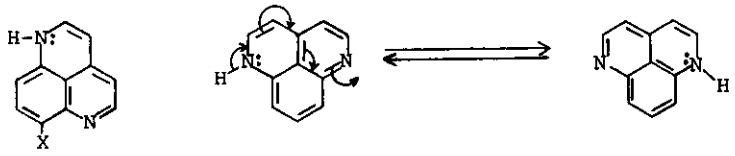
SYNTHESIS OF 1,6-DIAZAPHENALENE, A VINYLOGOUS IMIDAZOLE

Jen-C. Chang, Mustafa I. El-Sheikh, and James M. Cook*
Department of Chemistry, University of Wisconsin-Milwaukee,
Milwaukee, Wisconsin 53201, USA

The simple synthesis of a new heterocycle, 1,6-diazaphenalene (2), a vinylogous imidazole is described; the key step in the synthesis was conversion of 7 to 8 by cleavage of the N-O bond followed by hydrogen shifts under modified Semmler Wolff conditions [CF_3COOH, $(CF_3CO)_2O$, HCl].

The emergence of drug-resistant strains[1] of Plasmodia facliparum has stimulated considerable interest in the synthesis of new antimalarial drugs.[2] In order to prepare agents (for example, 1) related to the active 8-aminoquinoline, primaquine[3], which are capable of forming quinonoid structures[4], we required a short synthesis of the new heterocyclic system 1,6-diazaphenalene 2. This molecule is interesting from a chemical and electronic point of view as well, for it can be viewed as a vinylogous imidazole, and would be expected to possess properties related to this heterocycle. Prototropic shift of the N-H proton in 2a to the pyridine nitrogen would lead to the identical structure 2b; however, the case would be entirely different when X=NHR (1). Furthermore, unlike phenalene, all three rings of 2 are capable of sustaining aromatic character due to the prototropic shifts and mesomeric effects illustrated below.



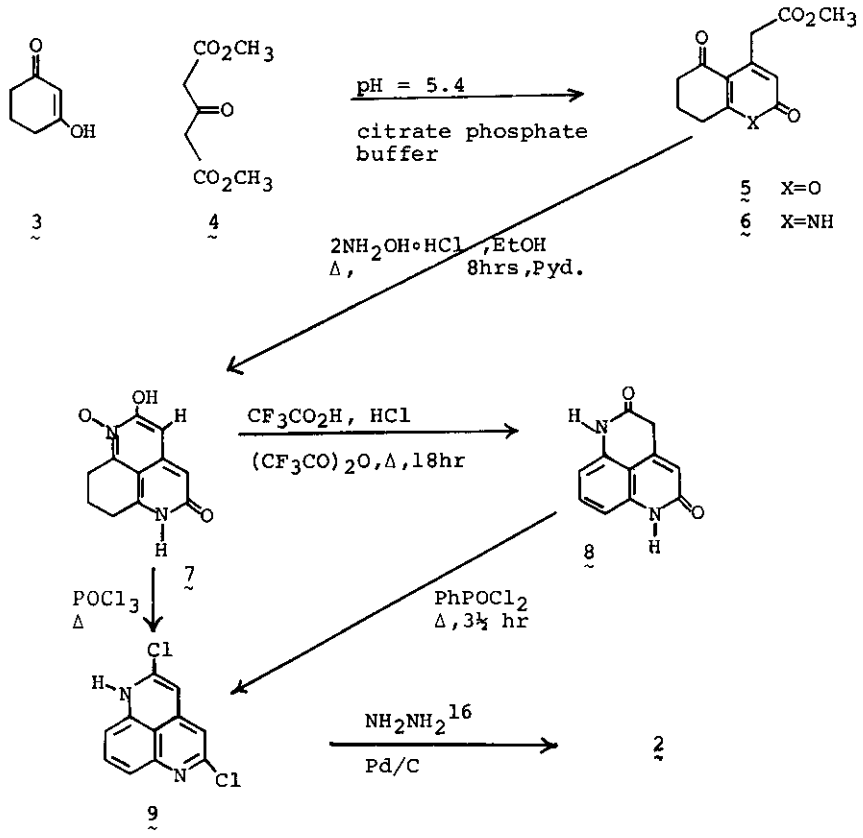
1, X=NHR 2a 2b

In previous studies in our laboratory, cyclohexane-1,3-dione (3) had been allowed to react with dimethyl β- ketoglutarate (4) to provide a good yield of the 5-oxo-5,6,7,8-tetrahydrocoumarin (5) which had subsequently been converted to the

5-oxo-2-quinolone 6 (92% yield) on treatment with ammonia,[5] as outlined in Scheme I. The readily available quinolone 6 permitted design of a synthetic route to 2 which avoided alkylation and nitration reactions of pyridine derivatives, which are known to be troublesome.[6] When the 5-oxo-quinolone 6 was heated with hydroxylamine hydrochloride in the presence of pyridine an 85% yield of the quinolone N-oxide 7 was obtained, the properties of which have been reported.[7] The pivotal step in the sequence rested on the conversion of the N-oxide 7 to the diazaphenalone 8. Our first attempts at this transformation were carried out by heating the N-oxide 7 for eighteen hours under Semmler Wolff conditions.[8] Although it was clear from spectral data a diazaphenalone had resulted from this treatment,[9] scale up of the reaction led to significant amounts of carbonization. It was then decided to modify the sequence to facilitate cleavage of the N-O bond permitting the aromatization to occur under milder conditions. When acetic acid/acetic anhydride were replaced with trifluoroacetic acid/trifluoroacetic anhydride analogous to the modified Polonovski conditions[10] employed in the Vinca alkaloid work,[11] a 90% yield of a crystalline diazaphenalone 8 was isolated.[12] Treatment of this compound with phenyl phosphonic dichloride analogous to the work of Robison,[13] gave 2,5-dichloro-1,6-diazaphenalene 9 in 88% yield.[14] The dichloro-compound 9 could also be obtained directly from 7 by treatment of the N-oxide with phosphoryl chloride; however, the yield by this route was only 48%. The parent 1,6-diazaphenalene 2[15] was obtained in 85% yield by hydrogenolysis (Pd/C, hydrazine)[16] in ethanol of the chlorine atoms present in 9.

1,6-Diazaphenalene 2 is a yellow solid which is quite polar as evidenced by its low R_f on tlc (R_f = 0.076, SiO_2/CH_3OH). Tautomerization between structures 2a and 2b is more rapid than the NMR time scale for the proton NMR spectrum contains only four C-H signals indicative of the symmetrical nature of 2 which can only arise by a rapid equilibrium between the two molecules. The same phenomenon occurs in the case of 2,5-dichloro-1,6-diazaphenalene 9 and imidazole.[17] The diazaphenalene 2, is soluble in polar solvents such as methanol, slightly soluble in benzene, and somewhat soluble in water.

Scheme I



3 4 5 X=O 6 X=NH 7 8 9 2

The synthesis of 2 has been accomplished in six simple steps from non-aromatic precursors and, indeed, the properties of 2 investigated to date resemble imidazole. Further work on the chemistry and electronic properties of 2 as well as the mechanism involved in conversion of 7 to 8 will be reported in due course.

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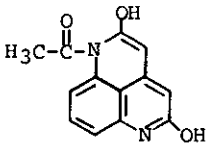
(9) From the standard Semmler Wolff reaction an amide was obtained whose properties are consistant with structure i: mp>350°C, ir(KBr) 3200, 1670, 1630, and 1600 cm^{-1}; NMRδ(warm DMSO) 2.50 (3H,S) 6.20-7.30 (5H,m), 10.57 (S,1H) and 11.60 (S,1H). The signals at 10.57 and 11.60 disappeared on addition of D_2O; Mass Spectrum C.I. (NH_3) M^+ at m/e 243(100), therefore M^+ = 242.



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(12) 8: mp = 390°(dec); ir(KBr) 1690, 1650, 1620, 1560, 1450, 1350 and 1190 cm^{-1}. NMR δ(CF_3COOH) 4.50 (2H,S), 7.10 (1H,S), 7.20 (1H,d,J=8H_z), 7.40 (1H,d,J=8H_z)

and 7.80 (1H,t,J=8H_z), Mass Spectrum C.I. (NH_3), m/e 201 (M+1, 100), M^+=200. The diazaphenalone 8 could also be obtained from 7 when HCl was excluded from the reaction mixture; although, the yield was lower.

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(14) 9: Obtained as yellow-green crystals, mp=223-225° (aq EtOH); ir(KBr) 3400, 1640, 1605, 1590, 1540, 930, 910, 820 and 770 cm^{-1}; NMR δ(CF_3COOH) 6.52 (2h, s), 7.28 (2H,d,J=8H_z) and 7.88 (1H,t,J=8H_z); Mass Spectrum, M^+ at m/e 238 (64%), 236 (100%).

(15) 2: Characterized as yellow crystals, mp=220-2°(dec), from benzene: ir(KBr) 3280, 3200, 1640, 1580, 1470, 815, 785 and 740 cm^{-1}; NMR δ(CD_3OD, 220 mH_z) 5.95 (2H,d,J=6H_z), 6.70 (2H,d,J=8.5H_z), 7.30 (1H,t,J=8.5 H_z) and 7.42 (2H,d, J=6H_z); Mass Spectrum, M^+ at m/e 168.

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