Synthesis of 1,6-Diazaphenalene[1]

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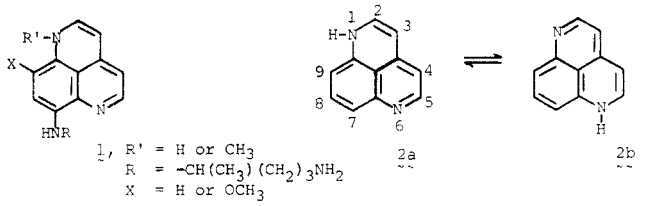
Received April 23, 1981

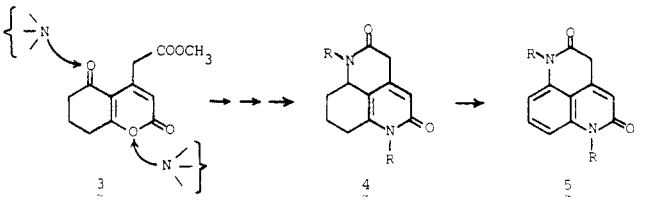
A simple synthesis of the new heterocycle 1,6-diazaphenalene (**2**) has been accomplished from cyclohexane-1,3-dione in a relatively straightforward fashion. The key step in the construction of **2** rested on the conversion of the mono-*N*-oxide **10** to the aromatic 1,6-diazaphenalone **17** under modified Semmler–Wolff conditions (trifluoroacetic anhydride–trifluoroacetic acid). This approach has recently been improved upon by replacement of the TFAA mixture with phenylphosphonic dichloride to provide 2,5-dichloro-1,6-diazaphenalene (**18**) directly from **10** in excellent yield. Treatment of the dichloro derivative **18** with hydrazine in the presence of palladium on carbon furnished 1,6-diazaphenalene (**2**). The proton NMR spectrum of **2** and pK_a (6.56) of this base both support our contention that **2** exhibits imidazole-like properties.

The emergence of drug-resistant strains[2] of *Plasmodia falciparum* has stimulated considerable interest in the synthesis of new antimalarial drugs.[3] To gain entry into new agents **1** of potential interest in this area, we under-



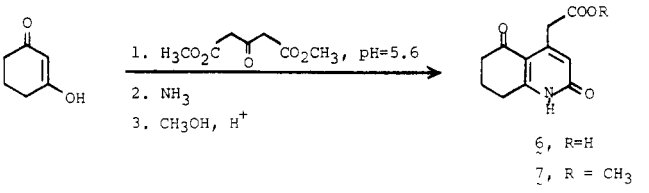
took a synthesis of 1,6-diazaphenalene (**2**). The molecule **2** is interesting from a chemical point of view as well, for proton transfer from **2a** to **2b** would generate a specie **2b** identical in structure with **2a**; moreover, if this process were as rapid as that found for imidazole[4] then both nitrogen atoms of **2** would become equivalent, at least with respect to the NMR time scale.

For design of a route to 1,6-diazaphenalene (**2**) which avoided alkylation and/or nitration reactions on a pyridine nucleus,[5] the plan of attack rested first on the construction of the tricyclic diazaphenalene ring system, followed by an aromatization step when appropriate. To accomplish this, we required a readily available starting material, and the 5-oxo-4-alkyl-5,6,7,8-tetrahydrocoumarin (**3**) appeared

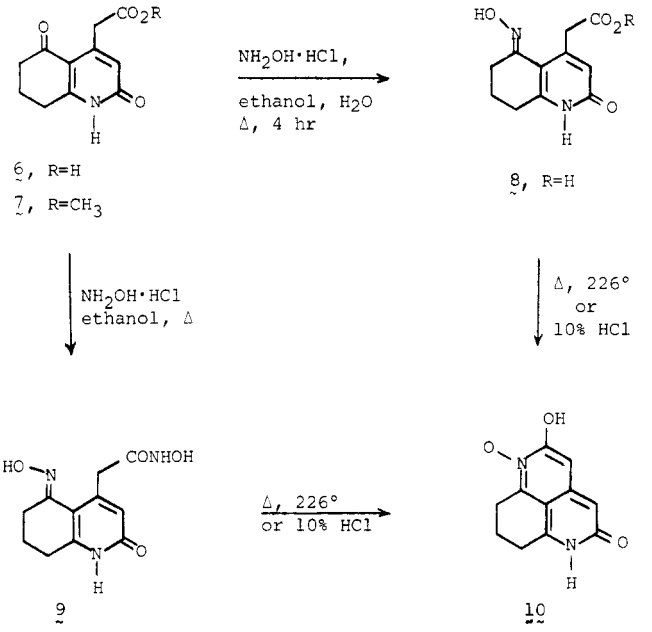


ideal for this purpose. Incorporation of two nitrogen atoms into this molecule at key positions followed by cyclization with the methoxycarbonyl group would generate a diamine

Scheme I



Scheme II



of the correct gross structure **4**, as shown. Further work would then center on conversion of **4** to the diazaphenalene **5** via some type of oxidative transformation.

The synthesis of the key intermediate (5,6,7,8-tetrahydro-2,5-dioxoquinoline-4-acetic acid (**6**) and its methyl ester (**7**) were accomplished by published methods,[6] as outlined in Scheme I. When 2,5-dioxo-5,6,7,8-tetrahydroquinolineacetic acid **6** was heated with hydroxylamine hydrochloride in the presence of sodium acetate, analogous to the conditions reported by Tamura et al.,[7] a 96% yield of the desired oxime **8** was realized (Scheme II). The presence of a carboxyl function and bands at 955 and 938 cm^{-1} in the IR spectrum of **8** supported the structure of the oxime,[8] while the parent peak in the

(1) This work has been published, in preliminary form: El-Sheikh, M. I.; Chang, Jen-C.; Cook, J. M. *Heterocycles* **1978**, *9*, 1561; **1979**, *12*, 1903.
(2) "Resistance of Malaria Parasite to Drugs"; World Health Organization: Geneva, 1965. *Ibid.*, 1967. Schmidt, L. H. *Annu. Rev. Microbiol.* **1969**, *23*, 427. Powell, R. D.; Tigerett, W. D. *Annu. Rev. Med.* **1968**, *19*, 81. Peters, W. *Trop. Dis. Bull.* **1967**, *64*, 1145. Moore, D. V.; Lanier, J. E. *Am. J. Trop. Med. Hyg.* **1961**, *10*, 5. Peters, W. *Trans. Rev. Soc. Trop. Med. Hyg.* **1969**, *63*, 25. Wahl, S. M., Altman, L. C.; Opennheim, J. J.; Mergenhagen, S. E. *Int. Arch. Allergy Appl. Immunol.* **1973**, *46*, 223.
(3) Wang, C. C.; Fischer, M. H. *Annu. Rep. Med. Chem.* **1977**, *12*, 140.
(4) Alei, M., Jr.; Wageman, W. E.; Morgan, L. O. *Inorg. Chem.* **1978**, *17*, 3314.
(5) Friedel–Crafts reactions generally fail with pyridine; see: Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds", 2nd ed.; Wiley: New York, 1967; p 197.
(6) Oehldrich, J.; Cook, J. M. *J. Org. Chem.* **1977**, *42*, 889.
(7) Tamura, Y.; Kita, Y.; Uraoka, J. *Chem. Pharm. Bull.* **1972**, *20*, 876.
(8) Nakanishi, K. "Infra-red Absorption Spectroscopy"; Holden-Day: San Francisco, 1962; p 50.

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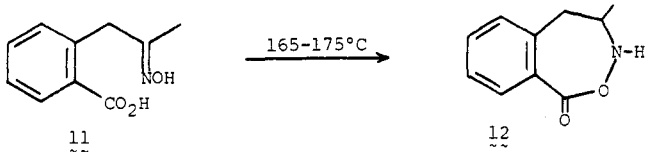
chemical-ionization mass spectrum (NH_3) appeared at m/e 237 ($M^+ + 1$). Furthermore, intense peaks were found at m/e 219 [$(M^+ + 1) - 18$ (H_2O)] and 203 [$(M^+ + 1) - H_2O - 16$ (O)]; the origin of these peaks will be made clear later in the discussion. The oxime **8** was also obtained when acid **6** was heated with hydroxylamine hydrochloride in pyridine–ethanol solution in the absence of sodium acetate. Interestingly, when **7** and hydroxylamine hydrochloride were heated in aqueous ethanol, the major product was not the expected oxime but a yellow oximinohydroxamic acid, **9** (mp >300 °C). For this high-melting solid the IR spectrum contained no carboxyl absorption, while elemental analysis indicated the presence of three nitrogen atoms. In addition, the parent peak observed in the mass spectrum of this material was found at m/e 218 which does not correspond to that expected for oxime **8** or its methyl ester.

In fact, both the oxime **8** and the hydroxamic acid **9** gave the same yellow-orange solid when treated with hydrochloric acid; furthermore, the spectral properties of this solid were identical with that obtained earlier, when a small amount of **8** had been heated to 226 °C in a capillary tube. In addition, prolonged heating of **7** with hydroxylamine hydrochloride in ethanol–pyridine solution gave the same yellow-orange compound directly. The mass spectrum of this high-melting solid contained a molecular ion at 218 mass units; moreover, the base peak in the mass spectrum occurred at $M^+ - 16$, a characteristic observed in the mass spectra of *N*-oxides due to loss of oxygen from the parent ion.[9] Furthermore, strong absorptions were present in the infra red spectrum of this material at 1595, 1290, and 1180 cm^{-1}, characteristic of *N*-oxides observed in similar environments.[10] The proton NMR spectrum [CF_3COOH; δ 2.48 (2 H, m), 3.56 (4 H, two overlapping triplets), 6.95 (1 H, s, vinylic), and 7.00 (1 H, s, vinylic)] contained two one-proton singlets in the region δ 6.00–7.00 which clearly were due to vinylic protons in environments where proton coupling was not possible. On the basis of the above data, the structure of this compound was assigned as 7,8-dihydro-2-hydroxy-5-oxo-1,6-diazaphenalene 1-oxide (**10**).

In summary, both the oxime **8** and the hydroxamic acid **9** gave a parent ion, on mass spectroscopy, at 218 mass units, consistent with the structure of the *N*-oxide **10**, a material which was also obtained on heating **8** or **9** above 226 °C. Moreover, oxime **8** also cyclized immediately to *N*-oxide **10** in trifluoroacetic acid (NMR tube), as well as when **8** was treated with hot hydrochloric acid solution. In none of this work has a carbonyl absorption been observed in the region of 1720 cm^{-1}, as observed in the IR spectrum of Gottlieb's "anhydroderivative" **12**,[11,12] pro-

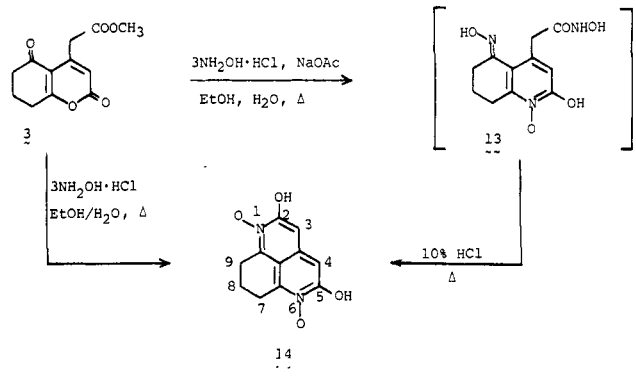


11 12

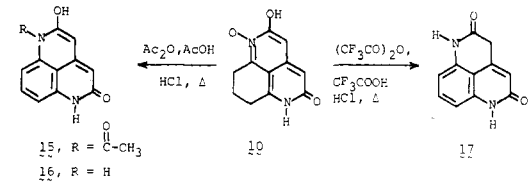
duced by heating ketoxime **11**. Apparently the peri position of the oxime **8**, as well as hydroxamic acid **9**, was perfectly set up to undergo the desired cyclization to **10**.

It has been shown that α-pyrones, on treatment with hydroxylamine, undergo facile ring opening and reclosure to provide 1-hydroxy-2-pyridones.[13] Therefore, an investigation of the reaction between oxocoumarin **3** and hydroxylamine was begun in order to develop a shorter route to the key diazatricyclic system represented by structure **14** (Scheme III). In addition, preparation of a symmetrical molecule such as **14** was considered important, for the proton NMR spectrum of this material would be expected to be quite simple, and comparison of the spectral data of **14** to those of the mono-*N*-oxide **10** would serve to further support the structure of **10**.

Scheme III



Scheme IV

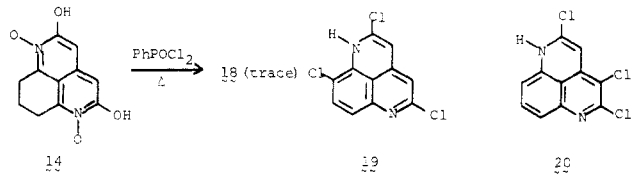


In this vein, **3** was heated with hydroxylamine hydrochloride in aqueous ethanol; prolonged heating provided an 88% yield of the dihydro-2,5-dihydroxyl-1,6-diazaphenalene 1,6-dioxide **14** (Scheme III). If the same reaction mixture was heated for a shorter time (10 h), only small amounts of **14** were isolated accompanied by a substantial amount of another compound felt to be the intermediate hydroxamic acid **13**. The mixture of **13** and **14** was converted quantitatively to **14** on treatment with hot hydrochloric acid. The physical and spectral data for this high-melting solid fully support the assigned structure. In particular, the symmetrical nature of the di-*N*-oxide was indeed reflected in the simple proton NMR spectrum which contained only three signals; furthermore, the CI mass spectrum of **14** contained, in addition to the parent ion, peaks at 219 and 203 mass units characteristic of the successive loss of two atoms of oxygen. This behavior is similar to that of other pyridine *N*-oxides reported in the literature.[9,14] The chemical shifts in the proton spectra of **10** and **14** were quite similar, the major difference arising from the lack of symmetry present in **10**.

With the successful completion of the synthesis of gram quantities of the diazatricyclic molecules **10** and **14** well in hand, it now became necessary to convert either of these two compounds into the aromatic diazaphenalene nucleus. In 1930 Schroeter and co-workers had reported a systematic study of the aromatization of various tetralone 1-oximes[15,16] to provide naphthylamines. They found that

(9) Weigele, M.; Leimgruber, W. *Tetrahedron Lett.* **1967**, 715.
(10) Shindo, H. *Chem. Pharm. Bull.* **1960**, *8*, 845. Delpierre, G. R.; Lamchen, M. *Q. Rev., Chem. Soc.* **1965**, 329.
(11) Gottlieb, G. *Ber.* **1899**, *32*, 966; *Beilstein* **1937**, *27*, 210. The carbon analysis was reported to be low.
(12) Moriconi, E. J.; Creegan, F. J.; Donovan, C. K.; Spano, F. A. *J. Org. Chem.* **1963**, *28*, 2215.
(13) Kartizky, A. R.; Lagowski, J. M. "Chemistry of the Heterocyclic N-Oxides"; Academic Press: New York, 1971; pp 76–77.
(14) Roberts, S. M.; Suschitzky, H. *Chem. Commun.* **1967**, 893.
(15) Schroeter, G.; Gluschke, A.; Gotsky, S.; Huang, J.; Irmisch, G.; Laves, E.; Schrader, O.; Stier, G. *Ber.* **1930**, *63*, 1308.

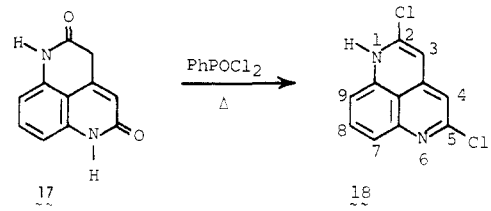
Scheme V



tetralone 1-oxime with substituents at position 8 failed to undergo the aromatization reaction but did give lactam.[15] Results obtained recently in our laboratory,[17] however, clearly indicated that a substituent located in a similar position in tetrahydrocarbostyrils does not impede the aromatization reaction (see ref 17 for details); therefore, we turned our attention to conversion of the mono-*N*-oxide **10** to the desired diazaphenalone **17** (Scheme IV).

The mono-*N*-oxide was heated under Semmler–Wolff conditions[16] with Beckmann's mixture for 18 h to provide an 86% yield of the 1-acetyldiazaphenalone **15**. Scale-up, however, of this reaction led to significant amounts of carbonized material; moreover, base-catalyzed hydrolysis of the amide was not a clean reaction, although a material whose properties were comensurate with those expected for **16** was isolated. These two observations led to the search for a milder method for carrying out this transformation which might lead directly to the diazaphenalone **17**. Since formation of a trifluoroacetate leaving group would facilitate cleavage of the *N*-oxide bond, the mono-*N*-oxide **10** was heated under "modified"[18] Semmler–Wolff conditions, as illustrated in Scheme IV. This modification provided 2,5-dioxo-3*H*-1,6-diazaphenalene (**17**) in greater than 90% yield.

Since the conversion of *N*-oxide **10** to **17** had been successfully completed, the task at hand was to convert the oxo functions of **10** into suitable leaving groups. This would facilitate later removal to provide the parent compound 1,6-diazaphenalene (**2**). In this vein, **17** was heated with phenylphosphoric dichloride, analogous to the work of Robinson,[19] which gave the desired 2,5-dichloro-1,6-diazaphenalene (**18**) in good yield. The mass and infrared



spectrum of the dichloro compound were in agreement with a structure for this molecule such as **18**. More importantly, the symmetrical nature of **18** was clearly observed on examination of the NMR spectrum of this yellow solid. Symmetry in such a molecule can only arise by rapid proton exchange (intermolecular) between the two nitrogen atoms, which would provide two molecules which contain the same amount of energy and are, in this case, identical. This phenomena was observed for the proton spectrum of **18** [δ 6.52 (2 H, s, C-3 and C-4 H), 7.28 (2 H, d, J = 8 Hz, C-7 and C-9 H), and 7.88 (1 H, t, J = 8 Hz, C-8 H)] was quite simple.

In an attempt to devise a simpler route to the diazaphenalene ring system, the reaction of di-*N*-oxide **14** with phenylphosphonic dichloride was studied, as illustrated in Scheme V. To this end **14** was heated for several hours with phenylphosphonic dichloride. From this sequence, two major products were isolated, the mass spectra of which indicated that three chlorine atoms had been incorporated into a diazaphenalene nucleus. Examination of the proton (220 mHz) NMR spectrum of the two isomeric trihalodiazaphenalenes was quite informative, for the spectrum of **19** contained two, one-proton singlets at δ 6.65 and 6.70 while two AB doublets were found at δ 7.36 and 8.00, respectively. This coupling pattern was clearly consistent with the spectrum of a trichloroderivative such as 2,5,9-trichloro-1,6-diazaphenalene (**19**). The NMR spectrum for the second isomer, **20**, contained a one-proton singlet located at δ 6.91, two AB doublets found at δ 7.36 and 7.38, respectively, and a one-proton triplet at δ 7.94 which was coupled to the AB system. This pattern indicated the phenyl ring had not been attacked by a chlorine atom; consequently, the third chlorine atom was placed in one of the heterocyclic rings. On the basis of data from the NMR and mass spectrum of this material, the structure of the second component was assigned as 2,4,5-trichloro-1,6-diazaphenalene (**20**). The third component, present in only small amounts, was found to be identical with **18**, prepared by an independent route detailed above.

Examination of a possible mechanism to rationalize this result led to the exciting realization that phenylphosphonic dichloride was involved in the aromatization of **14** in much the same manner as trifluoroacetic anhydride was in the "modified" Semmler–Wolff reaction. In the case of di-*N*-oxide **14**, it is proposed that one of the *N*-oxide functions attacks the phenylphosphonic dichloride to expel a chloride ion (Scheme VI) followed by an intramolecular rearrangement of the chlorine atom which had remained on phosphorus. This same sequence of steps is expected to occur at the second *N*-oxide function to generate the dichloro intermediate **22**. Loss of the elements of hydrogen chloride from **22**, as shown, would afford 9-chloro-2,5-dihydroxy-1,6-diazaphenalene (**23**) which could then be converted to the trichlorodiazaphenalene **19** via a known pathway, analogous to the earlier work of Robinson.[19] A similar series of transformations can be employed to explain the origin of **20** in the same reaction (see Scheme VII for details). In particular, the diphosphonate ester **21** could undergo attack by chloride anion with concomitant cleavage of the N–O bond to provide **24** followed by loss of a proton to furnish the key intermediate **25**. Loss of a proton by either path a or path b would ultimately result in aromatization of ring A via intermediates **26** or **27**, respectively. The product **28** of this rearrangement could then be converted to **20** analogous to chemistry previously reported in the literature.[19]

On the basis of the above mechanistic hypothesis, it was anticipated that use of the mono-*N*-oxide **10** in place of the di-*N*-oxide **14** in this reaction would provide the desired 2,5-dichlorodiazaphenalene **18** instead of the trichlorodiazaphenalenes **19** and **20**. Indeed, when the *N*-oxide **10** was heated in phenylphosphoric dichloride under similar conditions to those employed above, a 77% yield of **18** was obtained directly. In addition, a small amount (<1%) of 7,8-dihydro-2,4,5-trichloro-1,6-diazaphenalene was also isolated.[20] The formation of 2,5-dichloro-1,6-

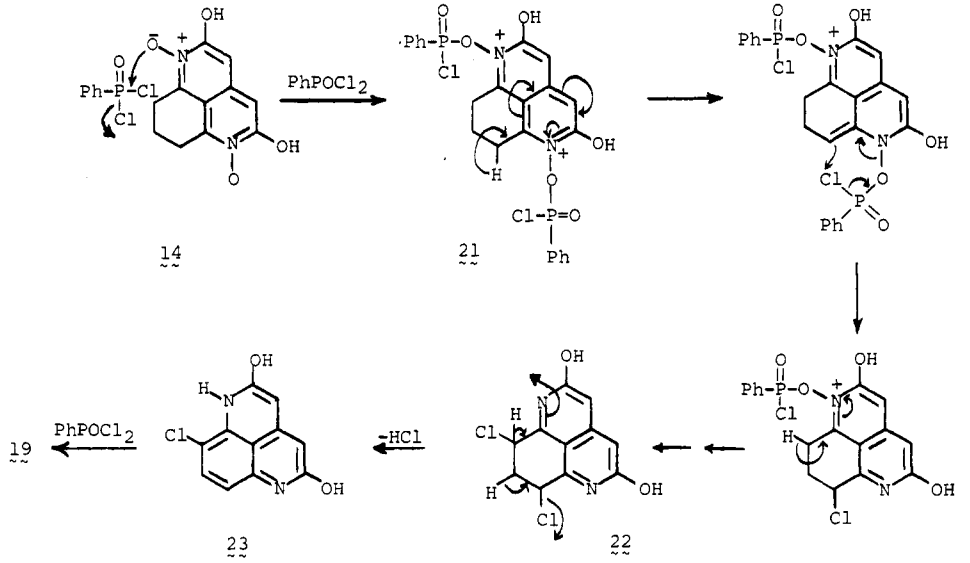
(16) (a) Conley, T.; Ghosh, S. "Mechanism of Molecular Migrations"; Thyagrajan, B. S., Ed.; Interscience: New York, 1971; Vol 4, pp 251–305. (b) Bhatt, M. V. *Experentia* **1957**, *13*, 70. (c) Voroshtsov, N. N.; Koptyug, V. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1958**, *28*, 1697. (d) Bauer, L.; Hewitson, R. E. *J. Org. Chem.* **1962**, *27*, 3982. (e) Balling, P. J. Ph.D. Thesis, Seton Hall University, 1966. (f) Watnick, C. M. Ph.D. Thesis, Seton Hall University, 1970.

(17) El-Sheikh, M. I.; Cook, J. M. *J. Org. Chem.* **1980**, *45*, 2585.

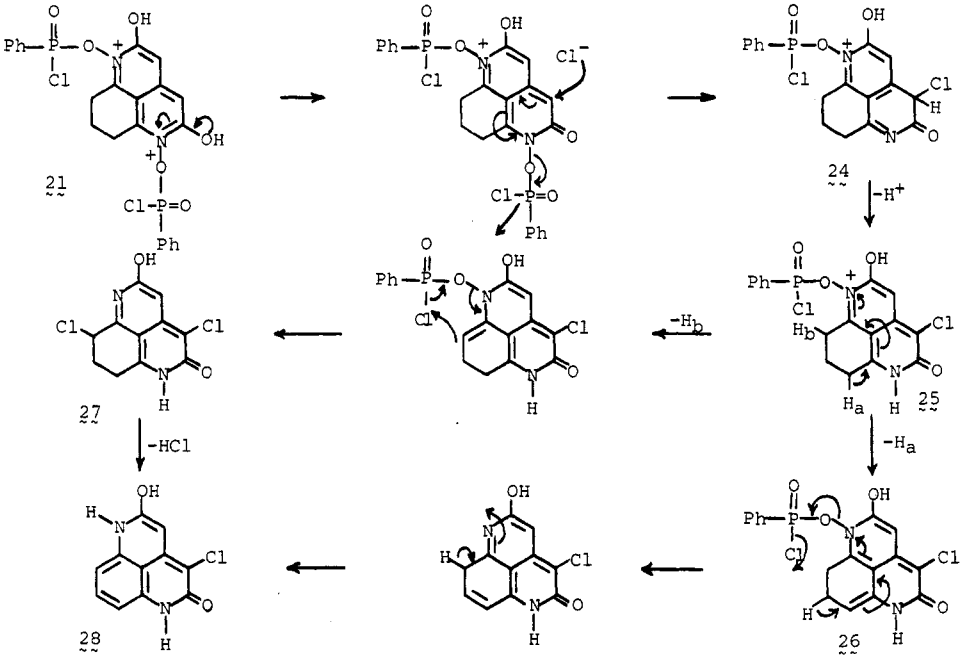
(18) (a) Ahond, A.; Cave, A.; Kan-Fan, C.; Langlois, Y.; Portier, P. *Chem. Commun.* **1970**, 517. (b) Kutney, J. P; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, W. *Heterocycles* **1975**, *3*, 639.

(19) Robinson, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 5481.

Scheme VI



Scheme VII

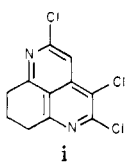


diazaphenalene (18) in good yield is perhaps the most convincing evidence obtained, to date, to support the mechanistic pathways outlined in Schemes VI and VII for formation of **19** and **20**. The ease with which **10** was converted to **18** was remarkable. Simply heating **10** in phenylphosphonic dichloride effected the cleavage of the N–O bond, introduced a unit of unsaturation, and converted the two hydroxy groups to chlorine atoms in the same one-pot reaction.

Several different methods were attempted to convert the chlorine atoms of **18** to hydrogen atoms (**18** → **2**); however, only one of these was found to be practical. Heating **18** for several hours with hydrazine in the presence of Pd/C[21] provided good yields of a yellow solid found to be 1,6-diazaphenalene (**2**). Interestingly, on some occassions, a minor product 2,3-dihydro-1,6-diazaphenalene was also isolated from this reduction, but in less than 10% yield, and was easily separated from **2** by chromatography.

The prototropic shift between molecules **2a** and **2b** is more rapid than the NMR time scale, which parallels the same phenomenon found in imidazole.[4] The evidence is quite clear on this point for there are only four signals present in the proton NMR spectrum of **2** [δ 5.95 (2 H, d, J = 6 Hz), 6.70 (2 H, d, J = 8.5 Hz), 7.30 (1 H, t, J = 8.5 Hz), 7.42 (2 H, d, J = 6 Hz)] which indicates that the two nitrogens are equivalent. This can only occur by a rapid tautomeric equilibration between **2a** and **2b**. Even though the spectral properties of **2** resemble those of imidazole, 1,6-diazaphenalene is only slightly soluble in water (~20

(20) When the reaction was carried out on a larger scale (ca. 55 g), the byproduct **i** was obtained (<1% yield). Anal. Calcd for $C_{11}H_7N_2Cl_3$: C, 48.29; H, 2.58; N, 10.24. Found: C, 48.48; H, 2.52; N, 10.44.



i

(21) (a) Mosby, W. L. *Chem. Ind. (London)* **1959**, 1348. (b) Parham, W.; Davenport, R.; Biasotti, J. B. *Tetrahedron Lett.* **1969**, 557.

mg/1000 mL of H_2O) while imidazole is quite soluble in this solvent.[22] This is not at all surprising, for **2** possesses much more of the character of an aromatic hydrocarbon than does imidazole. The pK_a data for **2**, however, again support our previous contention that 1,6-diazaphenalene has "imidazole-like" properties. The pK_a value (6.56) for **2** was determined by a potentiometric method[23] and is similar to that of imidazole (6.95),[24] while the value for quinoline is 4.94.[25]

The six-step synthesis of 1,6-diazaphenalene (**2**) from cyclohexane-1,3-dione provides for the first time a facile route to gram quantities of this material for further study. Because of the catalytic properties exhibited by imidazole in many organic reactions, we are currently involved in an extensive study of the chemistry of **2** with regard to similarities between 1,6-diazaphenalene (**2**) and imidazole. In addition, calculations on the charge densities for the neutral molecule are underway, as well as calculations on both the anion of **2** and the protonated form of the molecule. These studies will be reported in due course, as well as the conversion of **2** into potential antimalarial agents.[26]

Experimental Section

Melting points were run on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann Acculab-1 spectrometer, and NMR spectra were taken on Varian T-60 and 220 spectrometers. The mass spectra were recorded on Finnigan and AEI mass spectrometers.

TLC plates employed in this work were Brinkmann silica or alumina on plastic, while cyclohexane-1,3-dione, dimethyl 3-oxoglutarate, hydroxylamine hydrochloride, and phenylphosphonic dichloride were purchased from Aldrich Chemical Co. The palladium on carbon catalyst was obtained from Pfaltz and Bauer.

5,6,7,8-Tetrahydro-5-(hydroxyimino)-2-oxoquinoline-4-acetic Acid (8). To a suspension of 5,6,7,8-tetrahydro-2,5-dioxoquinoline-4-acetic acid (**6**; 22.1 g, 0.10 mol) in 95% ethanol (100 mL) was added a solution of hydroxylamine hydrochloride (10.44 g, 0.15 mol) and sodium acetate (12.6 g, 0.153 mol) in water (70 mL). The mixture was gently refluxed for 4 h and cooled. The precipitate was filtered from the solution and washed with water followed by methanol to provide a 96% yield of **8** (22.8 g) as yellow plates: mp 226–230 °C; IR (KBr) 3310 (m), 2860 (br), 1702 (s), 1642 (s), 1598 (s), 955 (m), 938 cm^{-1}; NMR (D_2O + NaOD) δ 1.82 (2 H, m), 2.61 (4 H, m), 3.80 (2 H, s, CH_2), 6.18 (1 H, s, vinyl proton); CI mass spectrum (NH_3), m/e (relative intensity) 237 (M^+ + 1, 1), 220 (6), 219 [(M + 1) − 18, 42], 218 (3), 20 (13), 203 [(M + 1) − 34, 100], 202 (8), 193 (48), 178 (29), 177 (10), 125 (12), 83 (24), 82 (12).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.89; H, 5.12; N, 11.68.

7,8-Dihydro-2-hydroxy-5-oxo-1,6-diazaphenalene 1-Oxide (10). (A) 5,6,7,8-Tetrahydro-5-(hydroxyimino)-2-oxoquinoline-4-acetic acid (**8**; 23.6 g, 0.10 mol) was heated for 30 min (boiling water bath) in hydrochloric acid (150 mL, 10%). The solution was cooled to room temperature and stirred for an additional 30 min. Crystals were then filtered from the mixture and washed with water and finally with a little methanol to give a yellow-orange solid (**10**): 21 g (96% yield); mp >350 °C; IR (KBr) 3400 (br), 3040 (m), 1620 (s), 1595 (m), 1180 (s), 960 (m), 830 (m), 740 (m) cm^{-1}; NMR (CF_3COOH) δ 2.38 (2 H, m), 3.4 (4 H, m), 6.95 (1 H, s), 7.0 (1 H, s); NMR (D_2O + NaOD) δ 2.20 (2 H, m), 2.94 (2 H, t), 3.20 (2 H, t), 6.05 (1 H, s), 6.2 (1 H, s); CI mass spectrum (NH_3), m/e (relative intensity) 219 (M^+ + 1, 80), 218 (4), 217 (2), 205 (5), 204 (14), 203 [(M + 1) − 16, 100], 202 (5), 201 (5), 200 (1).

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.36; H, 4.55; N, 12.53.

(B) Compound **10** was also obtained in a similar yield when hydroxamic acid **9** was treated with 10% HCl in a similar manner.

(C) To a suspension of methyl 5,6,7,8-tetrahydro-2,5-dioxoquinoline-4-acetate (**7**; 2,35 g, 0.01 mol) in absolute ethanol (15 mL) were added hydroxylamine hydrochloride (1.05 g, 0.03 mol) and dry pyridine (5 mL). The mixture was refluxed for 6 h, and the solid which precipitated was collected by filtration. The yellow-orange solid was washed with water followed by methanol to provide compound **10**, 1.81 g (84% yield).

(D) A small amount of 5,6,7,8-tetrahydro-5-(hydroxyimino)-2-oxoquinoline-4-acetic acid (**8**) was heated to 226 °C in a capillary tube. The yellow-orange solid which resulted had an IR spectrum which was identical with to that of 7,8-dihydro-2-hydroxy-5-oxo-1,6-diazaphenalene 1-oxide (**10**) prepared by method A.

2,5-Dioxo-3*H*-1,6-diazaphenalene (17). 7,8-Dihydro-2-hydroxy-5-oxo-1,6-diazaphenalene 1-oxide derivative **10** (8.0 g, 0.037 mol) was dissolved in trifluoroacetic acid (30 mL), and the solution was saturated with HCl gas. To the cold solution was added trifluoroacetic anhydride (15 mL), and the solution was refluxed for 18 h. The reaction mixture was cooled and diluted with water, whereupon a heavy precipitate formed. The precipitate was filtered from the solution and washed with water to furnish **17** (7.0 g, 96%) as an off-white solid: mp >300 °C; IR (KBr) 1690 (sh, m), 1650 (s), 1620 (s), 1560 (m), 1450 (m), 1350 (m), 1190 (m) cm^{-1}; NMR (CF_3COOH) δ 4.50 (2 H, s), 7.10 (1 H, s), 7.20 (1 H, d, J = 8 Hz), 7.40 (1 H, d, J = 8 Hz), 7.80 (1 H, t, J = 8 Hz); CI mass spectrum (NH_3), m/e (relative intensity) 202 (13), 201 (M^+ + 1, 100), 200 (5).

Anal. Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.78; H, 3.76; N, 14.31.

7,8-Dihydro-2,5-dihydroxy-1,6-diazaphenalene 1,6-Dioxide (14). A solution of hydroxylamine hydrochloride (10.44 g, 0.15 mol) and sodium acetate (12.67 g, 0.0154 mol) in water (60 mL) was added to a suspension of methyl 5,6,7,8-tetrahydro-5-oxocoumarin-4-acetate (**3**) in 95% ethanol (60 mL). The resulting mixture was refluxed for 10 h. A yellow solid was filtered from the solution and washed with water to provide a mixture of the title compound (**14**) and another compound felt to be the intermediate hydroxamic acid (**13**). To the mother liquor was added another portion of hydroxylamine hydrochloride (3.48 g, 0.05 mol) and sodium acetate (4.13 g, 0.05 mol), and the mixture was refluxed for 8 h. This provided an additional 3.8 g of yellow solid. The combined precipitates were treated with hot hydrochloric acid (90 mL, 10%) to furnish pure **14** (10.3 g, 88% yield) obtained as yellow-orange crystals: mp >300 °C; IR (KBr) 3450 (br), 3050 (s), 1630 (s), 1610 (s), 1295 (s), 1185 (s) cm^{-1}; NMR (CF_3COOH) δ 2.52 (2 H, m, C-8H's), 3.62 (4, H, t, J = 6 Hz, C-7 and C-9H's) and 7.00 (2 H, s, C-3 and C-4, vinylic protons); mass spectrum (70 eV), m/e (relative intensity) 203 (14), 202 (M^+ − 32, 100), 201 (20), 200 (61), 177 (23), 174 (39), 149 (46); CI mass spectrum (NH_3), m/e (relative intensity) 237 (4), 236 (16), 235 (M^+ + 1, 100), 234 (10), 233 (4), 220 (16), 219 [(M + 1) − 16, 92], 218 (17), 217 (10), 204 (9), 203 [(M + 1) − 32, 52], 202 (8), 201 (6).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.27; N, 11.97. Found: C, 56.65; H, 4.27; N, 11.73.

1-Acetyl-2-hydroxy-5-oxo-1,6-diazaphenalene (15). The 7,8-dihydro-2-hydroxy-5-oxo-1,6-diazaphenalene 1-oxide derivative **10** (2.0 g, 0.009 mol) was dissolved in acetic acid (32 mL) and acetic anhydride (12 mL), and the solution which resulted was saturated with HCl gas. The mixture was then refluxed for 18 h, cooled and diluted with water. The precipitate which formed when the mixture was allowed to stand was filtered from the solution and washed with water to provide **15** (1.7 g, 86%) as an olive-green solid: mp >350 °C; IR (KBr) 3200 (br), 1670 (s), 1630 (s), 1600 (m), 1370 (w), 1300 (m) cm^{-1}; NMR (warm Me_2SO-d_6) δ 2.50 (3 H, s), 6.20–7.30 (5 H, overlapping multiplets), 10.57 (1 H, s), 11.60 (1 H, s); the signals at δ 10.57 and 11.60 disappeared on addition of D_2O; NMR (CF_3COOH) δ 2.8 (3 H, s), 7.0–8.0 (5 H, overlapping multiplets); CI mass spectrum (NH_3) m/e (relative intensity) 244 (19), 243 (M^+ + 1, 100), 242 (17), 201 (13).

Anal. Calcd for $C_{13}H_8N_2O_3$: C, 64.46; H, 4.13; N, 11.57. Found: C, 64.43; H, 3.97; N, 11.48.

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2,5-Dichloro-1,6-diazaphenalene (18). (A) To 2,5-dioxo-3*H*-1,6-diazaphenalene (17; 16.0 g, 0.08 mol) was added phenylphosphonic dichloride (80 mL). The mixture was slowly warmed to 90 °C (oil bath) with stirring and held at that temperature for 30 min. At the end of the 30-min period, the temperature was increased to 120–125 °C and held there for 3 h. After cooling, the mixture was poured into ice–water (300 mL) with stirring. The resulting mixture was carefully basified with ammonium hydroxide, and the solid which precipitated was collected by filteration to provide a solid (15.1 g, 80% yield). This material was further purified by elution through a short column of alumina (tetrahydrofuran) to give 18 as a yellow solid: mp 223–225 °C; IR (KBr) 3400 (br), 1640 (s), 1605 (s), 1590 (s), 1540 (m), 1370 (s), 910 (s), 820 (s), 770 (m) cm^{-1}; NMR (CF_3COOH) δ 6.52 (2 H, s), 7.28 (2 H, d, J = 8 Hz), 7.88 (1 H, t, J = 8 Hz); mass spectrum (70 eV), m/e (relative intensity) 240 (12), 238 (62), 236 (M^+, 100), 200 (58), 165 (50); CI mass spectrum (NH_3), 238 (64), 237 (M^+ + 1, 100), 236 (30).

Anal. Calcd for $C_{11}H_6N_2Cl_2$: C, 55.69; H, 2.53; N, 11.81; Cl, 29.96. Found: C, 55.96; H, 2.78; N, 11.74; Cl, 30.26.

(B) A mixture of the *N*-oxide **10** (4.36 g, 0.02 mol) and phenylphosphoric dichloride (30 mL) was heated in an oil bath; the temperature was increased to 90 °C over a 20-min period in order to permit slow evolution of HCl gas. As the reaction proceeded, the *N*-oxide started to dissolve. After most of the starting material had dissolved, the temperature was raised to 100 °C and held there for 12 h. Finally, the dark orange reaction mixture was heated at 120–125 °C for 3 h. The reaction mixture was then cooled and added, with stirring, to crushed ice (ca. 100 g). Decomposition of the reaction mixture gradually produced a rather tarry residue. Ammonium hydroxide (14%) was added carefully to the residue with strong stirring and external cooling to basify the solution. This produced a thick precipitate. The brown-green precipitate was filtered, washed with water, and dried to provide crude 2,5-dichloro-1,6-diazaphenalene (18, 6.1 g). This was taken up in tetrahydrofuran (300 mL), refluxed for 30 min, cooled, and filtered to remove insoluble material. A dark yellow-green filtrate was then passed through a short wash column of alumina. Elution with tetrahydrofuran provided an yellow-green solid, 18 (3.67 g, 77% yield), which was identical in all respects with the product described in experiment A.

2,5,9-Trichloro-1,6-diazaphenalene (19) and 2,4,5-Trichloro-1,6-diazaphenalene (20). To solid 7,8-dihydro-2,5-dihydroxy-1,6-diazaphenalene 1,6-dioxide (**14**; 1.17 g, 0.005 mol) was added phenylphosphonic dichloride (10 mL), and the resulting suspension was heated under reflux (oil bath). The temperature of the reaction mixture was increased from room temperature to 80 °C over a 30-min period. Gentle evolution of HCl gas started and the di-*N*-oxide began to dissolve. After 20 min, the reaction bath temperature was increased to 98–100 °C and was heated for 10 h. Finally, the reaction mixture was cooled and worked up as described above (procedure B) for 2,5-dichloro-1,6-diazaphenalene. The yellow solid obtained consisted of two major components which were separated by column chromatography (silica gel; benzene–chloroform). The first fraction gave 2,5,9-trichloro-1,6-diazaphenalene (**19**; 0.23 g, 17%) as a yellow powder: mp 218–220 °C dec; IR (KBr) 3370 (s, NH), 1625 (s), 1605 (s), 1360 (m), 1124 (s), 830 (s), 780 (m) cm^{-1}; NMR (CF_3COOH, 220 M Hz) δ 6.65 (1 H, s), 6.70 (1 H, s), 7.36 (1 H, d, J = 9 Hz), 8.00 (1 H, d, J = 9 Hz); CI mass spectrum (NH_3), m/e (relative intensity) 275 (36), 273 (86), 271 (M^+ + 1, 100).

Anal. Calcd for $C_{11}H_5N_2Cl_3$: C, 48.62; H, 1.84; N, 10.33. Found: C, 48.96; H, 1.61; N, 10.34.

The second fraction provided 2,4,5-trichloro-1,6-diazaphenalene (**20**) as a yellow powder: 0.16 g (12%); mp 228–230 °C dec; IR (KBr) 3390 (w), 3100 (w), 2910 (br), 1630 (s), 1600 (s), 1580 (s), 1360 (s), 1350 (s), 1130 (s), 810 (s), 760 (s) cm^{-1}; NMR (CF_3COOH, 220 MHz) δ 6.91 (1 H, s), 7.36 (1 H, d, J = 8.5 Hz), 7.38 (1 H, d, J = 8.5 Hz), 7.94 (1 H, t, J = 8.5 Hz); CI mass spectrum (NH_3), m/e (relative intensity) 275 (27), 273 (79), 271 (M^+ + 1, 100).

Anal. Calcd for $C_{11}H_5N_2Cl_3$: C, 48.62; H, 1.84; N, 10.33. Found: C, 48.51; H, 1.59; N, 10.30.

Further elution of the column gave a small amount of 2,5-dichloro-1,6-diazaphenalene (**18**, ca. 5%). Yields of **19** and **20** by NMR were 35% and 25%, respectively.

1,6-Diazaphenalene (2). The 2,5-dichloro-1,6-diazaphenalene (**18**; 7.0 g, 0.03 mol) was dissolved in absolute ethanol (300 mL), followed by addition of palladium on carbon (5%, 2.5 g) to the solution. Hydrazine hydrate (50 mL of 95% NH_2NH_2) taken up in ethanol (50 mL) was added to the solution at reflux with stirring. After 5 h of reflux, another portion of hydrazine hydrate (10 mL of N_2H_4 and 10 mL of ethanol) was added and refluxing continued for another 10 h. The catalyst was removed by filtration and the solvent removed from the mother liquor under reduced pressure. The bright orange-yellow residue which resulted was filtered off after the addition of water (5 mL). The solid was washed once with a saturated aqueous solution of sodium bicarbonate to give a mixture (4.4 g). This material was separated by column chromatography on alumina (tetrahydrofuran). The least polar compound 2,3-dihydro-1,6-diazaphenalene (0.47 g) was obtained as a pale yellow solid: mp 128 °C; IR (KBr) 3240, 3120, 3000, 2960, 2822, 1620, 1590, 1510, 1410, 1230, 1130, 1080, 840, 740 cm^{-1}; NMR ($CDCl_3$) δ 2.9–3.6 (4 H, m), 4.67 (1 H, br, NH) 6.53 (1 H, t, J = 4 Hz), 6.9 (1 H, d, J = 4 Hz), 7.4 (2 H, d, J = 4 Hz, 8.97 (1 H, d, J = 4 Hz); CI mass spectrum (CH_4), m/e (relative intensity) 171 (M^+ + 1, 100), 170 (26).

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.57; H, 6.02; N, 16.38.

Further elution provided the more polar compound as a yellow solid (**2**): 3.45 g; mp 221–222 °C; IR (KBr) 3420, 1640, 1625, 1580, 1350, 825, 750 cm^{-1}; NMR (CD_3OD, 220 M Hz) δ 5.95 (2 H, d, J = 6 Hz), 6.70 (2 H, d, J = 8.5 Hz), 7.30 (1 H, t, J = 8.5 Hz), 7.42 (2 H, d, J = 6 Hz); CI mass spectrum (NH_3), m/e (relative intensity) 169 (M^+ + 1, 100), 168 (29), 167 (12).

Anal. Calcd for $C_{11}H_8N_2$: C, 78.57; H, 4.76; N, 16.67. Found: C, 78.17; H, 4.94; N, 16.54.

An analytical sample of **2** could be obtained by dissolving the crude solid in THF and then passing the solution through a short column of alumina. 1,6-Diazaphenalene (**2**) when freshly prepared is a bright yellow solid and is not overly soluble in the common organic solvents (e.g., chloroform, benzene, ether, ethyl acetate, acetone). It is freely soluble in trifluoroacetic acid and dimethyl sulfoxide, while the heterocycle is soluble in tetrahydrofuran to a limited extent.

Acknowledgment. We thank Dr. Herman Ziffer and Dr. Ulrich Weiss for the high-resolution NMR spectra and Mr. Noel Whittaker for the chemical-ionization mass spectra. We also acknowledge Walter Reed Army Institute of Research, Department of the Army, for generous financial support and Dr. Richard Strube for his interest in this work. Special thanks are in order to Debby Warner for technical assistance.

Registry No. **2**, 27212-02-8; **3**, 61062-39-3; **6**, 61062-45-1; **7**, 61062-43-9; **8**, 68871-42-1; **9**, 68871-43-2; **10**, 68871-44-3; **13**, 78803-87-9; **14**, 68871-45-4; **15**, 78803-88-0; **17**, 71570-13-3; **18**, 71570-14-4; **19**, 78803-89-1; **20**, 78803-90-4; 2,3-dihydro-1,6-diazaphenalene, 78803-91-5.