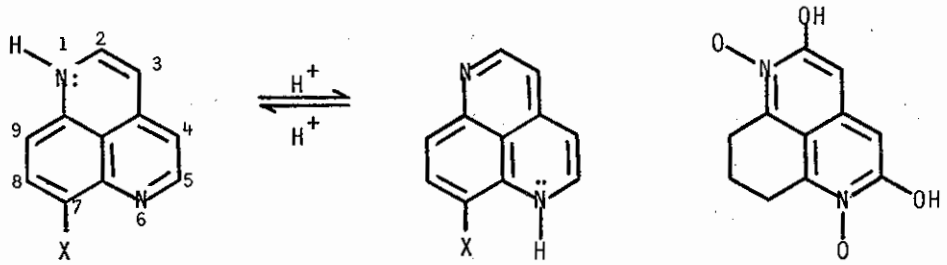
Simple Entry into the 1,6-Diazaphenalene Ring System

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

A facile synthesis of the dihydro-1,6-diazaphenalene ring system has been developed by heating one equivalent of methyl-1,2,3,4-tetrahydro-5-oxocoumarin-4-yl acetate (5) with three equivalents of hydroxylamine hydrochloride in aqueous ethanol; 7,8-dihydro-2,5-dihydroxy-1,6-diazaphenalene-1,6-dioxide (2) was produced in this manner in 88% yield.

We have investigated synthetic routes to the 1,6-diazaphenalenes (1a) and (1b) and the corresponding 2,3-dihydro derivatives for the past several months. Impetus for this research stemmed from the reported potent activity of 8-aminoquinoline derivatives in the treatment of malaria,[1] and also from the unique chemical properties expected for the 1,6-diazaphenalene (1a). Prototropic shift of the N-H proton (1a) to the pyridine nucleus would lead to the identical structure when X=H; however, the case would be entirely different with X=NHR (1b). Furthermore, unlike phenalene, all three of the rings in (1) would be expected to demonstrate aromatic character *via* prototropic shifts or mesomeric effects.

We wish to report a two-step entry into the 1,6-diazaphenalene ring system (2), the structure of which shows excellent promise for further elaboration into diazaphenalenes (1a and b).

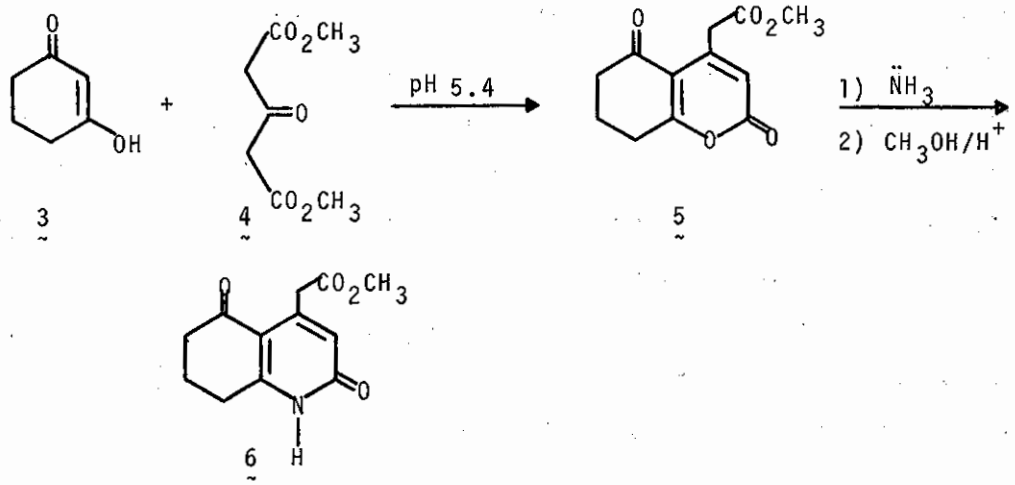


1a X=H
1b X=NHR

2

Early during the investigation of the reaction of dicarbonyl compounds with dimethyl β-ketoglutarate, it was found that stirring a solution of cyclohexane-1,3-dione (3) in citrate-phosphate buffer[2] with dimethyl β-ketoglutarate (4) provided a very good yield of the 5-oxo-4-alkyl-5,6,7,8-tetrahydrocoumarin (5), as illustrated in Scheme I. The oxocoumarin appeared to be an excellent precursor for the tricyclic system, for replacement of the 1- and 5-oxo-functions with nitrogen atoms might well provide the basic skeleton (1).

SCHEME I

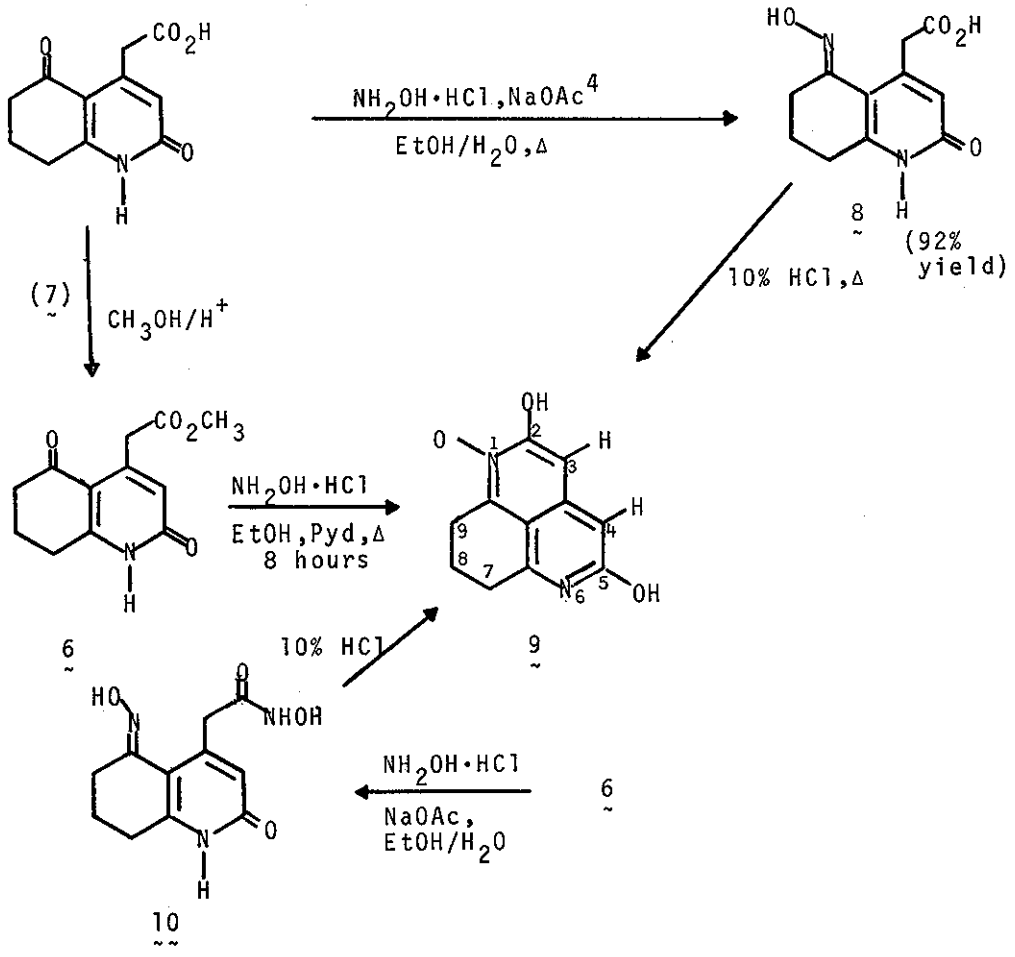


3 4 5

6

Conversion of the 5-oxocoumarin (5) to the 5-oxo-4-alkyl-5,6,7,8-tetrahydro-2-quinolone (6) was carried out by published methods[2,3] in 90% yield (see Scheme I); but, addition of the second nitrogen function was not as straight-forward. The 5-oxoquinolone ester 6 was reacted with a variety of amines including ammonia and benzylamine; unfortunately, these attempts ended in failure. In contrast, heating the 5-oxo-tetrahydroquinolone acetic acid derivative (7) for four hours with hydroxylamine hydrochloride in aqueous ethanol in the presence of sodium acetate, analogous to conditions reported by Tamura et al.,[4] provided a 96% yield (Scheme II) of the desired oxime (8): mp = 226-230°; IR (KBr) 3310, 2860, 1702, 1642, 1598, 955, and 938 cm^{-1}. The presence of the carboxyl function and the bands at 955 and 938 (oxime)[4] in the infrared spectrum of the yellow solid supported the structure of the oxime, 8. The NMR spectrum in D_2O,NaOD contained signals at δ 1.82 (2H,m), 2.61 (4H,m), 3.80 (2H,s, $-CH_2-$) and 6.18 (1H,s,vinyl proton), while the C.I. mass spectrum (NH_3) had a parent ion (1%) at 237 (M+1); furthermore intense peaks occurred at 219 [$(M^+ +1)-18,H_2O$)] and 203 [$(M^+ +1)-H_2O-16$ (O)]. The origin of the peaks at 219 and 203 will become clear later in the discussion. In addition, the oxime (8) when heated above 226°C turned from a light yellow solid to a yellow-orange compound whose IR spectrum no longer resembled that of the original oxime (8). The same oxime (8) was obtained when (7) and $NH_2OH\cdot HCl$ were heated in a pyridine/ethanol solution for several hours (no NaOAc added); but, when the 5-oxoquinolone ester (6) and $NH_2OH\cdot HCl$ were heated in an ethanol-water solution for several hours the major product was not the oxime (8) but the yellow colored oximino

SCHEME II

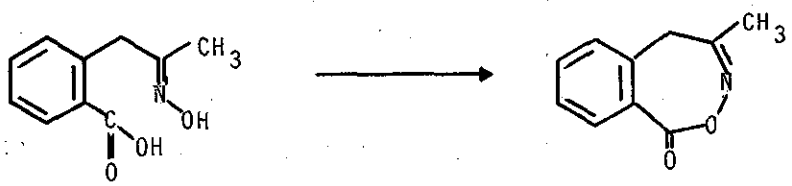


hydroxamic acid 10 (mp > 300°C); IR (KBr) 3100-2300 (broad bands), 1640, 1620, 1588, 1516, 1422, 1170, (955 and 980 oxime)[4] cm^{-1}. The carboxyl function was absent in the spectrum of 10 as compared to that of (8) while elemental analysis clearly indicated the molecule contained three nitrogen atoms. All attempts to obtain a mass spectrum led to an ion at m/e 218 which was not the parent peak (see below).

However, both the oxime 8 and the hydroxamic acid 10 gave the same orange,yellow-orange solid when treated with hot 10% hydrochloric acid. Furthermore, the IR spectrum of this solid was identical to that obtained earlier, when a small amount of 8 was heated to 226° in a capillary tube. In addition, prolonged heating of the 5-oxoquinolone methyl ester (6) with hydroxylamine hydrochloride in an ethanol-pyridine solution provided the same yellow-orange precipitate (9) directly. The structure of this yellow-orange solid was proven, unequivocally, to be that represented by structure (9). This high melting solid (mp > 350°) had a molecular ion at 218 mass units (E.I. and C.I. spectra); furthermore the base peak in the C.I. spectrum occurred at M^+-16 characteristic for the loss of oxygen from N-oxides;[5] similar results were seen in the electron impact spectrum. The IR spectrum contained bands at 3400, 3040 (OH) and 1620 (pyridone C=O), furthermore strong signals were found at 1595, 1290, and 1180 cm^{-1} characteristic of absorptions from N-oxides observed in similar environments.[6] Although 9 was insoluble in most organic solvents, NMR spectra could be obtained both in trifluoroacetic acid and D_2O (NaOD) solution: δ (CF_3CO_2H), 2.48 (2H,m), 3.56 (4H, two overlapping triplets), 6.95 (1H,s, vinyl) and 7.00 (1H,s, vinyl proton); δ (D_2O, NaOD), 2.20 (2H,m), 2.94 (2H,t), 3.20(2H,t), 6.05 (1H,s) and 6.20 (1H,s). When the spectrum was run in DMSO-d_6 the two vinyl signals were found at δ 5.94; this surprising result may be due simply to solvent shifts, or in fact might originate from chemical interaction of DMSO with 9.[7]

Some review of the pathways to the N-oxide 9 should be presented for the sake of clarity. We have observed the consistent

cyclization of either the oxime (8) or hydroxamic acid 10 in the mass spectrometer to provide a molecular ion (218) consistant with structure 9. We have also observed this on heating 8 or 10 to temperatures > 226°C. Moreover, the oxime (8) was converted to the dihydrodiazaphenalene-1-N-oxide derivative (9) in 96% yield on treatment with hot 10% hydrochloric acid. Furthermore, when the NMR spectrum of either 8 or 10 was run in trifluoroacetic acid, the spectrum of the cyclized N-oxide (9) was observed, immediately. In none of our work have we observed a carbonyl absorbtion at 1721 cm^{-1} which is reported[6c] to be present in "Gottlieb's anhydroderivative, 12* produced by heating the oximino acid 11 at 175°, as shown below.[8]



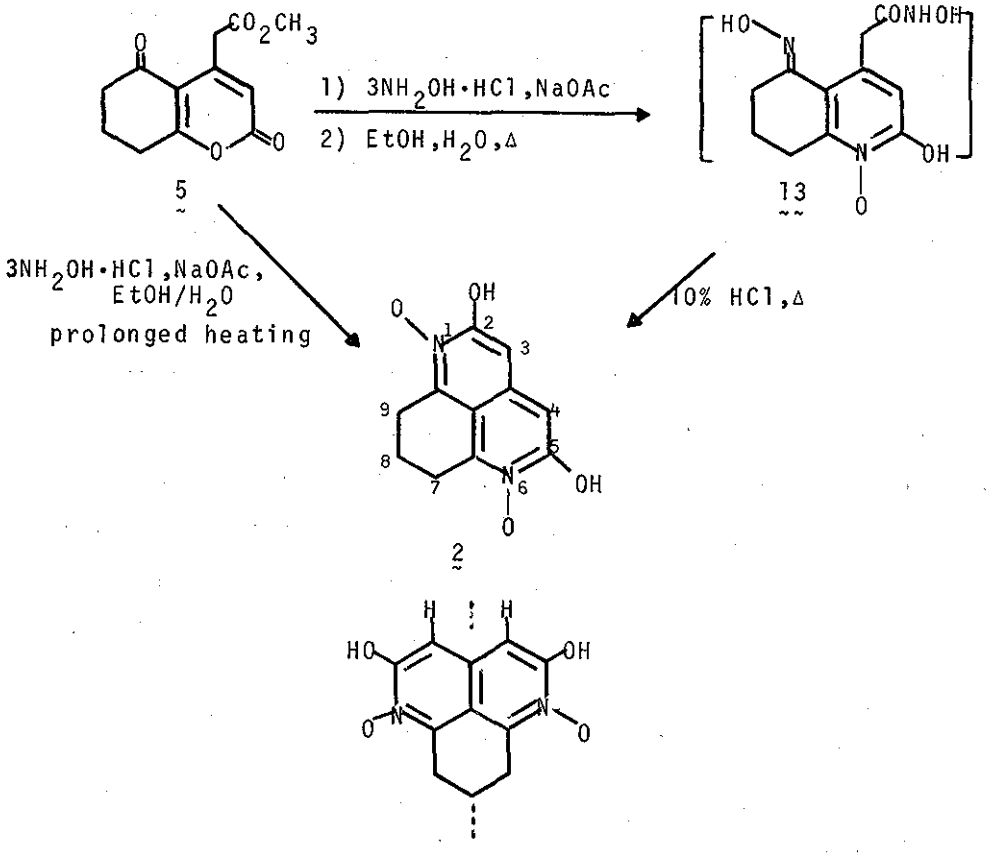
11 12

Also, the signal for the methylene function which would result from this attack studied by Gottlieb and later reinvestigated by *Moriconi*[6c] was absent from the NMR spectrum of (9). Apparently the peri position of the oxime 8 is perfectly set up for the desired cyclization to take place in the case of 8 or 10.

It is obvious that harsh conditions are required to force bases 6, 8, and 10 to cyclize to the N-oxide 9; however, the yields are quite high in all these conversions (transformation of 7 to 9 can be carried out in better than 80% overall yield).

Although the yield of the diazatricyclic system (9) from 7 was good, it was felt a shorter route might be developed if better use was made of the 5-oxo-4-alkyl-5,6,7,8-tetrahydrocoumarin (5). To this end the two-step synthesis of the key tricyclic ring system (2) has been developed as outlined in Scheme III. Reaction of 3 with 4 gave (5) in good yield, as described before. The 5-oxocoumarin derivative was then heated with three moles of hydroxylamine hydrochloride in aqueous alcohol; prolonged heating, with further addition of $NH_2OH \cdot HCl$ to the mixture, provided an 88% yield of the dihydro-2,5-dihydroxyl-1,6-diazaphenalene-1,6-dioxide 2, while heating the same

SCHEME III



solution for only 10 hours furnished a mixture of 2 and another compound felt to be the intermediate hydroxamic acid 13. The mixture of 2 and 13 was converted quantitatively to 2 on treatment with hot 10% hydrochloric acid.

The physical and spectral data are in complete agreement with the structure of 2. The orange colored solid which has a high melting point (>300°C), characteristic of similar quinolones was insoluble in most organic solvents. The chemical ionization mass spectrum (NH_3) showed successive losses of 16 (O) at 219 and 203 mass units, respectively, confirming the bis-N-oxide nature of 2.[5] In addition, IR (KBr) bands were found at 3450 (OH), 3050, 1630 (C=O), 1610, 1295 and 1185 cm^{-1}; the strong bands at 1610, 1295, and 1185 are due to $C=\overset{+}{N}-\overline{O}$ and $N^{+}-O^{\theta}$ stretching vibrations characteristic of pyridine and pyridine-N-oxides.[6] The symmetrical character of the diazaderivative (2) was clearly shown by its NMR spectrum (CF_3CO_2H) which contained only three signals: δ 2.52 (2H,m, C-8H's), 3.62 (4H,t,J=6Hz,C-7 and C-9H), and 7.00 (2H,s,C-3 and C-4, vinyl protons).

The simple synthesis of the dihydrodiazaphenalene derivatives 2 and 9 from readily available starting materials will certainly make diazaphenalenes such as 1a and 1b more accessible. It should now be possible to employ standard methods to convert 5 into 1a or 1b. Work is in progress at the present time to effect such conversions.[9]

ACKNOWLEDGMENT. The authors wish to thank Mr. Noel Whittaker for mass spectral measurements, Ms. Olivia Campos for helpful discussions and Dr. Alan Harmon for his interest and advice.

This is Contribution No.1518 to the Army Research Program on Malaria (contract number DAMD17-78-C-8003).

References and Notes

[1]H. W. Brown, "Basic Clinical Parasitology," 4th Ed., Appleton-Century Crofts, New York, 1975, pp. 75-98; P. Thompson and L. Werbel, "Antimalarial Agents," Chemistry and Pharmacology, Academic Press, New York; D. Botha, S. African Med. J., 1974, 48, 1263.

[2]J. Oehldrich and J. M. Cook, J. Org. Chem., 1977, 42, 889.

[3]M. Guthzeit, Chem. Ber., 1893, 26, 2795; L. Smith and R. Kelly, J. Amer. Chem. Soc., 1952, 74, 2300.

[4]Y. Tamura, Y. Kita, and J. Uraoka, Chem. Pharm. Bull., 1972, 20, 876.

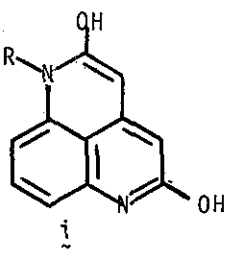
[5]M. Weigele and W. Leimgruber, Tetrahedron Lett., 1967, 715.

[6]H. Shindo, Chem. Pharm. Bull., 1960, 8, 845; G. R. Delpierre and M. Lamchen, Quart. Rev., 1965, 329; E. Moriconi, F. Creegan, C. K. Donovan, and F. A. Spano, J. Org. Chem., 1963, 28, 2215.

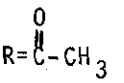
[7]This phenomenon is under investigation in our laboratory.

[8]J. Gottlieb, Ber., 1899, 32, 966; Beilstein, 1937, 27, 210, carbon analysis reported to be low.

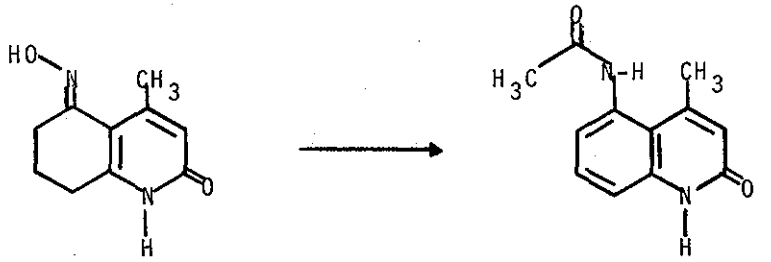
[9]Very recently in our laboratory M. I. El-Sheikh has effected a Semmler-Wolff"type" rearrangement by treatment of the N-oxide 9 with acetic anhydride/acetic acid, saturated with anhydrous hydrogen chloride. The spectral data for the product of this rearrangement are consistent with the structure of the diazaphenalene (i).



i



In an analogous manner, the 4-methyl-5-oximino derivative ii was converted to the 5-amino-2-quinolone, iii, based on similar reactions reported by Y. Tamura, O. Nishikawa, T. Shimizu, M. Akita, and Y. Kita, Chem. Ind., 1975, 922.



ii iii

M. I. El-Sheikh and J. M. Cook, unpublished results.

Received, 31st July, 1978