Chemistry of 1,6-Diazaphenalene. Reaction with Alkylating and Acylating Agents

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A study of the reactivity of 1,6-diazaphenalene (**1**) toward alkylating and acylating agents has been carried out in order to investigate the chemistry of this new heterocycle. Attempts to alkylate **1** were successfully completed by stirring the lithium stabilized anion of **1** with either methyl iodide or benzyl bromide to provide *N*-alkyldiazaphenalenes **4** and **5**, respectively, whereas, experiments performed to alkylate **1** under conditions employed for alkylation of imidazole were unsuccessful. Studies directed toward acylation of **1** did not lead, in general, to isolable acyldiazaphenalenes; however, in one specific case successful acylation of 2-chloro-9-methoxy-1,6-diazaphenalene (**10**) did provide a characterisable amide (**14**). Where possible the chemistry of 1,6-diazaphenalene has been compared to that reported for imidazole.

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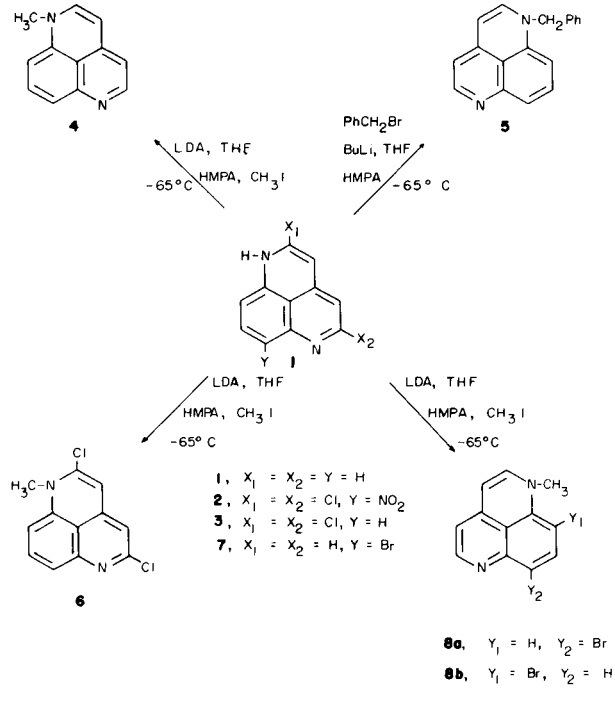
Recently we reported the synthesis (1,2) of the new heterocycle 1,6-diazaphenalene (**1**). Because the rapid proton transfer between forms **1a** and **1b** generate two structures which are degenerate in energy and therefore identical, this heterocycle in many respects resembles imidazole (3-5). This phenomenon is particularly evident on comparison of both the nmr spectrum and *p*Ka value of **1** to those reported for imidazole (6,7). Calculations of the electron densities of the atoms in **1** have recently been completed, and indicate the protonated form of **1** would be expected to react with electrophiles with a different orientation than the free base **1** with the same electrophile (5a). Treatment of **1** with bromine under both neutral and acidic conditions has provided halogenated diazephenalenes (5b) in agreement with the predictions based on theoretical grounds. In order to further define the chemistry of this interesting heterocycle, **1**, the reaction of 1,6-diazaphenalene and derivatives with alkylating and acylating agents has been examined; this paper describes our findings in this area.

1a **1b**

Alkylation of imidazoles at nitrogen has been achieved under a variety of conditions (8). For example, reaction of imidazole with one equivalent of an alkyl halide or sulfate in the presence of base effects *N*-alkylation in a straightforward manner (8); however, *N*-alkylation of the 1,6-diazaphenalene (**1**) nucleus has proven to be a more difficult task. Attempts to *N*-methylate **1** with dimethylsulfate returned only starting material, moreover, 7-nitro-2,5-dichloro-1,6-diazaphenalene (**2**), when heated with either benzyl chloride or bromide in xylene (9), did not lead to any detectable reaction. Similarly, heating 1,6-diazaphenalene (**1**) with a host of other alkylating agents under conditions analogous to those employed for the alkylation of imidazole (10,11,12,13) were uniformly unsuccessful. Furthermore, in all of the attempts discussed above, nearly quantitative recovery of starting diazaphenalene was observed.

The failure of 1,6-diazaphenalene (**1**) to undergo *N*-alkylation under mild conditions was somewhat surprising for the p*K*a of **1** was quite similar to that of imidazole (4,7). In the context of these observations, attention was now turned toward alkylation of diazaphenalene under more vigorous conditions. When **1** was treated with lithium di-

Scheme I



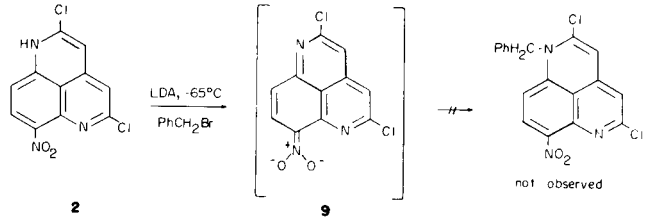
isopropylamide (tetrahydrofuran/hexamethylphosphoramide) at -65°, followed by addition of methyl iodide, good yields of *N*-methyl-1,6-diazaphenalene (**4**) were realized, as illustrated in Scheme I. The hexamethylphosphoramide cosolvent was necessary to solubilize the lithium stabilized anion of **1**. The proton nmr spectrum of **4** was quite complex which reflected the fact that the pseudoplane (**1a** ⇌ **1b**) of symmetry originally present in **1** was no longer present in the *N*-alkylated derivative. The presence of a three-proton singlet at δ 3.05 in the spectrum of **4** indicated that *N*-alkylation had taken place instead of *C*-alkylation, moreover, there was no evidence for an absorption due to N-H stretching present in the infrared spectrum of **4**. As expected, *N*-methyl-1,6-diazaphenalene (**4**) melted at a lower temperature (104°) than the parent (**1**, mp 228°), moreover, **4** was readily soluble in chloroform while 1,6-diazaphenalene (**1**) was much less soluble in this solvent; these properties are indicative of the absence of hydrogen bonding in **4**. The nmr and ir spectra of **4**, coupled with the physical properties support the assigned structure. In similar fashion, benzylation (lithium diisopropylamide, benzyl bromide) of **1** was carried out, albeit in lower yield; however, stirring **1** with butyl lithium at -65° followed by addition of benzyl bromide did provide the desired *N*-benzyl-1,6-diazaphenalene (**5**) in greater than 80% yield.

In a related set of experiments 2,5-dichloro-1,6-diazaphenalene (**3**) was stirred with *n*-butyllithium (hexamethylphosphoramide/tetrahydrofuran, -10°), followed by addition of methyl iodide, to furnish small quantities of *N*-methyl-2,5-dichloro-1,6-diazaphenalene (**6**), in addition to the other products present in too small amount to characterize. A three-proton singlet (δ 4.05) was observed in the proton nmr spectrum of **6** while the infrared spectrum of this material was devoid of a band due to N-H absorption. The physical properties (mp, solubility) of this base were also in agreement with a structure such as **6**. Since metal-halogen exchange or aryne formation might result on treatment of **3** with *n*-butyllithium, the dichlorodiazaphenalene **3** was subsequently treated with lithium diisopropylamide at -65°, followed by addition of the alkyl halide. This procedure effectively suppressed the formation of byproducts to provide **6** in better than 85% yield. While lithium diisopropylamide is obviously the base of choice for these alkylations, it is felt the lower temperature (-65°) is equally as important for prevention of aryne formation.

Since *N*-alkylation of an unsymmetrical 1,6-diazaphenalene could give rise to two different *N*-alkyl diazaphenalenes (Scheme I), it was of interest to study the methylation of 7-bromo-1,6-diazaphenalene (**7**). The lithium salt of **7** was reacted with methyl iodide at -65°, analogous to the conditions employed for methylation of **1**, to give *N*-methyl-7-bromo-1,6-diazaphenalene (**8**) in greater than 70% yield. No other product of alkylation was either observed or isolated from this reaction. The proton nmr spectrum (three-proton singlet at δ 4.95), ir spectrum (no N-H absorption), and physical properties (mp, solubility) of **8** all confirmed that alkylation of **7** had occurred on nitrogen. It is not clear at the moment whether the structure of the *N*-methyl-7-bromo-1,6-diazaphenalene is correctly represented by **8a** or **8b**; however, only one *N*-alkyl derivative was produced in this sequence.

In contrast to the preparation of *N*-alkyldiazaphenalenes substituted with halogen, the alkylation of a 1,6-diazaphenalene which carried a nitro substituent either does not occur, or proceeds only sluggishly. For example, several attempts to form the *N*-benzyl derivative of 7-nitro-2,5-dichloro-1,6-diazaphenalene (**2**) in the presence of potassium carbonate or lithium diisopropylamide were not successful; quantitative recovery of **2** was realized in both cases. It is felt the negative charge on nitrogen is effectively delocalized onto the oxygen atoms of the nitro group of **9** (Scheme II) which retards the reactivity of nitrogen

Scheme II



2 **9**

toward electrophiles. In addition, removal of a proton from **2** generates the aromatic naphthyridine system of **9**, a factor which also favors delocalization of the electrons of **9** in the fashion illustrated in Scheme II. The *N*-methylation of 7-nitro-1,6-diazaphenalene has been successfully carried out with methyl iodide in the presence of lithium diisopropylamide (hexamethylphosphoramide/tetrahydrofuran), but the yield of alkylated product was less than 8% (14). This and the previous examples support our contention that the 7-nitro group is primarily responsible for the lesser reactivity of the anion generated at position-1 of diazaphenalenes presumably *via* structures such as **9**.

The esteratic properties of the imidazole nucleus in compounds of biological importance is well known (15). This catalysis has been shown to occur in the hydrolysis of many esters including phenyl acetates, moreover, during extension of these results to homopolymers containing imidazole or benzimidazole, Overberger (16) has demonstrated that bifunctional esterolytic catalysis was more rapid in the case of the polymers than with the corresponding monomeric analogues, imidazole or benzimidazole. In addition, the use of reactive heterocyclic amides (azolides), especially acylimidazoles, to activate compounds for

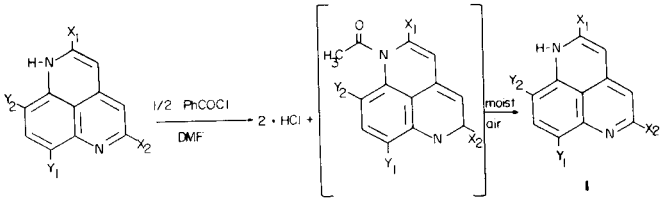
chemical reactions continues to be of importance in a synthetic sense (17,18).

Since the solubility properties (19) of **1** are somewhat different than those of imidazole, and because of the continuing interest in the catalysis of organic reactions *via* imidazoles (see above), a study of the reaction of 1,6-diazaphenalenes (**1, 2, 3** and **10**) with acylating agents was begun. Imidazoles are known to undergo *N*-acylation on heating in acetic anhydride (20); however, none of the *N*-acyl derivatives **11** or **13** were isolated when either **1** or **3**, respectively, were treated in this manner. It was felt that the *N*-acyl diazaphenalenes had formed but that the amides were simply too unstable to isolate. This lack of stability would not be surprising for *N*-acylimidazoles are known to undergo rapid hydrolysis when exposed to nucleophiles such as water (21). In this vein, 2-chloro-9-methoxy-1,6-diazaphenalene (**10**) was treated with hot acetic anhydride which did indeed provide the *N*-acyl derivative **14**. The ir spectrum of **14** contained a carbonyl band at 1700 cm^{-1} indicative of amide formation, moreover, a three proton singlet due to an acetyl function was found at δ 2.54 in the proton nmr spectrum of this derivative. In addition, the parent and base peak in the chemical ionization mass spectrum of **14** was located at 275 mass units in complete agreement with the assigned structure. It is felt, the 2-chloro and 9-methoxy groups in **14** flank the *N*-acyl function, and inhibit the rapid hydrolysis of this material which permitted its isolation. Since only one amide was isolated from this process, it is felt the amide which would result from acylation of position-6 would decompose to starting **10** on exposure to nucleophiles. The *N*-acyldiazaphenalene **14** although isolable, was quite labile for it reverted to starting **10** when subjected to column chromatography. This is interesting for in this respect the *N*-acyldiazaphenalene **14** has behaved in similar manner to azolides, especially acylimidazoles (21).

In 1962 Boyer reported that imidazole, when heated with isopropenyl acetate, was converted to *N*-acetylimidazole in greater than 90% yield (22); however, treatment of **1** under somewhat similar conditions again returned **1**, after workup. In contrast to the behavior of **1**, though, the 2-chloro-9-methoxy analog **10** was transformed to the *N*-acyl derivative **14** when heated with isopropenyl acetate. The formation of the *N*-acyldiazaphenalene **14** from **10** by this second method, in contrast to the failure to isolate a similar species from **1**, again indicates that simple acyl diazaphenalenes such as **11** may form in this process, but are too labile to isolate.

Indirect evidence for the existence of acyldiazaphenalenes was also observed when two equivalents of **3** were stirred with one equivalent of benzoyl chloride in scrupulously dried dimethylformamide (23). Although the solution was clear initially, after several hours a precipitate deposited on the walls of the reaction vessel. The solid (nearly one equivalent) was filtered from the solution, and was found to be the hydrochloride salt of **3**, which had also been prepared by an independent route. The filtrate, however, after careful removal of solvent, returned only **3** and benzoic acid. It appears the desired *N*-benzoylation has taken place, but the reactive benzamide on exposure to moist air reverts to starting material (Scheme III). Similar results were obtained with **1** and **2**, and were also observed when acetyl and tosyl chlorides were substituted for benzoyl chloride.

Scheme III



1, $X_1 = X_2 = Y_1 = Y_2 = H$
2, $X_1 = X_2 = Cl$, $Y_1 = NO_2$, $Y_2 = H$
3, $X_1 = X_2 = Cl$, $Y_1 = Y_2 = H$
10, $X_1 = Cl$, $X_2 = Y_1 = H$, $Y_2 = OCH_3$

11, $X_1 = X_2 = Y_1 = Y_2 = H$, not observed
12, $X_1 = X_2 = Cl$, $Y_1 = NO_2$, $Y_2 = H$, not observed
13, $X_1 = X_2 = Cl$, $Y_1 = Y_2 = H$, not observed
14, $X_1 = Cl$, $X_2 = Y_1 = H$, $Y_2 = OCH_3$

The formation of *N*-acyldiazaphenalene **14** and its inherent lability, coupled with the isolation of **3** and benzoic acid from the acyl halide experiments serve to indicate that *N*-acyldiazaphenalenes are forming, but are generally too unstable to isolate. The behavior of diazaphenalene **10**, toward acylation shows a striking similarity to similar reactions reported on imidazole for both heterocycles produce rather labile *N*-acyl derivatives. It is probable that diazaphenalenes such as **1** and **3** are also undergoing a similar transformation. In view of the interest in "imidazole-like" heterocycles for the catalysis of organic reactions (15-17), additional studies are underway in our laboratory, and will be reported in due course.

EXPERIMENTAL

Microanalysis were performed on an F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Some analysis were performed at the National Institutes of Health, Bethesda, Maryland. Melting points were taken on a Thomas-Hoover melting point apparatus and are not corrected. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer and a JEOL FX-90. Infrared spectra were taken on a Beckman Acculab-1 instrument, and mass spectra were recorded on an HP 5855 GC/MS.

Analytical tlc plates used were E. Merck Brinkman uv-active silica gel or alumina on plastic. Benzyl bromide, methyl iodide, diisopropyl amine, *n*-butyllithium and hexamethylphosphoramide were purchased from Aldrich Chemical. The preparations of **1, 2, 3, 7,** and **10** have been described elsewhere (see references 1, 3, and 4 for details).

1-Methyl-1,6-diazaphenalene (**4**).

To a stirred solution of lithium diisopropylamide (6.5 mmoles, -65°) in tetrahydrofuran [prepared by the addition of 0.66 g (6.5 mmoles) of diisopropylamine to one equivalent of *n*-butyllithium] was added a solution of 1,6-diazaphenalene (**1**, 1.0 g, 5.94 mmoles in 60 ml of tetrahydrofuran

and 6 ml of hexamethylphosphoramide) from a dropping funnel at a rapid rate. The deep orange-red solution was stirred for another 10 minutes at -65° followed by the addition of methyl iodide (0.92 g, 6.5 mmoles) *via* a syringe. The reaction mixture was stirred at the same temperature for 10 minutes and then allowed to come to room temperature without removing the cooling-bath. A few drops of water were added, and the solvent removed under reduced pressure to furnish a dark brown viscous oil. Addition of water (100 ml) gave a yellow precipitate which was filtered from the solution, and was washed several times with water to remove residual hexamethylphosphoramide. This material was dried to give a yellow solid, mp 94-96° and was further purified by elution through a short column of alumina (eluent, tetrahydrofuran). The product **4** was a nicely crystalline yellow solid, mp 104-105°; ir (potassium bromide): 1630 (s), 1575 (s), 1342 (s), 825 (m), 740 (s); nmr (deuteriochloroform): δ 3.04 (3H, s), 5.64 (1H, d, J = 7 Hz), 6.11 (1H, dd, $J_1 = J_2$ = 7 Hz), 6.27 (1H, d, J = 4.5 Hz), 6.48 (1H, d, J = 7 Hz), 7.11-7.47 (2H, m), 8.23 (1H, d, J = 4.5 Hz); ms: (C.I., NH_3) 183 ($M^+ + 1$, 100%).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.11; H, 5.53; N, 15.37. Found: C, 79.00; H, 5.50; N, 15.30.

1-Benzyl-1,6-diazaphenalene (**5**).

A.

To a stirred solution of lithium diisopropylamide [4.59 mmoles, 50% excess, -10°, (ice-salt bath) in tetrahydrofuran prepared by the addition of one equivalent of diisopropylamine to one equivalent of *n*-butyllithium] was added 1,6-diazaphenalene (**1**, 0.514 g, 3.06 mmoles) dissolved in 60 ml of tetrahydrofuran and 5 ml of hexamethylphosphoramide. Soon afterward the color of the reaction mixture changed from green-yellow to orange. By the end of the addition (2-3 minutes), the reaction mixture was brownish orange in color, and was allowed to stir at this temperature for another 10 minutes. Benzyl bromide (0.57 g, 30% excess, 3.33 mmoles) was then added to the reaction mixture *via* a syringe. During the addition, the color of the reaction mixture faded and was gradually replaced by a light green color. The reaction mixture was then stirred for 30 minutes at -10° and then allowed to come to room temperature and stirred for another 30 minutes. A few drops of water were then added to destroy any excess base. The solvent was then removed under reduced pressure to give a reddish-brown oil. To this residue, water (100 ml) was added, and the resulting solid was filtered. This green-yellow solid was washed several times with water to remove hexamethylphosphoramide. This crude product was purified by column chromatography (alumina, tetrahydrofuran) to provide a greenish-yellow crystalline solid **5** (0.46 g, 58% yield), mp 138-139°; ir (potassium bromide): 3025 (w), 1625 (s), 1590 (s), 1570 (s), 1420 (m), 1340 (s), 820 (m), 740 (m); nmr (deuteriochloroform): δ 4.47 (2H, s), 5.60 (1H, d, J = 7 Hz), 6.01 (1H, dd, J_1 = 7 Hz, J_2 = 7 Hz), 6.24 (1H, d, J = 5 Hz), 6.51 (1H, d, J = 7 Hz), 6.94-7.34 (7H, m) and 8.21 (1H, d, J = 5 Hz); ms: (C.I., NH_3) 259 ($M^+ + 1$, 100%).

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.85; H, 5.35; N, 11.06.

B.

In a similar experiment use of *n*-butyllithium (20% excess) directly in place of lithium diisopropylamide provided an 82% yield of the 1-benzyl-1,6-diazaphenalene (**5**). This reaction was carried out at -65°.

1-Methyl-2,5-dichloro-1,6-diazaphenalene (**6**).

This compound was prepared in 86% yield under analogous conditions to that described for 1-methyl-1,6-diazaphenalene (**4**), mp 167-168° (yellow solid, acetone); ir (potassium bromide): 3100 (w), 1624 (s), 1585 (s), 1500 (s), 1382 (s), 820 (m), 750 (m); nmr (deuteriochloroform): δ 3.27 (3H, s), 5.72 (1H, s), 6.10 (1H, s), 6.25 (1H, d, J = 7 Hz), 7.0-7.42 (2H, m); nmr (trifluoroacetic acid): δ 4.05 (3H, s), 6.58 (1H, s), 6.75 (1H, s), 7.22-7.60 (2H, overlapping doublets, J = 8 Hz), 7.95 (1H, dd, $J_1 = J_2$ = 8 Hz); ms: (C.I., NH_3) 250 (100%), 252 ($M^+ + 1$, 67%).

Anal. Calcd. for $C_{12}H_8Cl_2N_2$: C, 57.39; H, 3.21; N, 11.16; Cl, 28.24. Found: C, 57.17; H, 3.03; N, 11.16; Cl, 27.99.

N-Methyl-7-bromo-1,6-diazaphenalene (**8**).

The title compound **8** was prepared in 74% yield in a similar fashion (lithium diisopropylamide, -65°) to that described previously for **4**, mp 238-240° (greenish-yellow solid); ir (potassium bromide): 3025 (broad), 1623 (s), 1582 (s), 1493 (m), 1213 (m), 822 (w), 769 (w); nmr (trifluoroacetic acid): δ 4.99 (3H, s), 6.63-6.70 (2H, unresolved overlapping doublets), 7.21 (1H, d, J = 9 Hz), 7.70-8.10 (2H, m), 8.22 (1H, d, J = 9 Hz); ms: (C.I., CH_4) 261 (M^+, 100%, $M^+ + 2$, 92%).

Anal. Calcd. for $C_{12}H_9BrN_2$: C, 55.19; H, 3.47; N, 10.73. Found: C, 55.00; H, 3.40; N, 10.75.

Attempted Benzylation (9) of 7-Nitro-2,5-dichloro-1,6-diazaphenalene (**2**).

A mixture of **2** and excess benzyl chloride (or bromide) was heated in xylene for 94 hours both in the presence and absence of potassium carbonate. At no time was any of the alkylated product observed on tlc and starting **2** was recovered in greater than 95% yield.

Preparation of 1-Acetyl-2-chloro-9-methoxy-1,6-diazaphenalene (**14**).

A sample of 2-chloro-9-methoxy-1,6-diazaphenalene (**10**, 0.52 g, 2.1 mmoles) prepared by the method of Weber (24) was heated for 3 hours in refluxing acetic anhydride (5 ml). The solution was then cooled and poured into cold water after which the *p*H was brought to neutral on addition of cold aqueous ammonium hydroxide (14%). A solid precipitated from the solution, and was collected by filtration to give the title compound **14** (0.47 g, 82% yield), mp 164-166°; ir (potassium bromide): 1700, 1640, 1290 and 1230 cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 2.54 (3H, s), 3.93 (3H, s), 6.78 (1H, d, J = 8 Hz), 6.92 (1H, s), 7.23 (1H, d, J = 9 Hz), 7.61 (1H, d, J = 8 Hz) and 8.48 (1H, d, J = 9 Hz); ms: (C.I., CH_4) 275 (P + 1, 100%).

This material was stable in a dessicator for several months as a solid, however, on chromatography it decomposed to provide **10**.

Reaction of **10** with Isopropenyl Acetate to Provide **14**.

A suspension of **10** (170 mg, 0.73 mmole) was heated in isopropenyl acetate (10 ml) for 24 hours (22). The reaction mixture was cooled and filtered to remove undissolved solids (70 mg). The filtrate was concentrated under reduced pressure to provide a solid (88 mg) which was identical to 1-acetyl-2-chloro-9-methoxy-1,6-diazaphenalene (**14**), mp 164-166°; ir (potassium bromide): 1700 cm^{-1} (C=O); ms: (C.I., CH_4) 275 (P + 1, 23%), 233 (100%); tlc (R_f value identical to the R_f of authentic **14**). Thin layer chromatography also indicated the presence of a small amount of starting material **10** in this solid, however, it is believed this phenomenon was due to the degradation of **14** on the silica gel plate.

When the same sequence was carried out with 1,6-diazaphenalene **1** in place of **10**, three new compounds were observed on tlc; however, at no time were we able to isolate the acetamide derivative **11**. On several occasions it appeared (nmr and ir spectroscopy) that a mixture of **1** and acetic acid had been produced, for treatment of the solid with sodium bicarbonate solution or water did regenerate **1**.

Acknowledgement.

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(14) This compound had mp 276-280°; ir (potassium bromide): 3086 (w), 3040 (w), 1630 (s), 1582 (s), 1480 (m), 1280 (s), 1235 (s), 1141 (s), 835 (s) and 736 cm^{-1}; nmr (deuteriotrifluoroacetic acid): δ 4.13 (3H, s), 7.20 (1H, d, J = 5 Hz), 7.26 (1H, d, J = 5 Hz), 7.40 (1H, d, J = 9.5 Hz), 8.18 (1H, d, J = 7 Hz), 8.28 (1H, d, J = 7 Hz), 8.95 (1H, d, J = 9.5 Hz); ms: (C.I. 228) ($M^+ + 1$, 100%): K. Avasthi, S.-J. Lee and J. M. Cook, unpublished results.

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