THE CHEMISTRY OF 1,6-DIAZAPHENALENE. ELECTROPHILIC SUBSTITUTION AND REACTION WITH *SINGLET OXYGEN*.

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Abstract --- The nitration, bromination, acylation, and alkylation of 1,6-diazaphenalene (1) have been investigated as well as the reaction of the title compound with singlet oxygen. These transformations have been compared to similar reactions known to take place with imidazoles.

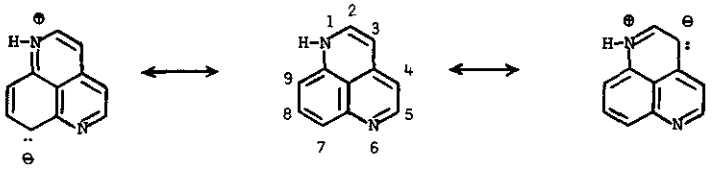
Recently we have had occasion to synthesize[1] the heterocycle, 1,6-diazaphenalene (1), as a template for preparation of potential antimalarial agents.[2,3] This brightly colored yellow solid, the first diazaphenalene to be prepared, is of special interest because of its similarity to imidazole in some of its chemical and physical properties. For instance, the proton transfer 1a to 1b is more rapid than the nmr time scale[4] which results in a much simplified nmr spectrum analogous to the case of imidazole.[5] Moreover, the pK_a of 1, as measured by a potentiometric titration, was found to be 6.56 while the value for imidazole is 6.95.[6] In contrast the pK_a of quinoline measured under analogous conditions has been reported to be 4.94.[7] Clearly the nmr spectrum and pK_a data recorded for 1 indicate the compound bears a strong resemblance to imidazole.

1a 1b

Because of continuing interest in the physical and chemical properties of imidazole, especially those related to the catalysis of hydrolytic reactions,[8] we have investigated a number of different reactions of 1 in an attempt to compare the chemical properties of 1 with those reported for imidazole. As we have previously noted[1] 1 appears to behave in many of its reactions as though

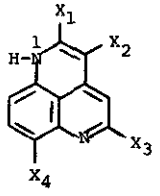
it were an imidazole vinylogue.

When 1,6-diazaphenalene was stirred with nitric acid in either acetic acid or sulfuric acid,



A 1 B

under a variety of conditions, the major product was 3,7-dinitro-1,6-diazaphenalene 2 with only traces of the 7-mononitro derivative 3 present. The failure to isolate significant amounts of the mononitro derivative 3 was not unexpected, and we turned to milder conditions under which to perform the nitration. It has been proposed[9] that nitration of aromatic substrates with sodium nitrite, in the presence of trifluoroacetic acid, proceeds through the weaker electrophile +NO rather than $+NO_2$, and we therefore turned our attention in this direction. In fact, when equimolar amounts of sodium nitrite and 1 were stirred at -60° in a solution of trifluoroacetic acid/chloro-



1, $X_1=X_2=X_3=X_4=H$

2, $X_1=X_3=H$, $X_2=X_4=NO_2$

3, $X_1=X_2=X_3=H$, $X_4=NO_2$

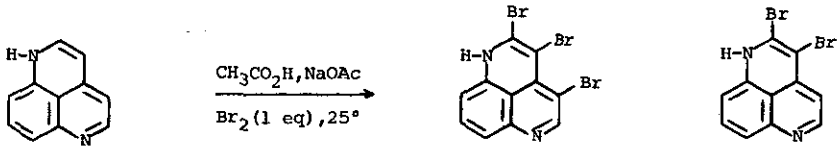
4, $X_1=X_3=Cl$, $X_2=X_4=H$

5, $X_1=X_3=Cl$, $X_2=H$, $X_4=NO_2$

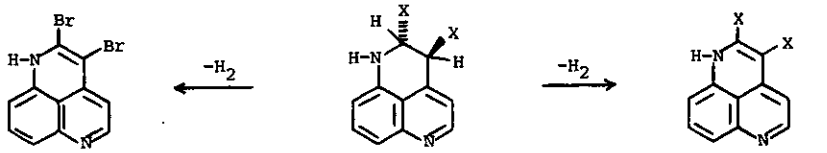
form, the major product (68% yield) was 7-nitro-1,6-diazaphenalene 3. In establishing the structure of 3, we compared the chemical shifts and coupling constants of 3 with those of 2,5-dichloro-1,6-diazaphenalene 4[1] and 7-nitro-2,5-dichloro-1,6-diazaphenalene 5.[4] The 7-nitro-dichlorodiazaphenalene 5 had been prepared previously by treatment of 4[4] under conditions analogous to those discussed above (TFAA/$NaNO_2$). Apparently, under the milder nitration conditions, the mononitro derivative 3 was formed predominantly from 1. This indicated the pyridine nitrogen was protonated and electrophilic substitution occurred by way of resonance structure A. This was not surprising since protonation of the pyridine portion of 1 serves to deactivate this ring to electrophilic substitution[11] while electron release from position -1 activates position -7 to attack. It must be remembered that both nitrogen containing rings of 1,6-diazaphenalene 1 at one time or another have pyridine character (1a ⇄ 1b) and hence would be deactivated to an equal extent in trifluoroacetic acid. Moreover, because of the rapid tautomerism of the type (1a ⇄ 1b) positions -3 and -4 can be considered equivalent, and in like manner positions -7 and -9 are interchangeable. For this reason nitration of 1 at either position -7 or -9 leads to the same mononitro derivative 3.

In contrast to the behavior on nitration, the 2-3 double bond, (resonance structure B), was the most reactive portion of the molecule in a medium of lesser acidity, as illustrated in Scheme I. When 1,6-diazaphenalene 1 was reacted with bromine, under conditions analogous to the bromination of imidazole,[12] the tribromo and dibromo derivatives 6 and 7 were isolated as the major products of this experiment accompanied by small amounts of three other halo compounds and a considerable amount of 1. The structures of 6 and 7 were established by spectroscopy. Again, comparison of chemical shifts and coupling constants of the bromo compounds[13] to the dichloro-derivative 4 was of major importance in the structural assignments. The substitution of bromine at positions -3 and -4 of diazaphenalenes 6 and 7, respectively, is not exceptional and probably reflects the reactivity of the free base 1 (CH_3CO_2H, NaOAc) rather than the protonated form which was present during nitration (CF_3CO_2H). The incorporation of bromine at position -2 of 1; however, requires some comment, for pyridines do not readily react with positive bromine at this position.[14] It is felt the 2,3-double bond may have reacted as an isolated double bond and underwent electrophilic addition of bromine to provide 8 followed by oxidation to reform the conjugated system. Indirect evidence for this process has been recently observed.[15] Thus, 2,3-dihydro-1,6-diazaphenalene 9, on standing in solution, lost the elements of hydrogen to reform the parent diazaphenalene 1, albeit in low yield, accompanied by other products of decomposition. All attempts to monobrominate 1 under mildly acidic conditions were unsuccessful; however, when 1 was dissolved in trifluoroacetic acid and then reacted with bromine, 7-bromo-1,6-diazaphenalene was obtained in better than 80% yield. This is consistant with results presented earlier on nitration of 1 in trifluoroacetic acid, although it should be pointed out that monobromination of imidazole has, to date, not been achieved.[16]

Scheme I



1 6 7

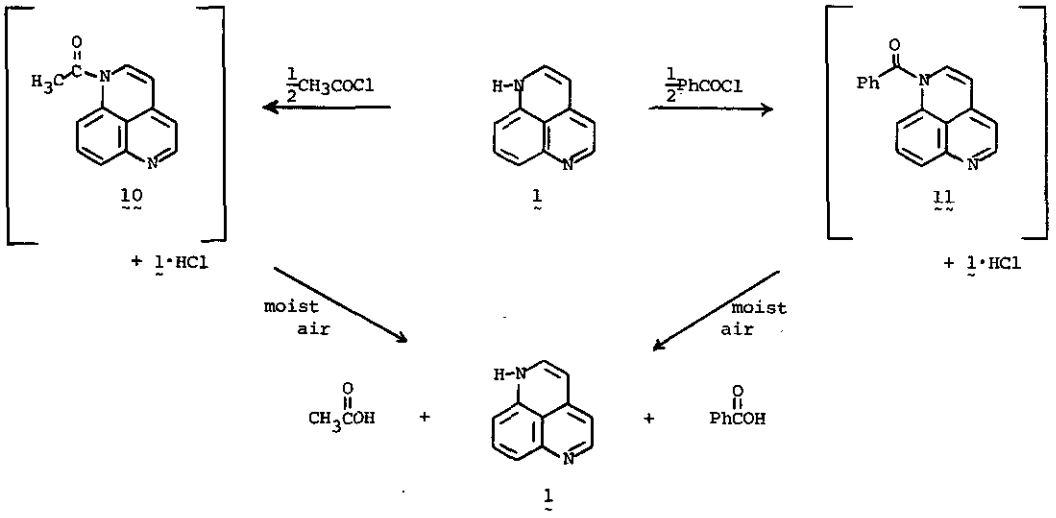


7 8, X = Br; 9, X = H 1, X=H

The reactions of 1 with acyl halides was next explored for comparison with the parallel reactions of imidazoles, which are known to lead to N-acyl derivatives. In this study two equivalents of 1,6-diazaphenalene 1 in dimethylformamide were stirred with one equivalent of the acyl halide, as illustrated in Scheme II. In each reaction (CH_3COCl, PhCOCl) nearly one equivalent of 1,6-diazaphenalene hydrochloride was isolated which indicated that the acylation had taken place; however, we were never able to isolate the acyl derivative either in the acetyl 10 or benzoyl 11 series. The presumed intermediates, acyl diazaphenalenes 10 and 11, respectively, appeared to revert to 1 and the corresponding acid even on standing in air. The stability, or lack there of, of amides 10 and 11 is not surprising, for acyl imidazoles[18] are extremely reactive in the presence of nucleophiles such as water. These experiments thus lend support to the view that 1 behaves as a vinylogous imidazole.[19]

Scheme II

Attempts to Acylate 1,6-Diazaphenalene (1)

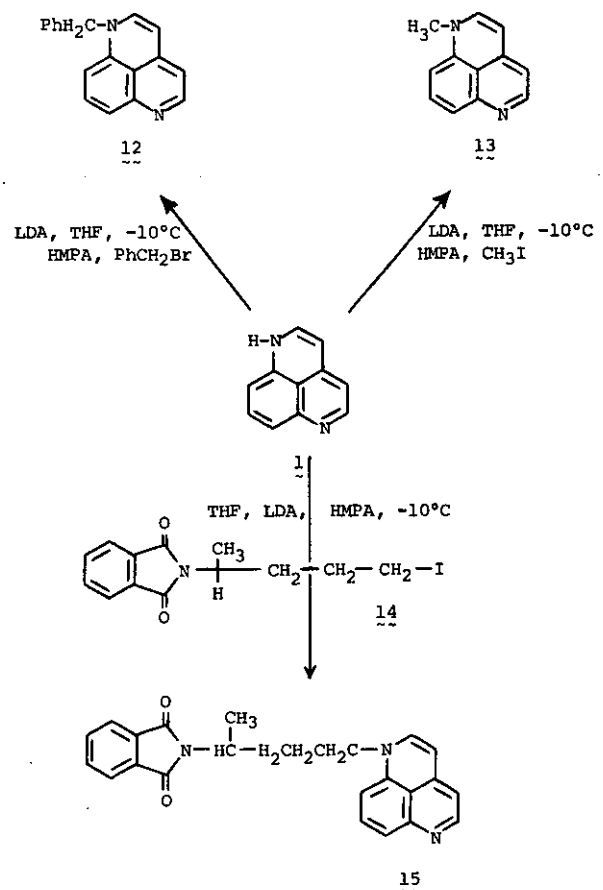


In a related study we investigated the alkylation of 1 with various alkyl halides. In fact, when 1 was heated with benzyl bromide in acetone (K_2CO_3), under conditions analogous to these reported for the preparation of N-benzylimidazole,[20] only starting material was recovered. This suggests that the amino group of 1 is not as nucleophilic as the corresponding nitrogen function of imidazole. Consequently, 1,6-diazaphenalene (1) was treated with lithium diisoproyl amide (see Scheme III) to generate the anion, followed by addition of benzylbromide to provide a 60% yield of N-benzyl-1,6-diazaphenalene 12.[21] The nmr spectrum[21] of this material was quite complex which indicated that the pseudo plane of symmetry present in 1,6-diazaphenalene was absent in 12. Moreover, it was quite apparent from the ir spectrum (no N-H absorption) and nmr spectrum (methylene func-

tion of N-benzylimidazole appears at 5.08 δ[5] while that of 12 is located at 4.60 δ[21]) of 12 that alkylation had occurred on nitrogen and not carbon. In addition, 12 was readily soluble in chloroform (no hydrogen bonding) while 1 was nearly insoluble in the same solvent further indicating that alkylation had occurred on nitrogen. The yield of this benzylation reaction improved to 82% when LDA was replaced with butyllithium (-65°). In similar fashion the anion of 1 was alkylated with

Scheme III

Alkylation of 1,6-Diazaphenalene



methyliodide to provide N-methyl-1,6-diazaphenalene 13, as shown in Scheme III. Correlations of the spectral data and solubility of 13[22] with 12 were sufficient to demonstrate that methylation (methyl function of N-methylimidazole is located at 3.73 δ[5] while the analogous signal for 13 was observed at 3.05 δ) had occurred exclusively on the nitrogen atom. In tandem with the above

reactions a more complex alkyliodide 14 has also been employed as a substrate for the alkylation of 1. Treatment of the phthalimido derivative[23] 14 with the lithium anion of 1 provided a 67% yield of the N-substituted-1,6-diazaphenalene 15;[24] a 5-aminoquinoline analog which may demonstrate potential antimalarial activity. In contrast to 1, the anion of 7-nitro-2,5-dichloro-1,6-diazaphenalene 5, prepared under analogous conditions, did not undergo alkylation with benzyl bromide. Apparently the anion, which formed in this case, is stabilized by the nitro and chloro groups, and will not react, at least under conditions (-10°C) that 1 undergoes alkylation. Steric factors may also play a role in this instance for the lithium anion of 5 is flanked by nitro and chloro moieties.

In studying the chemistry of 1,6-diazaphenalene (1) there is special interest in its reaction with singlet oxygen particularly with respect to the analogous oxidation of imidazole.[25] Dye-sensitized photooxidation of (1) was therefore studied under a variety of conditions.

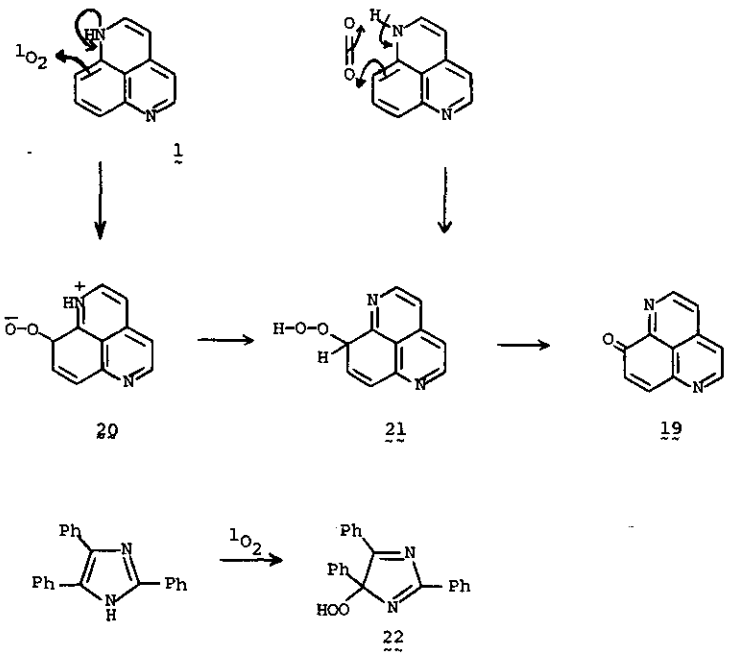
Like many electron-rich heterocyclic systems such as pyrroles and imidazoles,[25] 1 suffered extensive decomposition when reacted with oxygen, Rose Bengal and light (650 w tungsten-halogen lamp) under moderate concentrations of $CHCl_3$/EtOH. On the other hand, in dilute solution (100 mg in 500 ml of solution) the photooxygenation took place smoothly yielding a single product (19) in 50% yield. The structure of 19[26] was established by infrared, NMR and mass spectrometry, all of the spectroscopic data being uniquely consistent with a naphthyridine system incorporating an α,β-unsaturated ketone function. Under the same conditions of dilution, 2,5-dichloro-1,6-diazaphenalene (4) yielded only tarry decomposition products on photooxygenation.

In Scheme IV we picture the uptake of oxygen at the 7-position of (1) as an ene-like reaction facilitated by electron release from the nitrogen at position-1. Electron-availability at C-3 might have rendered this position a competitive site for attack by the electrophilic oxygen, but reaction at C-7 has the advantage of a favorable 6-membered transition state for C-O bond formation coincident with the breaking up of the N-H bond.

Alternatively, a zwitterionic product (20) may be initially formed by release of electrons to oxygen from the enamine. Formed by either process, the intermediate hydroperoxide (21) would then suffer ready dehydration to yield the observed ketone (19). Loss of water would be expected to take place readily from 21 since the proton at C-9 of the hydroperoxide is relatively acidic. It is interesting to note that hydroperoxides of type 22 are formed as intermediates in the photooxygenation of aryl imidazoles.[27]

Many, although not all, of the reactions of 1 discussed above resemble similar transformations previously carried out on imidazoles. Further work is in progress to examine this correlation in more detail.

Scheme IV



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References and Notes

1. J. C. Chang, M.I. El-Sheikh and J. M. Cook, Heterocycles, 1979, 12, 903.
2. This is contribution number 1607 from the Army's Program on Malaria, contract # DAMD-17-78-C-8003.
3. This work was presented in preliminary form at the Great Lakes Meeting of the American Chemical Society, Western Illinois University, Macomb Illinois, R. Weber, J. Cheng, M. I. El-Sheikh, and J. M. Cook, June 4-6, 1980, abstract #140.
4. Jen-Chun Chang, M.S. Thesis, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin 1979.
5. C. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra," Vol. VIII, 1974, p. 127.
6. G. Dedichen, Ber., 1906, 39, 1831; A. H. M. Kirby and A. Neuberger, Biochem. J., 1938, 32, 1146.
7. A. Albert and R. Goldacre, Nature, 1944, 153, 468.
8. See for example: M. Caplow and W. P. Jencks, Biochem., 1962, 1, 883; J. Milstien and T. H. Fife, J. Am. Chem. Soc., 1968, 90, 2164; M. L. Bender and B. W. Turnquest, J. Am. Chem. Soc., 1957, 79, 1652 and 1656; T. C. Bruice and G. L. Schmir, J. Am. Chem. Soc., 1957, 79, 1663.

9. U. Spitzer and R. Stewart, J. Org. Chem., 1974, 39, 3936; S. Uemura, A. Toshimitsu, and M. Okano, J. Chem. Soc., Perkin I, 1978, 1076.

10. 3: mp >300°C; ir(KBr) 3160(w), 1620(s), 1600(s), 1440(s), 1220(s), 1162(s), 822(s), 792(s), 731(s); NMR (CF_3COOH) δ 7.27 (2H, d, J=7Hz), 7.58 (1H, d, J=9Hz), 8.20 (1H, d, J=7Hz), 8.42 (1H, d, J=7Hz) and 9.01 (1H, d, J=9Hz); mass spectrum (C.I., CH_4) 214 (P + 1, 100).

11. M. J. S. Dewar and P. M. Maitlis, J. Chem. Soc., 1957, 2521; M. W. Austin and J. H. Ridd, J. Chem. Soc., 1963, 4204; R. D. Brown and R. D. Harcourt, J. Chem. Soc., 1959, 3451.

12. K.-E. Stensio, K. Wahlberg and R. Wahren, Acta. Chemica. Scand., 1973, 27, 2197.

13. 6: 2,3,4-tribromo-1,6-diazaphenalene; mp >300°C; ir(KBr) 3325(b), 1585(s), 1340(s), 1265(s), 1235(s), 790(s), 765(s) and 685(s) cm^{-1}; nmr(CF_3COOH) δ 5.51 (1H, d, J=7Hz), 7.58 (1H, t, J=7Hz), δ 7.69 (1H, d, J=7Hz) and 9.01 (1H, s); mass spectrum (C.I., CH_4) 405 (P + 1, 100). 7: 2,3-dibromo-1,6-diazaphenalene; mp >300°; ir(KBr) 3065(b), 1592(s), 1338(s), 1262(s), 1239(s), 804(s), 785(s), 760(s); nmr(CF_3COOH) δ 5.13 (1H, d, J=7Hz), 5.75 (1H, d, J=9Hz), 7.27 (1H, t, J=7Hz), 7.33 (1H, d, J=7Hz) and 7.44 (1H, d, J=9Hz); mass spectrum (C.I., CH_4) 327 (P + 1, 100).

14. R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 2nd Ed., Interscience, N.Y., 1967, pps. 250 and 254.

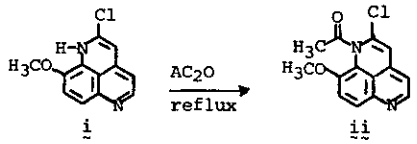
15. K. Avasthi and J. M. Cook, unpublished results.

16. K. Hofmann, "Imidazole and its Derivatives," Interscience N.Y., 1953; V. Calo, F. Ciminale, L. Lopez, F. Naso and P. E. Todesco, J. Chem. Soc., Perkin Trans., 1972, 1, 2567.

17. H. A. Staab, Chem. Ber. 1956, 89, 1927; T. H. Fife, G. S. Reddy, L. Mandel and J. A. Goldstein, J. Chem. Soc., 1963, 1414.

18. S. Marburg and W. P. Jencks, J. Am. Chem. Soc., 1962, 84, 232; C. Bunton, J. Chem. Soc., 1963, 6045; J. A. Fee and T. H. Fife, J. Org. Chem., 1966, 31, 2343; W. P. Jencks and J. Carriuolo, J. Biol. Chem., 1959, 234, 1272 and 1280.

19. In a related study the N-acyl diazaphenalene ii has been prepared by heating 2-chloro-9-methoxy-1,6-diazaphenalene i in acetic anhydride. The acyl compound ii has been characterized. Since 1 does not provide an N-acyl halide under analogous conditions, it is



i ii

believed that the chloro and methoxy groups which flank the acyl function of ii inhibit the rapid hydrolysis of this material. This acyl derivative is, however, quite labile for it reverts to i on chromatography. R. Weber and J. M. Cook, unpublished results.

20. K. H. Baggaley, M. Heald, R. M. Hindley, B. Morgan, J. L. Tee and J. Green, J. Med. Chem., 1975, 18, 833.

21. 12: mp 138-9°; ir(KBr) 3025(w), 1625(s), 1590(s), 1570(s), 1420(m), 1340(s), 820(m), 740(m); nmr($CDCl_3$) δ 4.47 (2H, s), 5.60 (1H, d, J=7Hz), 6.01 (1H, d, J_1=7Hz, J_2=7Hz), 6.24 (1H, d, J=5Hz), 6.51 (1H, d, J-7Hz), 6.94-7.34 (7H, m), and 8.21 (1H, d, J=5Hz); mass spectrum (C.I., NH_3) 259 (P + 1, 100).

22. 13: mp 94-96°; ir(KBr) 1630(s), 1595(s), 1575(s), 1342(s), 825(m), 740(s); nmr ($CDCl_3$) δ 3.05 (3H, s), 5.60 (1H, d, J=7Hz), 5.90-6.40 (2H, m), 6.48 (1H, d, J=7Hz), 7.00-7.30 (2H, m) and 8.18 (1H, d, J=5Hz); mass spectrum (C.I., NH_3) 183 (P + 1, 100).

23. The phthalimido derivative was kindly provided by the Walter Reed Army Research Institute, Medicinal Chemistry Section.

24. 15: mp 220°(d); ir(KBr) 3400 (H_2O), 3070 (w), 2990(w), 1635(s), 1600(s), 1586(s), 830(w), 750-(w); nmr (DMSO-d_6) δ 1.10 (3H, d, J=6.8Hz), 1.60 (4H, m), 3.83 (3H, m, N-CH_2 and N-CH), 5.87 (1H, d, J=8Hz), 6.45 (1H, d, J=5Hz), 6.60 (1H, d, J=8Hz), 6.83-7.73 (7H, m) and 8.10 (1H, d, J=5Hz); mass spectrum (C.I., NH_3) 384 (P + 1, 100).

25. H. Wasserman, K. Stiller and M. B. Floyd, Tetrahedron. Lett., 1968, 3277; H. H. Wasserman, and B. Lipshutz, in "Singlet Oxygen," Ed. by H. H. Wasserman and R. W. Murry, Academic Press, N.Y., 1979, pp. 481-490.

26. 19: ir($CHCl_3$), 1667(s), 1621(s), 1587(w), 1226(m), and 1212(m) cm^{-1}; nmr ($CDCl_3$), 6.99 (1H, d, J=10.3Hz), 7.75 (1H, d, J=5.8Hz), 7.84 (1H, d, J=10.3Hz), 7.95 (1H, d, J=5.5Hz), 8.86 (1H, d, J=5.9Hz), and 9.15 (1H, d, J=9.15Hz), mass spectrum (E.I.) 182 (P).

27. E. H. White and M. J. C. Harding, J. Am. Chem. Soc., 1964, 86, 5686.

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