CHEMISTRY OF 1,6-DIAZAPHENALENE. HALOGENATION

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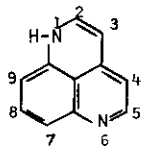
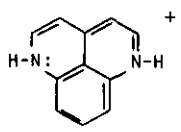
Abstract --- The reaction of neutral species, 1,6-diazaphenalene, with halogen provided principally 2,3-dihalo- and 2,3,4-trihalodizaphenalenes in addition to lesser quantities of other isomers, whereas, halogenation of the protonated form 1b of 1,6-diazaphenalene gave a 7-substituted diazaphenalene as the major product.

The heterocycle 1,6-diazaphenalene 1a has recently been prepared[1] and is of special significance for some of its properties[2,3] are similar to those of imidazole.[4] Because of these similarities and the interest in imidazole for the catalysis of organic reactions,[5] a study of the behavior of 1 in the presence of electrophilic halogen has been undertaken. This investigation has centered on the reaction of bromine with the neutral molecule 1a and, where possible, the analogous transformation has been carried out on the protonated form 1b of 1,6-diazaphenalene.



1a



1b

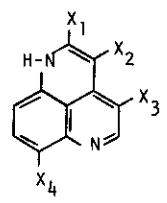
Extrapolation of these results have also provided a means in which to prepare both 7-chloro and 7-iodo substituted 1,6-diazaphenalenes.

If 1,6-diazaphenalene 1a was reacted with bromine in the presence of sodium acetate (1:40 ratio of 1a to sodium acetate), under conditions analogous to the bromination of imidazole,[6] the tribromo derivatives 3,4,7-tribromo-1,6-diazaphenalene 2 and 2,3,4-tribromo-1,6-diazaphenalene 3 were formed along with significant amounts of the 2,3-dibromo derivative 4, as illustrated in Scheme I. The yields (see Table I) under these conditions (one equivalent of bromine) were low due to the recovery of starting 1a and the formation of small quantities of four other halo isomers.[7a] The structures of 2, 3 and 4 were determined by ir, nmr and mass spectroscopy (see Table II for the pertinent NMR data).[7b] When the ratio of 1a to sodium acetate was altered to 1:24, the 2,3,4-tribromo and 2,3-dibromo derivatives 3 and 4, respectively, comprised much of the product mixture; however, in addition a small amount of 7-bromo-1,6-diazaphenalene was now isolated, as

well as starting 1a.

Since the excess sodium acetate in acetic acid served to neutralize any hydrogen bromide generated in the process, the conditions described above dealt essentially with the neutral species 1a. In order to study the reaction under more acidic conditions, the ratio of 1a to

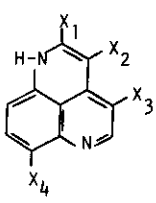
Scheme I



2, X_1=H, X_2=X_3=X_4=Br

3, X_1=X_2=X_3=Br, X_4=H

4, X_1=X_2=Br, X_3=X_4=H



4, X_1=X_2=Br, X_3=X_4=H

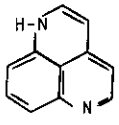
5, X_1=X_2=X_3=H, X_4=Br

6, X_1=X_3=X_4=H, X_2=Br

7, X_1=X_3=H, X_2=X_4=Br

1/NaOAc(1:40) HOAc, Br_2

1/NaOAc(1:1) HOAc, Br_2



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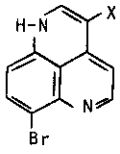
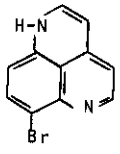
NBS, CF_3COOH

Br_2, CF_3COOH



5, X=H

7, X=Br(trace)



5

sodium acetate was then altered to 1:1. As illustrated in Scheme I, four bromodiazaphenalenes 4, 5, 6, and 7 were isolated from this experiment, furthermore, 7-bromo-1,6-diazaphenalene 5 now became the major product at the expense of the 2,3- and 2,3,4-halo isomers previously formed. The trend appeared clear at this point; the more acidic reaction medium definitely favored formation of the 7-bromodiazaphenalene in preference to the other isomers. The change in

orientation during electrophilic substitution of protonated versus neutral pyridines and quinolines has been reported.[8] While this is similar to results described herein, caution must be exercised at this juncture in direct extrapolation of this phenomenom to that of 1,6-diazaphenalene.

Earlier, on examination of the nmr spectrum of 1a[2] it had been found that this base, as expected, was protonated in trifluoroacetic acid, and it was felt this reagent would provide a medium in which to brominate species 1b. In complete agreement with this hypothesis, the bromination of 1,6-diazaphenalene in trifluoroacetic acid gave an 81% yield of 7-bromo-1,6-diazaphenalene 5. This follows the trend described above, and served to illustrate that halogenation

Table I

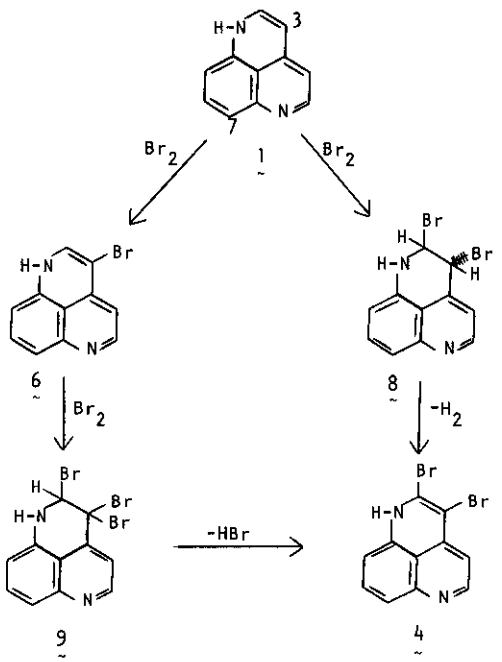
Substrate	Conditions[a]	Product (yield %)[e]
1	Br_2, NaOAc(1:40)[b], HOAc	2 (10.5), 3 (6.2), 4 (5.1), others (trace)
1	Br_2, NaOAc(1:24), HOAc	3 (8.0), 4 (6.3), 5 (4.16), others (trace)
1	Br_2, NaOAc (1:1), HOAc	5 (9.5), 4(6.1), 6 (4.0), 7 (3.1)
1	Br_2, NaOAc(1:24), HOAc[c]	4 (11.8), 3 (2.1), others (trace)
1	Br_2(1/2eq.), NaOAc(1:24), HOAc	6 (11.4), 5 (7.7), 7 (trace) 4 (trace)
1	Br_2, CF_3COOH, CH_2Cl_2[d]	5 (81.0), others (trace)
1	NBS, CF_3COOH, CH_2Cl_2	5 (64.8), 7 (trace)
1	NCS, CF_3COOH, CH_2Cl_2	10 (33.5), 11 (27), 12 (11.5), 13 (7.9)
1	NIS, CF_3COOH, CH_2Cl_2	14 (45.6), 15 (trace)

[a] Reactions were carried out at room temperature unless otherwise indicated.
[b] The ratio set in parenthesis is the ratio of 1 to sodium acetate employed in the experiment.
[c] -10°C
[d] -60°C, a similar result was observed at room temperature.
[e] The yields in the reactions run with bromine are low because of difficulties encountered during separation of these materials; however, the relative amounts of the isomers present are quite representative, as indicated.

of 1b should occur preferably at the 7-position of the molecule, in contrast to the substitution pattern observed on the neutral species.

While attack of an electrophile on either position-3 or -7 of 1a is not exceptional and has been discussed,[7b] the formation of 2,3-disubstituted derivatives deserves some comment. Two obvious pathways for formation of 4 or the related derivative 3 are depicted in Scheme II. Indirect evidence has been presented which[7b] indicates that a path 1→8→4 is possible; however, the sequence 1→6→9 would also appear quite reasonable, in a mechanistic sense, for the bromine at position-3 of 6 would be expected to polarize this bond to permit eventual attack at position-2. Examination of the data in Table I indicates that use of one half equivalent of bromine in the reaction (1 to sodium acetate ratio 1:24) provided very little 2,3-dibromodiazaphenalene 4, moreover, the major product was 3-bromo-1,6-diazaphenalene 6, substantial quantities of which

Scheme II



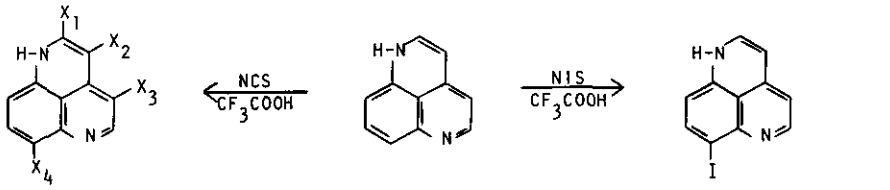
were not isolated when one equivalent of bromine was used. This would seem to indicate that 6 may form first, and then goes on to form 9 followed by loss of hydrogen bromide to provide 4. This evidence is certainly indirect, furthermore, since bromine is an oxidizing agent, the lesser concentration of this reagent may have impeded conversion of 8 to 4 also resulting in isolation of only trace amounts of 4 from this experiment. Although there is no direct data to implicate either of these mechanisms at present, both appear feasible in terms of the experimental data at hand.

More importantly, in the context of the present discussion, calculations (electron densities and localization energies) recently carried out on 1a and 1b[9] indicate that positions-2 and -3 of 1a are highly polarized which would allow eventual attack of halogen (anion) at position-2; moreover, the three position of 1a in the neutral species appears more susceptible to electrophilic attack, than other sites in the molecule, as implied in Scheme II (1→6→9). Position-7, however, appears to be the site of choice for attack of halogen on the protonated molecule 1b[9] in complete agreement with the data illustrated in Table 1.

In keeping with the desire to convert 1 into potential antimalarial agents[1,2,10] a number of methods have been examined to incorporate functionality into position-7 of 1. Since halogen has been displaced by amines in the quinoline series[11] and also can undergo lithium-halogen exchange to generate a carbanionic center, this group appeared useful as a precursor to other 7-substituted diazaphenalenes.

Although the reaction of 1 with chlorine or iodine would be expected to be troublesome, experimentally, recent results in the bromine area provided a solution to this problem. Since it was known (see above) that 1b preferentially reacted at position-7 with bromine, a 1:1 mixture of 1,6-diazaphenalene 1 and N-bromosuccinimide[12] was stirred in trifluoroacetic acid. This procedure cleanly furnished a 64.8% yield of the 7-bromo compound 5. Simple extrapolation of this technique to N-chlorosuccinimide did provide 7-chloro-1,6-diazaphenalene 10, as illustrated in Scheme III, however use of this more reactive chlorine reagent[13] also gave 3-chloro-1,6-diazaphenalene 11, 2,3-dichloro-1,6-diazaphenalene 12 and 3,7-dichloro-1,6-diazaphenalene 13. Since both chlorine and the chloronium ion are more reactive toward electrophilic substitution[13] than the corresponding bromine analogs, it is not surprising that substantial amounts of 11, 12 and 13 were formed under these conditions. More importantly, however, use of N-iodosuccinimide under the same conditions, furnished a 45.6% yield of 7-iodo-1,6-diazaphenalene 14 contaminated with only trace amounts of other products such as 15; no attempts to maximize the yields in this series have been made to date. The lower yield of 7-iodo-1,6-diazaphenalene 14 in comparison to the yield of the 7-bromo derivative 5, coupled with the higher selectivity of both bromine and iodine for position-7 of 1b, is in accord with the reactivity of these reagents toward aromatic nuclei.[13]

Scheme III



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

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

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

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

1

14

15, 3-iodo isomer

The incorporation of halogen at position-7 of the protonated 1,6-diazaphenalene 1b is significant for not only should it provide entry into 7-substituted-1,6-diazaphenalenes via a variety of methods, but the pattern established follows exactly what is predicted to occur on the basis of recent calculations.[9] In addition, although direct iodination of aromatic compounds presents rather special problems[14], the N-iodosuccinimide, trifluoroacetic acid technique employed here provides the iodo derivative 14 in rather simple fashion.

Acknowledgement. The author wishes to thank Professor Peter Kovacic and Mr. Robert Weber for helpful suggestions. A special thanks to Dr. Herman Ziffer (NIH) for the 220 MHz NMR spectra, and Mr. Frank Laib for the mass spectra are in order. Many stimulating discussions with Dr.

Ulrich Weiss and Dr. Kamlakar Avasthi concerning this work are also gratefully acknowledged. Funding was provided by a grant from the Department of the Army's Program on Antiparasitic Drugs, Walter Reed Army Institute of Research.

Table II

NMR Data for Substituted Diazaphenalenes

2 (DMSO-d_6, 60 mHz) δ 6.20 (d, 1H, J=8Hz), 7.42 (d, 1H, J=8Hz), 7.88 (s, 1H) and 8.26 (s, 1H).

3 (DMSO-d_6, 60 mHz) δ 6.22 (d, 1H, J=8Hz), 7.40 (t, 1H, J=8Hz), 7.58 (d, 1H, J=8Hz) and 8.02 (s, 1H).

4 (TFAA, 220 mHz) δ 7.08 (d, 1H, J=7Hz), 7.42 (d, 1H, J=9Hz), 8.18 (t, 1H, J=7Hz), 8.26 (d, 1H, J=9Hz), and 8.51 (d, 1H, J=7Hz).

5 (DMSO-d_6, 60 mHz), δ 6.15 (d, 1H, J=7Hz), 6.35 (d, 1H, J=5Hz), 6.60 (d, 1H, J=8Hz), 7.40 (d, 1H, J=7Hz), 7.64 (d, 1H, J=8Hz) and 8.20 (d, 1H, J=5Hz).

6 (DMSO-d_6, 60 mHz), δ 5.83 (d, 1H, J=7Hz), 6.72 (d, 1H, J=8Hz), 7.00 (d, 1H, J=8Hz), 7.36 (d, 1H, J=7Hz), 7.41 (t, 1H, J=7Hz), 8.15 (s, 1H).

7 (DMSO-d_6, 220 mHz) δ 6.42 (d, 1H, J=7Hz), 7.21 (d, 1H, J=8Hz), 7.55 (d, 1H, J=8Hz), 8.04 (d, 1H, J=7Hz) and 8.61 (s, 1H).

10 (DMSO-d_6, 60 mHz) δ 5.98 (d, 1H, J=6.5 Hz), 6.21 (d, 1H, J=5Hz), 6.60 (d, 1H, J=7.5 Hz), 6.87 (d, 1H, J=6.5 Hz), 7.41 (d, 1H, J=7.5 Hz) and 7.82 (d, 1H, J=5Hz).

11 (DMSO-d_6, 60 mHz) δ 5.79 (d, 1H, J=7Hz), 6.60 (d, 1H, J=8Hz), 6.95 (d, 1H, J=8Hz), 7.29 (d, 1H, J=7Hz), 7.34 (t, 1H, J=8Hz) and 8.03 (s, 1H).

12 (DMSO-d_6, 60 mHz) δ 6.22 (d, 1H, J=7.0Hz), 6.98 (d, 1H, J=9.0Hz), 7.54 (t, 1H, J=9Hz), 7.65 (d, 1H, J=7.0Hz) and 8.14 (d, 1H, J=9Hz); spectrum complicated by proton transfer.

13 (DMSO-d_6, 60 mHz) δ 5.94 (d, 1H, J=7Hz), 6.70 (d, 1H, J=8Hz), 7.02 (d, 1H, J=8Hz), 7.48 (d, 1H, J=7Hz) and 8.18 (s, 1H).

14 (DMSO-d_6, 60 mHz) δ 5.98 (d, 1H, J=7Hz), 6.32 (d, 1H, J=5Hz), 6.43 (d, 1H, J=8Hz), 7.22 (d, 1H, J=7Hz), 7.81 (d, 1H, J=8Hz) and 8.06 (d, 1H, J=5Hz)

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10. This is contribution number (1630) to the Army's Program on Antiparasitic Drugs, Walter Reed Army Institute of Research (contract #DAMD17-78-8003).

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Received, 22nd August, 1981