenazines or analogues. Some of these compounds have been demonstrated to have important therapeutic utility, mainly as antibiotic and anticancer agents.[2] This has renewed the interest in the progress of the synthesis of phenazines. Because of the remarkable reluctance of phenazines to undergo electrophilic substitution reactions, the displacement of the halogen atoms of chlorophenazines by a variety of nucleophiles can play an important role in the production of a wide variety of phenazine derivatives. However, the difficulty in preparing the appropriate chlorinated starting materials frequently results in a lack of applicability of the procedure. Chlorophenazines have, in fact, provided good entries to a number of functionalized phenazine derivatives via nucleophilic substitution.[3] The development of improved methods for the synthesis of chlorophenazines is, therefore, of substantial interest. However, 1-chlorophenazines still remain almost inaccessible.[4–10]

The main general methods[1] for the synthesis of phenazines include cyclization of 2-nitro- and 2-aminodiphenylamines, coupling between anilines and nitrobenzenes, treatment of benzofuroxans with dienophiles, and double condensation of 1,2-benzoquinones with phenylene diamines. Some other preparative methods of less extensive use have also been reported. However, when these approaches are applied in preparing chlorophenazines they frequently fail in both versatility and yield. It is apparent that the procedures reported for synthesizing 1-chlorophenazines are remarkably deficient mainly because of the inherent low activity of the aromatic intermediates implied in nucleophilic substitution processes. The drastic experimental conditions that are normally required to promote these reactions cause the removal of the majority of the functional groups present in the starting materials as well as a remarkable loss of yields. On the other hand, direct chlorination of phenazine by treatment with chlorine under different conditions[4] has been found to be remarkably unselective, leading to very complex mixtures of monochloro and polychlorophenazines. Results for chlorination reactions applied to functionalized phenazines have not been reported to date.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.089

Keywords: Phenazines; 1,2-Phenylenediamines; α,α′-Polychloro-1,2-cyclohexanodiones; Electrosynthesis; Reduction; Dehydrochlorination; Aromatization.

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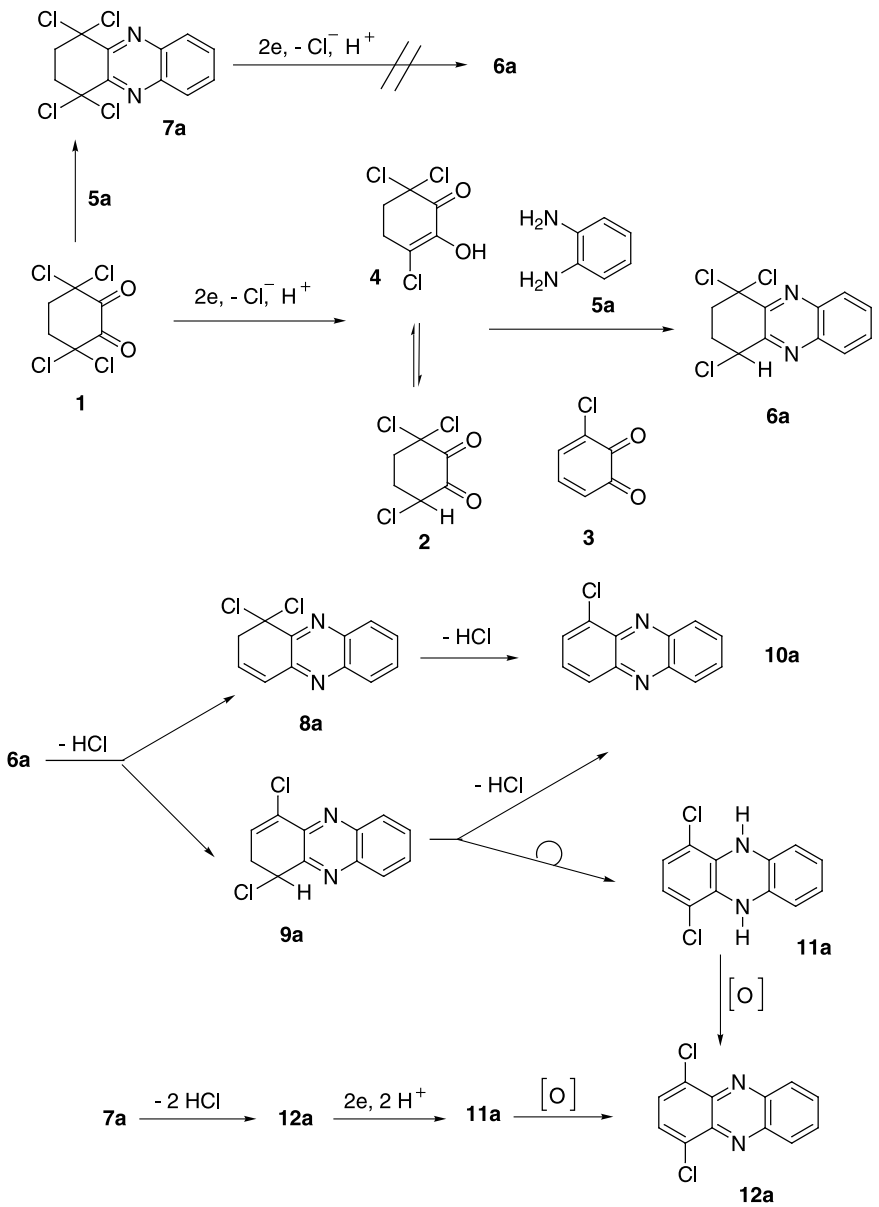
doi:10.1016/j.tet.2004.06.089

Regarding the above, it is clear that a good and versatile method for preparing 1-chlorophenazines does not seem likely to be available on this basis. Thus, the synthesis of the parent compound 1-chlorophenazine **10a** has been achieved by different procedures, involving thermal cyclation of 2′-chloro-2-nitrodiphenylamine in the presence of ferrous oxalate[5] (4.4%), a Wohl-Aue reaction[6] (18%), treatment of phenazine-N-oxide with thionyl chloride[7] (23%), chlorination of catechol followed by oxidation with silver oxide and treatment with 1,2-phenylenediamine[8] (16% overall yield) or direct chlorination of phenazine[4a] (negligible yield). Some low yield preparations of polychlorinated phenazines bearing one of the chlorine substituents at C-1 have also been reported.[9,10] These procedures seem to be incompatible with the synthesis of functionalized 1-chlorophenazines.

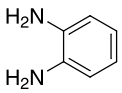
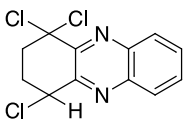
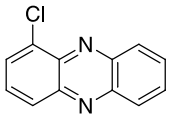
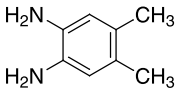
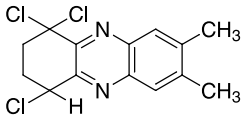
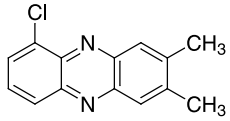
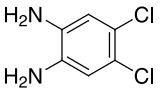
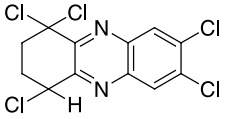
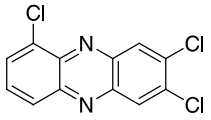
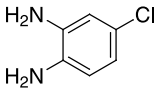
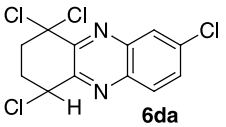
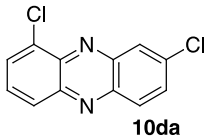
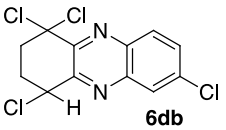
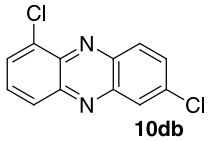
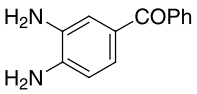
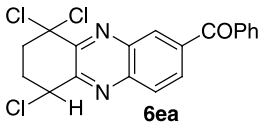
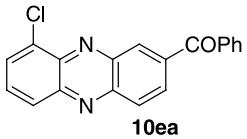
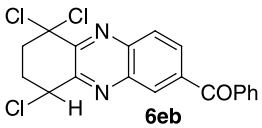
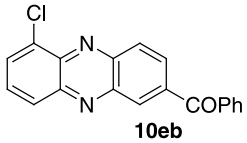
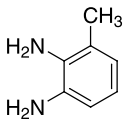
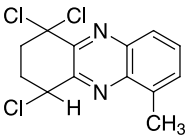
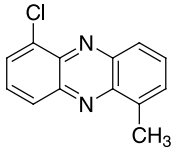
Given the precariousness of the reported syntheses of some classes of chlorophenazines, we focused on the research of improved synthetic methods for these compounds on the basis of the search for good synthetic equivalents of chlorinated *o*-quinones. It should be noted that condensation of *o*-quinones with aromatic 1,2-diamines leads directly to phenazines. However, this process appears to be unsatisfactory since the reaction of *o*-phenylenediamine with *o*-benzoquinone gives phenazine[11] in remarkable low yield (35%). Moreover, in most of cases the difficulty in preparing the appropriate *o*-quinone is an extreme synthetic problem.

Working in this project, we first reported[12] a new, efficient and versatile method for the synthesis of 1,4-dichlorophenazines by starting from 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**. It is a cheap, readily available compound. Its peculiar reactivity was found to be usable as an excellent synthetic equivalent of 3,6-dichloro-1,2-benzoquinone, which is a practically unavailable compound, whereas this synthetic equivalent can be easily obtained in quantitative yield by direct treatment of commercial *trans*-cyclohexanediol with chlorine.[12,13]



Scheme 1.

Table 1. Preparation of 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines **6a-f** and 1-chlorophenazines **10a-f**

Entry	Diamines **5**	Intermediates **6**	Yield (%)	Products **10**	Yield (%)
a			85		96
b			90		93
c			83		89
d		 **6da**	46	 **10da**	96
		 **6db**	35	 **10db**	96
e		 **6ea**	45	 **10ea**	91
		 **6eb**	41	 **10eb**	93
f			92		91

As was reported in a preliminary communication,[13] we successfully extended the above novel synthetic methodology to the synthesis of 1-chlorophenazines. In this paper we describe full details of the previous report on this subject as well as new outcomes of this preparative procedure which is illustrated in Scheme 1 and Table 1. The aim of this approach is to circumvent the use of 3-chloro-1,2-benzoquinone **3** which is a rare and practically inaccessible compound.[8,14–16] Moreover, the advantage of a highly efficient reaction between vicinal dicarbonyl groups with aromatic 1,2-diamines instead of *o*-quinonoid ones is another attractive feature of this procedure.

2. Results and discussion

The preparation of 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **4** was attempted by reaction of cyclohexanone with copper dichloride[17] (ratio 1:20) in dioxane–water. Because of the low yield and the requirement of a difficult chromatographic isolation of the product, this reaction was found to be of little synthetic use. However, this obstacle could be satisfactorily overcome by an efficient and highly selective electrochemical reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**. Thus, electrolysis of **1** under a constant cathodic potential in a protic medium gave a single product quantitatively, which was isolated and identified as the compound **4** which corresponds to the enol form of the intended key intermediate **2**.

In order to achieve the synthesis of 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines **6** to be used as precursors of the targeted 1-chlorophenazines, reactions of **4** with 1,2-phenylenediamines **5** were carried out. The reactivity of **4** was observed to be similar to that predictable for the dione **2**. High yields in the expected products **6** were obtained by

performing the reaction in benzene with continuous azeotropic removal of water. These products were easily obtained in a crystalline state and were stable enough to permit prolonged storage without receiving any special care. There are no precedents for this family of compounds. It should be noted that reactions with symmetrical diamines such as **5a**-**c** gave the corresponding single products **6a**-**c**. However, the reactions with nonsymmetrical diamines **5d**,**e** gave two pairs of the possible isomeric products (**6d**-**a**,**b** and **6e**-**a**,**b**), which were formed in a comparable ratio. All these isomers could be definitively differentiated by X-ray crystallographic analysis of either a member of each product pair or a phenazine derivative, thus single crystals of compound **6ea** and **10db** were analyzed by X-ray crystallography. The molecular structures are illustrated in Figures 1 and 2, respectively. Selected bond lengths are given in Tables 2 and 3, respectively.

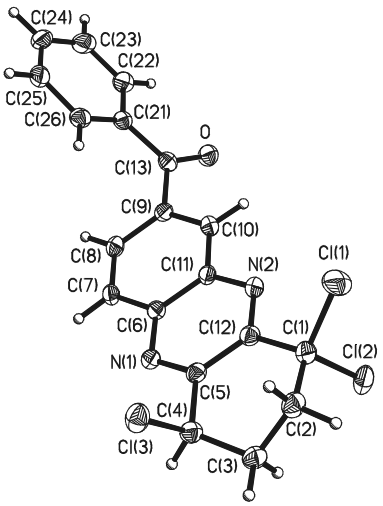


Figure 1. Molecular structure of **6ea**, showing the crystallographic numbering system used.

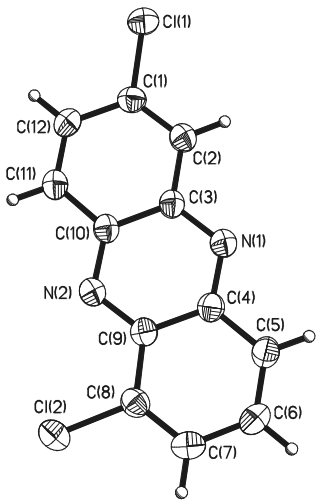


Figure 2. Molecular structure of **10db**, showing the crystallographic numbering system used.

The reaction with 3-methyl-1,2-phenylenediamine **5f** was found to be fully selective towards the formation of 1,1,4-trichloro-1,2,3,4-tetrahydro-6-methylphenazine **6f**. The molecular structure of this product was corroborated by

Table 2. Selected bond lengths in crystal structure of **6ea**

Cl(1)–C(1)	1.788(2)	C(1)–C(2)	1.521(3)
Cl(2)–C(1)	1.804(2)	C(3)–C(4)	1.513(3)
Cl(3)–C(4)	1.824(2)	C(4)–C(5)	1.502(3)
O–C(13)	1.222(2)	C(9)–C(13)	1.503(3)
C(1)–C(12)	1.521(3)	C(13)–C(21)	1.488(3)

Table 3. Selected bond lengths in crystal structure of **10db**

Cl(1)–C(1)	1.740(2)	N(2)–C(9)	1.340(2)
Cl(2)–C(8)	1.736(2)	N(2)–C(10)	1.343(2)
N(1)–C(4)	1.341(2)	C(3)–C(10)	1.436(2)
N(1)–C(3)	1.343(2)	C(4)–C(9)	1.439(2)

single crystal X-ray diffraction analysis. It seems reasonable to presume that steric factors are implied in the exclusive formation of this product

In the search for an alternative approach to 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines **6**, the electrochemical reduction of 1,1,4,4-tetrachloro-1,2,3,4-tetrahydrophenazine **7a** at constant potential in a protic medium was carried out. However, this electrolysis was found to be remarkably unselective and it led to a complex mixture of products with a different dechlorination degree.

The first experiments, focused on establishing effective experimental conditions to achieve the conversion of intermediates **6** to the corresponding 1-chlorophenazines **10**, gave surprising and somewhat disappointing results. Thus, the treatment of **6a** with pyridine yielded the expected 1-chlorophenazine **10a** in moderate yield (62%) but accompanied by a considerable amount of 1,4-dichlorophenazine **12a** (26%). The reaction with sodium methoxide gave a similar result. Some other experiments were carried out, showing the generation of 1-chlorophenazines along with the undesired 1,4-dichlorophenazines as a general synthetic limitation of these reactions.

It was considered that the formation of the targeted 1-chlorophenazines implies an aromatization process associated with a double elimination of hydrogen chloride from intermediates **6**. However, aromatization leading to 1,4-dichlorophenazines obviously involve a monodehydrohalogenation process of the same intermediates. Therefore, the collaboration of an oxidation process must be necessarily postulated to clarify the formation of the lateral products **12**. This hypothesis leads us to conclude that a crucial influence of the site where the intermediates **6** undergo a first deprotonation provides the most plausible explanation that may be offered for these facts. Thus, deprotonation at C-3 would promote the formation of intermediates **8**, which would give the targeted products **10** exclusively. However, deprotonation at C-2 would generate the intermediates **9**, which could reasonably undergo dehydrochlorination to give products **10**, but also rearrangement to 1,4-dichloro-5,10-dihydrophenazines **11**, whose oxidation explains the formation of products **12**.

This reaction route is well supported by the following facts: (1) the great proclivity of 5,10-dihydrophenazines towards undergoing oxidation yielding phenazines is well known;[14] (2) a sample of 1,4-dichloro-5,10-dihydrophenazine **11a**

was prepared by electrochemical reduction of **12a** in a protic medium. When compound **11a** was exposed to a similar experimental conditions as those operating in the conversion of **6a** to **10a**, an almost instantaneous quantitative formation of 1,4-dichlorophenazine **12a** was observed even when working under nitrogen atmosphere; (3) the generation of product **12a** was fully prevented by treatment of **6a** with 2,6-lutidine instead of pyridine. In this case the exclusive formation of 1-chlorophenazine **10a** (96%) occurred. This result is in excellent agreement with the expected effect of a bulky base determining regioselectivity towards the less hindered reactive site. It seems reasonable, therefore, in this case to assume a process with the exclusive generation of **10a** without participation of the intermediates **9a** and **11a**.

In conclusion, a simple and effective method for the synthesis of 1-chlorophenazines **10** is reported whose selectivity is helped by steric effects developed by the base promoting aromatization. Nearly quantitative yields, easy availability of starting materials are valuable, noteworthy advantages of the method which allows the access to previously unattainable compounds. It is also to be noted that this work has revealed 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **4** as an excellent synthetic equivalent of 3-chloro-1,2-benzoquinone **3**. Since the usefulness of quinones in organic synthesis is well known the compound **4** seems likely to be a promising intermediate in allowing the selective synthesis of a wide variety of specifically chlorinated compounds.

3. Experimental

3.1. General

NMR spectra were determined on Bruker AC-200 or Varian Unity 300 Unity instruments with tetramethylsilane as internal reference. Electron-impact mass spectra were obtained on Hewlett–Packard 5995 and Autospect 5000 VG spectrometers under an ionizing voltage of 70 eV. IR spectra (Nujol emulsions) were recorded on a Nicolet Impact 400 spectrophotometer. Microanalyses were performed on a Carlo Erba EA-1108 analyzer. Melting points were determined on a Kofler hot-plate melting point apparatus, and are uncorrected. Electrochemical experiments were performed with an Amel 557 potentiostat coupled to an Amel 558 integrator. 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1** was prepared as previously described.[12]

X-ray crystallographic data were collected using Mo K_α radiation (λ=0.71073 Å). For compounds **6f** and **6ea** a Siemens P4 diffractometer was used (ω-scans, $2\theta_{max}$ 50°); for the structure of **10db**, a Bruker SMART CCD (ω and ø-scans, $2\theta_{max}$ 56°, absorption correction using multiple scans). Structures were refined anisotropically on F^2 using the program SHELXL-93 (G. M. Sheldrick, University of Göttingen). Hydrogen atoms were included using rigid methyl groups or a riding model. Full structural information has been deposited with the Cambridge Crystallographic Data Centre.[18]

3.1.1. Preparation of 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one (4). A reductive electrolysis[19] of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1** was carried out under a constant cathodic potential in a concentric cylindrical cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm; Luggin-capillary situated to the side of the pool) was used as the cathode and a platinum plate as the anode. The current intensity was 240 mA at the beginning, and 10 mA at the end. The cell voltage remained below 6 V. The catholyte was magnetically stirred. The temperature was kept at approximately 18 °C by external cooling. The reduction was performed in MeCN (40 mL)—AcOH (10 mL)—$LiClO_4$ (3 g); 35 mL and 15 mL were placed in the cathodic and the anodic compartments, respectively. Sodium acetate (0.2 g) was placed in the anode compartment. A solution of **1** (5 mmol) was electrolyzed under a cathodic potential of −0.05 V versus SCE. The electricity consumption was 2 F/mol. Isolation of product **4** was carried out by removing the solvent in vacuo,[20] adding water (150 mL) and extracting the mixture with chloroform (3×40 mL). The combined organic layers were washed with cold water and dried on anhydrous sodium sulphate. After evaporation of chloroform under reduced pressure the solid residue was crystallized from petroleum ether, yield 95%, white needles; mp 120–121 °C (lit.[17] 119–120 °C) (Found: C, 33.30; H, 2.40; $C_6H_5Cl_3O_2$ requires: C, 33.45; H, 2.34); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 2.84–2.95 (m, 4H), 6.20 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 30.47, 42.46, 82.70, 129.2, 140.70, 180.52; MS *m/z* (%) 218 [M^++4] (5), 216 [M^++2] (15), 214 [M^+] (18), 179 (15), 161 (7), 153 (55), 151 (100), 118 (66), 90 (43), 54 (90); IR (Nujol) 3389, 1698, 1638, 1355, 1273, 1152, 1132, 1056, 970, 910, 876, 808, 702 cm^{-1}.

This synthesis was found to be reproducible when using graphite instead of mercury as cathodic material. The preparation of **4** was achieved in 83% yield by a procedure as described above but with an operating potential of −0.30 V versus SCE. The current intensity was 310 mA at the beginning, and 10 mA at the end. The cell voltage remained below 8 V. The electricity consumption was 2 F/mol.

3.1.2. Preparation of 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines (6). A benzene solution (75 mL) of **4** (5.56 mmol) and the appropriate diamine **5** (5.48 mmol) was refluxed with a Dean–Stark water separator for 24 h. The solvent was evaporated under reduced pressure and the residue was shaken with ether (75 mL). The small amount of a white solid remaining in suspension was removed by filtration. After evaporation of ether, highly pure products **6** were isolated and crystallized in the appropriate solvent. Products **6d-a**,**b** and **6e-a**,**b** were isolated by column chromatography.

3.1.3. 1,1,4-Trichloro-1,2,3,4-tetrahydrophenazine (6a). (85%); Crystallization from petroleum ether gave white prisms; mp 135–137 °C. (Found: C, 49.33; H, 3.23; N, 9.86; $C_{12}H_9Cl_3N_2$ requires: C, 50.12; H, 3.15; N, 9.74); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 2.49–2.59 (m, 1H), 2.81–2.94 (m, 1H), 3.05–3.14 (m, 1H), 3.41–3.53 (m, 1H), 5.53–5.56 (m, 1H), 7.80–7.87 (m, 2H), 8.09–8.15 (m, 1H) 8.19–8.26 (m, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 29.73, 40.77, 57.18,

85.59, 129.05, 129.59, 131.48, 131.86, 142.39, 142.69, 146.97, 149.65; MS, *m/z* (%): 290 [M^++4] (3), 288 [M^++2] (9), 286 [M^+] (9), 251 (21), 215 (100), 217 (31), 181 (23), 108 (21), 102 (33), 76 (67). IR (Nujol) 1556, 1356, 1235, 948, 921, 900, 832, 787, 769, 689 cm^{-1}.

3.1.4. 1,1,4-Trichloro-1,2,3,4-tetrahydro-7,8-dimethylphenazine (6b). (90%); Crystallization from petroleum ether gave white prisms; mp 197–198 °C. (Found: C, 52.97; H, 4.09; N, 8.96; $C_{14}H_{13}Cl_3N_2$ requires: C, 53.28; H, 4.15; N, 8.88); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.41–2.58 (m, 1H), 2.50 (s, 6H), 2.77–2.95 (m, 1H), 3.00–3.13 (m, 1H), 3.37–3.53 (m, 1H), 5.49–5.53 (m, 1H), 7.85 (s, 1H), 7.98 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz) 20.49, 20.58, 29.78, 40.78, 57.45, 85.91, 127.83, 128.36, 141.49, 141.82, 142.67, 143.13, 145.81, 148.63; MS *m/z* (%) 318 [M^++4] (1), 316 [M^++2] (3), 314 [M^+] (3), 279 (15), 243 (76), 245 (25), 209 (22), 193 (13), 103 (79), 89 (25), 77 (99), 51 (100); IR (Nujol) 1357, 1205, 1009, 942, 922, 871, 806, 782, 760, 655 cm^{-1}.

3.1.5. 1,1,4,7,8-Pentachloro-1,2,3,4-tetrahydrophenazine (6c). (83%); Crystallization from petroleum ether gave white prisms; mp 152–153 °C. (Found: C, 40.60; H, 2.04; N, 7.99; $C_{12}H_7Cl_5N_2$ requires: C, 40.43; H, 1.98; N, 7.86); ^{1}H NMR δ ($CDCl_3$, 200 MHz): 2.47–2.61 (m, 1H), 2.78–2.96 (m, 1H), 3.02–3.14 (m, 1H), 3.36–3.53 (m, 1H), 5.47–5.52 (m, 1H), 8.25 (s, 1H), 8.37 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 29.53, 40.53, 56.73, 85.02, 129.54, 130.04, 136.64, 136.99, 140.99, 141.30, 148.25, 150.74; MS *m/z* (%) 354 [M^+] (2), 321 (8), 285 (30); 283 (30), 249 (12), 213 (14), 134 (19), 124 (27), 109 (52), 100 (32), 75 (76), 61 (46), 51 (100); IR (Nujol) 1380, 1229, 1111, 985, 942, 922, 891, 847, 802, 753 cm^{-1}.

3.1.6. 1,1,4,8-Tetrachloro-1,2,3,4-tetrahydrophenazine (6da). (46%); Chromatography (AcOEt/petroleum ether, 15:85) gave white powder; mp 150–151 °C. (Found: C, 44.61; H, 2.41; N, 8.77; $C_{12}H_8Cl_4N_2$ requires: C, 44.76; H, 2.50; N, 8.70; ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.47–2.61 (m, 1H), 2.79–2.97 (m, 1H), 3.03–3.15 (m, 1H), 3.38–3.54 (m, 1H), 5.49–5.54 (m, 1H), 7.79 (dd, *J*=9.1, 2.3 Hz, 1H), 8.12 (d, *J*=2.3 Hz, 1H), 8.18 (d, *J*=9.1 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz) 29.57, 40.59, 56.86, 85.29, 127.87, 130.76, 132.74, 138.09, 140.88, 142.84, 148.01, 149.81; MS *m/z* (%) 324 [M^++4] (3), 322 [M^++2] (6), 320 [M^+] (4), 287 (21), 285 (21), 251 (62), 249 (100), 215 (38), 179 (28), 163 (20), 100 (35), 75 (99). IR (Nujol) 1607, 1354, 1188, 1064, 951, 928, 844, 836, 817, 723, 653 cm^{-1}.

3.1.7. 1,1,4,7-Tetrachloro-1,2,3,4-tetrahydrophenazine (6db). (35%); Chromatography (AcOEt/ petroleum ether, 15:85) gave white powder; mp 194–195 °C. (Found: C, 44.53; H, 2.58; N, 8.61; $C_{12}H_8Cl_4N_2$ requires: C, 44.76; H, 2.50; N, 8.70.); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.48–2.61 (m, 1H), 2.79–2.97 (m, 1H), 3.02–3.16 (m, 1H), 3.38–3.54 (m, 1H), 5.49–5.54 (m, 1H), 7.79 (dd, *J*=9.0, 2.3 Hz, 1H), 8.07 (d, *J*=9.0 Hz, 1H), 8.25 (d, *J*=2.3 Hz, 1H). ^{13}C NMR δ ($CDCl_3$, 50.3 MHz) 29.64, 40.61, 57.00, 85.24, 128.43, 130.29, 133.16, 137.80, 141.27, 142.65, 147.25, 150.63. MS *m/z* (%) 324 [M^++4] (2), 322 [M^++2] (4), 320 [M^+] (4), 287 (9), 285 (9), 251 (41), 249 (63), 215 (21), 179 (17), 163 (15), 100 (31), 75 (92), 51 (100). IR (Nujol) 1601, 1351, 1233, 1128, 1096, 955, 930, 841, 799, 753, 721, 640 cm^{-1}.

Crystallographic details. Yellow needle-like single crystals were grown from a solution in chloroform. A crystal of approximate dimensions 0.40×0.05×0.03 mm^3 was selected and mounted on a glass fiber. A total of 6632 reflections ($-5\le h\le 5$, $-16\le k\le 10$, $-28\le l\le 27$) were collected at T=173(2) K in the θ range from 1.88 to 28.31° of which 2509 were unique (R_{int}=0.0277; Mo K_α radiation (λ=0.71073 Å). The residual peak and hole electron density were 0.306 and −0.200 e/Å^3. The absorption coefficient was 0.601 mm^{-1}. The least-squares refinement converged normally with residuals of R_1=0.0628 (all data), wR_2=0.0934, and GOF=1.065 [$I>2\sigma(I)$]. $C_{12}H_6Cl_2N_2$, monoclinic, space group $P2_1/c$, a=3.9055(10) Å, b=12.130(4) Å, c=21.623(8) Å, α=90°, β=92.00(3)°, γ=90°, V=1023.7(6) Å^3, Z=4, ρ_{calc}=1.616 g/cm^3, F(0,0,0)=504, $R(F)$=0.0385, $wR(F_2)$=0.0835.

3.1.8. 8-Benzoyl-1,1,4-trichloro-1,2,3,4-tetrahydrophenazine (6ea). (45%); Chromatography (CH_2Cl_2/AcOEt/hexane, 80:10:10) gave white powder; mp 161–162 °C. (Found: C, 57.32; H, 3.21; N, 7.22; $C_{19}H_{13}Cl_3N_2O$ requires: C, 58.26; H, 3.35; N, 7.15; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 2.52–2.62 (m, 1H), 2.84–2.97 (m, 1H), 3.06–3.15 (m, 1H), 3.41–3.52 (m, 1H), 5.55–5.58 (m, 1H), 7.54 (tt, *J*=7.5, 1.5 Hz, 2H), 7.66 (tt, *J*=7.5, 1.5 Hz, 1H), 7.88 (dt, *J*=7.5, 1.5 Hz, 2H), 8.25 (dd, *J*=8.6, 0.6 Hz, 1H), 8.33 (dd, *J*=8.6, 1.8 Hz, 1H), 8.57 (dd, *J*=1.8, 0.6 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 29.42, 40.46, 57.79, 85.10, 128.59, 129.53, 129.99, 131.55, 132.28, 133.04, 136.59, 139.64, 141.40, 144.06, 148.76, 150.74, 195.11; MS *m/z* (%) 394 [M^++4] (2), 392 [M^++2], (6), 390 [M^+] (6), 357 (9), 355 (13), 319 (97), 321 (32), 179 (20), 105 (91), 77 (100). IR (Nujol) 1666, 1355, 1267, 946, 894, 846, 827, 790, 711, 676 cm^{-1}.

Crystallographic details. Colourless block-like crystals were obtained by slow diffusion of *n*-hexane into a solution of **6ea** in chloroform. A crystal of approximate dimensions 0.60×0.40×0.20 mm^3 was selected and mounted on a glass fiber. A total of 3304 reflections ($-9\le h\le 9$, $-10\le k\le 1$, $-15\le l\le 15$) were collected at T=173(2) K in the θ range from 3.16 to 24.99° of which 2989 were unique (R_{int}=0.0248; Mo K_α radiation (λ=0.71073 Å). The residual peak and hole electron density were 0.239 and −0.227 e/Å^3. The absorption coefficient was 0.545 mm^{-1}. The least-squares refinement converged normally with residuals of R_1=0.0358 (all data), wR_2=0.0863, and GOF=1.087 [$I>2\sigma(I)$]. $C_{19}H_{13}Cl_3N_2O$, triclinic, space group P-1, a=7.6607(7) Å, b=8.8706(6) Å, c=13.1580(12) Å, α=75.939(7)°, β=82.475(7)°, γ=83.248(6) °, V=856.5(2) Å^3, Z=2, ρ_{calc}=1.519 g/cm^3, F(0,0,0)=400, $R(F)$=0.0301, $wR(F^2)$=0.0824.

3.1.9. 7-Benzoyl-1,1,4-trichloro-1,2,3,4-tetrahydrophenazine (6eb). (41%); Chromatography (CH_2Cl_2/AcOEt/hexane, 80:10:10) gave white powder; mp 138–140 °C. (Found: C, 58.59; H, 3.44; N, 7.03; $C_{19}H_{13}Cl_3N_2O$ requires: C, 58.26; H, 3.35; N, 7.15); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 2.52–2.61 (m, 1H), 2.83–2.96 (m, 1H), 3.07–3.16 (m, 1H), 3.43–3.54 (m, 1H), 5.52–5.55 (m, 1H), 7.54 (tt, *J*=7.4, 1.6 Hz, 2H), 7.66 (tt, *J*=7.4, 1.6 Hz, 1H), 7.88 (dt, *J*=7.4, 1.6 Hz, 2H), 8.31 (dd, *J*=9.0, 1.8 Hz, 1H), 8.36 (dd, *J*=9.0, 0.6 Hz, 1H), 8.47 (dd, *J*=1.8, 0.6 Hz, 1H); ^{13}C

NMR δ ($CDCl_3$, 75.4 MHz) 29.63, 40.63, 56.93, 85.23, 128.70, 130.13, 130.16, 131.31, 131.81, 133.22, 136.71, 140.11, 141.88, 143.95, 148.31, 151.35, 195.24; MS *m/z* (%) 394 [M^++4] (12), 392 [M^++2], (36), 390 [M^+] (40), 357 (33), 355 (49), 319 (65), 290 (43), 179 (92), 105 (78), 77 (100); IR (Nujol) 1666, 1378, 1265, 949, 847, 830, 792, 730, 715 cm^{-1}.

3.1.10. 1,1,4-Trichloro-1,2,3,4-tetrahydro-6-methylphenazine (6f). (92%); Crystallization from acetonitrile gave white microcystals; mp 140–142 °C. (Found: C, 51.74; H, 3.74; N, 9.37; $C_{13}H_{11}Cl_3N_2$ requires: C, 51.77; H, 3.68; N, 9.29); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 2.48–2.58 (m, 1H), 2.78 (s, 3H), 2.80–2.93 (m, 1H), 3.04–3.12 (m, 1H), 3.42–3.54 (m, 1H), 5.53–5.57 (m, 1H), 7.63 (br d, *J*=6.9 Hz, 1H), 7.67–7.74 (m, 1H), 8.05 (dd, *J*=8.4, 0.6 Hz, 1H). ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 17.20, 29.82, 40.87, 57.54, 85.80, 127.33, 131.35, 131.50, 137.77, 142.04, 142.59, 145.62, 149.11. MS *m/z* (%) 304 [M^++4] (3), 302 [M^++2] (7), 300 [M^+] (8), 265 (16), 231 (29), 229 (100), 193 (48), 97 (40), 89 (43), 75 (25), 63 (47); IR (Nujol) 1378, 1238, 947, 919, 817, 788, 767, 760, 679 cm^{-1}.

Crystallographic details. Colourless block-like single crystals were obtained by slow diffusion of petroleum ether into a solution of **6f** in chloroform. A crystal of approximate dimensions 0.42×0.35×0.32 mm^3 was selected and mounted on a glass fiber. A total of 2836 reflections ($-8\leq h\leq 8$, $-23\leq k\leq 4$, $-10\leq l\leq 0$) were collected at T=173(2) K in the θ range from 3.12 to 24.99° of which 2235 were unique (R_{int}=0.0387; Mo K_α radiation (λ=0.71073 Å). The residual peak and hole electron density were 0.428 and −0.411 e/Å^3. The absorption coefficient was 0.699 mm^{-1}. The least-squares refinement converged normally with residuals of R_1=0.0619 (all data), wR_2=0.1227, and GOF=1.100 [$I>2\sigma(I)$]. $C_{13}H_{11}Cl_3N_2$, monoclinic, space group $P2_1/n$, a=7.4190(10) Å, b=19.689(2) Å, c=8.7640(10) Å, α=90°, β=94.420(10)°, γ=90°, V=1276.4(3) Å^3, Z=4, ρ_{calc}=1.569 g/cm^3, F(0,0,0)=616, $R(F)$=0.0447, $wR(F^2)$=0.1138.

3.2. Preparation of 1-chlorophenazines (10)

A dimethylformamide solution (30 mL) of the appropriate intermediate **6** (3.5 mmol) and 2,6-lutidine (2 mL) was refluxed for 2 h. After cooling the reaction products were isolated by dropping the solution onto cold brine (400 mL) and filtration. The directly collected solid crude products were washed with cold water, dried and crystallized from the appropriate solvent.

3.2.1. 1-Chlorophenazine (10a). (96%); Crystallization from hexane gave yellow needles; mp 123–124 °C (lit.[6] 122 °C). ^{1}H NMR δ ($CDCl_3$, 200 MHz): 7.62–7.71 (m, 1H), 7.76–7.91 (m, 3H), 8.05–8.19 (m, 2H), 8.26–8.35 (m, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 128.77, 129.28, 129.58, 129.69, 129.93, 130.94, 131.16, 132.97, 139.87, 143.13, 143.46, 143.67; MS *m/z* (%) 216 [M^++2] (32), 214 [M^+] (93), 179 (49), 152 (23), 129 (10), 125 (11), 107 (18), 100 (20), 89 (11), 75 (100), 63 (32), 50 (92). IR (Nujol) 1510, 1380, 958, 821, 762, 742, 676 cm^{-1}.

3.2.2. 1-Chloro-7,8-dimethylphenazine (10b). (93%); Crystallization from petroleum ether/Cl_3CH gave yellow needles; mp 224–225 °C. (Found: C, 69.19; H, 4.62; N, 11.60. $C_{14}H_{11}ClN_2$ requires: C, 69.28; H, 4.57; N, 11.54); ^{1}H NMR δ ($CDCl_3$, 200 MHz): 2.56 (s, 6H), 7.64–7.73 (m, 1H), 7.90 (dd, *J*=7.3, 1.0 Hz, 1H), 7.95 (s, 1H), 8.11–8.16 (m, 2H). ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 20.75, 20.83, 127.69, 128.41, 128.83, 129.05, 129.24, 132.97, 139.74, 142.73, 142.87, 142.96, 143.19, 143.57; MS *m/z* (%) 244 [M^++2] (31), 242 [M^+] (100), 229 (8), 227 (28), 205 (16), 179 (15), 136 (10), 121 (18), 103 (37), 89 (30), 75 (81), 63 (60), 51 (85). IR (Nujol) 1505, 1380, 1353, 956, 860, 823, 779, 743, 727 cm^{-1}.

3.2.3. 1,7,8-Trichlorophenazine (10c). (89%); Crystallization from petroleum ether gave yellow needles; mp 237–238 °C. (Found: C, 50.98; H, 1.83; N, 9.11; $C_{12}H_5Cl_3N_2$ requires: C, 50.83; H, 1.78; N, 9.88); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.73–7.79 (m, 1H), 7.96 (dd, *J*=7.5, 1.2 Hz, 1H), 8.14 (dd, *J*=8.7, 1.2 Hz, 1H), 8.32 (s, 1H), 8.52 (s, 1H). ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 129.10, 129.82, 130.43, 130.65, 130.72, 133.68, 136.42, 136.62, 140.75, 141.93, 142.37, 144.56; MS *m/z* (%) 286 [M^++4] (7), 284 [M^++2] (23), 282 [M^+] (24), 249 (7), 247 (11), 141 (10), 136 (15), 134 (11), 124 (15), 109 (31), 100 (47), 75 (100), 50 (57); IR (Nujol) 1613, 1378, 1103, 994, 958, 884, 871, 825, 775, 753, 738 cm^{-1}.

3.2.4. 1,8-Dichlorophenazine (10da). (96%); Crystallization from Cl_3CH gave yellow needles; mp 226–227 °C (lit.[6] 219–220 °C). ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.67–7.77 (m, 2H), 7.91 (dd, *J*=7.2, 1.2 Hz, 1H), 8.10 (dd, *J*=9.1, 1.2 Hz, 1H), 8.19 (dd, *J*=1.2, 0.6 Hz, 1H), 8.26 (dd, *J*=9.1, 0.6 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 127.92, 128.91, 130.02, 130.30, 131.41, 132.43, 133.55, 137.48, 140.20, 141.84, 143.69, 144.39; MS *m/z* (%) 252 [M^++4] (24), 250 [M^++2] (87), 248 [M^+] (100), 215 (17), 213 (50), 178 (8), 124 (15), 75 (19); IR (Nujol) 1508, 1411, 1344, 1067, 957, 935, 888, 885, 811, 739, 713 cm^{-1}.

3.2.5. 1,7-Dichlorophenazine (10db). (96%); Crystallization from Cl_3CH gave yellow needles; mp 259–260 °C. (Found: C, 58.02; H, 2.48; N, 11.20; $C_{12}H_6Cl_2N_2$ requires: C, 57.86; H, 2.43; N, 11.25); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.70–7.81 (m, 2H), 7.95 (br d, *J*=7.2 Hz, 1H), 8.13–8.19 (m, 2H), 8.37 (dd, *J*=1.8, 0.6 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 128.66, 129.14, 130.02, 130.52, 130.89, 132.78, 133.52, 137.41, 140.69, 142.36, 143.41, 144.11; MS *m/z* (%) 252 [M^++4] (12), 250 [M^++2] (70), 248 [M^+] (100), 215 (10), 213 (29), 124 (8), 100 (5), 75 (11); IR (Nujol) 1619, 1593, 1419, 1061, 956, 946, 856, 835, 766, 738, 715 cm^{-1}.

3.2.6. 8-Benzoyl-1-chlorophenazine (10ea). (91%); Crystallization from Cl_3CH gave yellow needles; mp 184–186 °C. (Found: C, 71.72; H, 3.54; N, 8.87; $C_{19}H_{11}ClN_2O$ requires: C, 71.59; H, 3.48; N, 8.79); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.55 (tt, *J*=7.5, 1.2 Hz, 2H), 7.66 (tt, *J*=7.5, 1.7 Hz, 1H), 7.76–7.83 (m, 1H), 7.91–7.99 (m, 3H), 8.19 (dd, *J*=9, 1.2 Hz, 1H), 8.31–8.39 (m, 2H), 8.68–8.70 (m, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 128.74, 129.11, 130.17, 130.43, 130.70, 130.95, 133.09, 133.53, 133.63, 137.05, 139.20, 140.91, 142.39, 144.83, 144.88, 195.59; MS *m/z* (%) 320 [M^++2] (68), 318 [M^+] (98), 289 (88), 243 (29), 241 (78), 215 (29), 213 (69), 178 (15), 105 (100), 77

(90); IR (Nujol) 1658, 1380, 1321, 1244, 953, 901, 856, 825, 728, 675 cm^{-1}.

3.2.7. 7-Benzoyl-1-chlorophenazine (10eb). (93%); Crystallization from Cl_3CH gave yellow needles; mp 277–279 °C. (Found: C, 71.44; H, 3.51; N, 8.63; $C_{19}H_{11}ClN_2O$ requires: C, 71.59; H, 3.48; N, 8.79); ^1H NMR δ ($CDCl_3$, 200 MHz): 7.55 (tt, J=7.3, 1.5 Hz, 2H), 7.68 (tt, J=7.3, 1.2 Hz, 1H), 7.91–8.04 (m, 3H), 8.17 (dd, J=8.8, 1.3 Hz, 1H), 8.35 (dd, J=9.0, 1.7 Hz, 1H), 8.49 (d, J=9.0 Hz, 1H), 8.60 (d, J=1.7 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 128.69, 129.12, 130.20, 130.41, 130.45, 130.72, 130.97, 133.06, 133.13, 133.41, 136.85, 139.26, 140.99, 142.72, 144.38, 144.61, 195.47; MS *m/z* (%) 320 [M^++2] (34), 318 [M^+] (100), 290 (77), 289 (58), 241 (52), 213 (42), 178 (10), 105 (84), 77 (57); IR (Nujol) 1661, 1380, 1322, 1302, 1245, 1112, 955, 899, 855, 725, 698, 673 cm^{-1}.

3.2.8. 1-Chloro-6-methylphenazine (10f). (91%); Crystallization from petroleum ether /Cl_3CH gave yellow needles; mp 316–317 °C. (Found: C, 68.41; H, 3.88; N, 12.31; $C_{13}H_9ClN_2$ requires: C, 68.28; H, 3.97; N, 12.25); ^1H NMR δ ($CDCl_3$, 300 MHz): 2.92 (s, 3H), 7.64–7.78 (m, 3H), 7.92 (dd, J=7.4, 1.4 Hz, 1H), 8.18–8.23 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 17.60, 128.18, 129.23, 129.49, 129.69, 130.37, 131.07, 133.22, 138.04, 140.02, 143.39, 143.62, 143.82; MS *m/z* (%) 230 [M^+ +2] (30), 228 [M^+] (100), 193 (16), 192 (30), 165 (21), 140 (10), 114 (26), 100 (19), 89 (31), 75 (58), 63 (61). IR (Nujol) 1618, 1558, 1378, 1346, 1119, 1075, 1057, 952, 849, 805, 747, 721, 670 cm^{-1}.

3.3. Preparation of 1,4-dichloro-5,10-dihydrophenazine (11a)

A cathodic reduction of 1,4-dichlorophenazine **12a** was carried out under a constant cathodic potential in a cell and an electrolysis medium like that described for the electrochemical reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**. The temperature was kept at approximately 18 °C by external cooling. The reduction was performed in MeCN (40 mL)—AcOH (10 mL)—$LiClO_4$ (3 g); 35 and 15 mL were placed in the cathodic and the anodic compartments, respectively. Sodium acetate (0.2 g) was placed in the anode compartment. A solution of **12a** (5 mmol) was electrolyzed under a cathodic potential of −0.70 V versus SCE. The electricity consumption was 2 F/mol. It was observed that the initial intensive yellow colour of the catholyte solution became progressively violet according to the progress of the electricity pass. Isolation of product **11a** was carried out by removing the solvent in vacuo,[20] adding water (150 mL) and collecting the blue solid precipitate by vacuum filtration. Crystallization from acetonitrile gave blue needles; mp 75 °C dec, yield 95%; (Found: C, 57.31; H, 3.18; N, 11.14; $C_{12}H_8Cl_2N_2$ requires: C, 57.40; H, 3.21; N, 11.16); ^1H NMR δ ($CDCl_3$, 200 MHz): 5.26 (br s, 2H), 6.16–6.21 (m, 2H), 6.38 (s, 2H), 6.46–6.53 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 113.07, 114.62, 121.01, 122.37, 130.75, 131.21; MS *m/z* (%) 254 [M^++4] (9), 252 [M^++2] (55), 250 [M^+] (100), 214 (26), 179 (68), 152 (25), 125 (48), 102 (35), 89 (38), 76 (48); IR (Nujol) 3423, 1615, 1516, 1287, 1169, 1110, 946, 908, 769, 738 cm^{-1}.

4. Supporting Information Available

Complex X-ray crystallographic data for **6f**, **6ea** and **10db**.

Acknowledgements

Author J.I.-L thanks the Fundación Séneca (Comunidad Autónoma de Murcia) for a postgraduate grant.

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18. Supplementary publication number CCDC-231412 (**6ea**), -231411 (**6f**), -231413 (**10db**) can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB12 1E2, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
19. For a review about electrochemistry of halogenated organic compounds see Peters, D. G. In *Organic Electrochemistry*; Lund, H., Hammerich, O., Eds.; Marcel Dekker: New York, 2001; Chapter 8.
20. Caution must be exercised when handling perchlorates in order to exclude explosion risk. Evaporation of organic solutions containing perchlorates requires to be carried out in vacuo and at moderate temperature. The contact with strong acids must be avoided.