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AROMATIC SUBSTITUTION BY N-ARYLHYDROXYLAMINES—I

FORMATION OF 8-AMINO-5,8'-IMINOBIS(6-METHOXYQUINOLINE) BY AN INTERMOLECULAR AROMATIC NITRENE INSERTION REACTION

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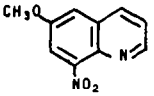
Abstract—Thermolysis of 8-hydroxylamino-6-methoxyquinoline at 65° in methanol gave 8-amino-5,8'-iminobis(6-methoxyquinoline), the same product being formed by thermolysis of 8-azido-6-methoxyquinoline as well as by deoxygenation of 6-methoxy-8-nitroquinoline with triethylphosphite in the presence of 8-amino-6-methoxyquinoline. Solvent effects were also consistent with the involvement of a nitrenoid species in these intermolecular aromatic substitutons. 8-Hydroxylaminoquinoline behaved in an analogous fashion but no iminobis compound was obtained from the corresponding 6-hydroxylaminoquinoline, indicating an internal interaction of the ring N atom with the 8-hydroxylamino function. Thermolysis of 8-hydroxylamino-6-methoxyquinoline in the presence of amines gave rise to *o*-diamines reconcilable with a nitrene intermediate.

The catalytic reduction of 6-methoxy-8-nitro quinoline (1) yielded, in addition to the expected amine 4, an unusual side product identified[1] as 8 - amino - 5,8' - iminobis[6 - methoxyquinoline] (3). No 5,8' - diquinolylamines had been reported previously and, in addition, no examples of this type of product formation in similar reductions were described, the by-products normally encountered being azo, azoxy, hydrazo, or hydroxylamino compounds.[2] A series of experiments established that 3 was formed by self-condensation of 8 - hydroxylamino - 6 - methoxyquinoline (2) under mildly basic conditions. Reactions of hydroxylamines[3-6] in the presence of base have been relatively neglected even though hydroxylamines are of considerable pharmacological interest,[7-11] and the formation of diarylamines under these conditions is unknown.



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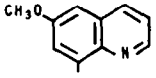

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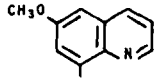

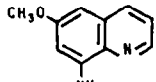

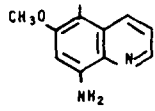

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4

The reaction of phenylhydroxylamine and benzenamine in the presence of dilute acid has been reported[12] to give some 4' - amino - 4 - phenylbenzenamine, the reaction being regarded as proceeding through a univalent, neutral, electron-deficient nitrogen species (now referred to as a nitrene) in analogy to the acid catalyzed reactions of phenyl azide. However, the current view is that the reaction involves a nitrenium ion which renders the aromatic nucleus vulnerable to nucleophilic attack.[13,14] The same mechanism accounts for the formation of diarylamines in the reduction of aromatic nitro compounds in hydrogen fluoride[15,16] and, aside from this type of reaction in which the hydroxylamine nitrogen does not participate in substitution, no examples of aromatic substitution by arylhydroxylamines have been reported. Direct amination of aromatic compounds with hydroxylamine-O-sulfonic acid[17] and alkylhydroxylamines/aluminum chloride[18] is well established, but a similar example employing an arylhydroxylamine is lacking. Several examples[19,20] of aromatic amination with these reagents where a free radical process is involved have been described. In the reaction of hydroxylamines with base it has been shown that in the presence of strong base arylhydroxylamines are converted into azo or azoxy compounds.[21a] It has recently been reported that phenyl nitrene was generated in the thermal α-deoxysilylation of N,O-*bis*(*trimethylsilyl*)-*phenylhydroxylamine*.[21b]

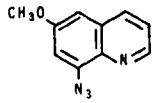
Consideration of these known reactions above, in terms of the hydroxylamine 2, led to the conclusion that an alternative reaction process was involved. On the basis of the evidence described below, the most plausible mechanism involves a nitrenoid species,[22] this being the first report of intermolecular aromatic substitution by an N-arylhydroxylamine involving a nitrene intermediate.

8 - Hydroxylamino - 6 - methoxyquinoline (2) was readily prepared by a carefully controlled catalytic reduction of the corresponding nitro compound 1, reduction with zinc dust in this case being unsuccessful. The identity of this hydroxylamine was clearly established by its spectral properties (Experimental), particularly by an ion, *m/e* 174 (100%) corresponding to $[M-16]^+$ and characteristic of hydroxylamines.[23] A series of experiments[24] established that the formation of 3 from 2 was not assisted by strong basic conditions, nor was it an acid-promoted reaction or a free-radical process. Particularly important was the result that 3 could be produced in

good yield from 2 in the absence of base or Pd-C in methanol at 65° with the latter actually resulting in a reduced yield of 3 due to some reduction to 4 by the hydrogen absorbed on the catalyst. The effect of the quinoline nucleus in these experiments is evidently comparable to that exerted by dialkylamines when comparable yields of 3 were obtained at 25°.

As a working hypothesis, the involvement of a nitrene in the formation of 3 was assumed. At the time of these initial experiments there was only one report of an intermolecular aromatic substitution by an aryl nitrene.[25] Nitrenopyrimidines and nitrenopyridines whose electrophilicity was enhanced by the ring–atom were found to undergo aromatic substitution with electron-rich substrates.

6 - Methoxy - 8 - nitrenoquinoline (6) was prepared from the corresponding azide 5, itself readily obtained from the amine 4. The azide was found to be reasonably stable but discolored on exposure to light. It was stable at 65–75° for prolonged periods in methanol or tetrachloromethane, and heating for 2 hr at 150° in 2,2'-dimethoxydiethyl ether produced no noticeable decomposition of 5. Thermolysis at 170° in Dowtherm, however, did produce a rapid reaction. This reaction gave rise to the iminobis compound 3 (8%) along with a 15% yield of the amino compound 4, indicating possible formation of 3 via a nitrene intermediate. As the concentration of 4 builds up, the nitrene reacts with it to form 3 and the reaction was found to be concentration dependent.



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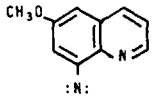


6

Shortly after these early experiments, a study of the intermolecular aromatic substitution by arylnitrenes was published.[26] Based on this work, the nitrene and substrate in the present study meet the requisites required for aromatic substitution to occur. The nitrene 6 should be electrophilic owing to the heterocyclic N atom and the OMe substituent, being *meta* to the nitreno function, exerts an electron-withdrawing inductive effect. Likewise, the substrate is electron-rich and this should favor the reaction.

The low yield of 3 in the azide reaction as compared to the hydroxylamine reaction can reasonably be expected when two factors are considered. Firstly, at 170° the lifetime of the singlet nitrene is unknown, but is most likely shorter than its lifetime would be at 25° or 65°. If the singlet nitrene were the attacking species, it would probably have less time to react at 170°. Secondly, in the decomposition of 2, the substrate is no doubt 2 itself. The hydroxylamino function induces an electron density in an aromatic ring as great as, if not greater than, that generated by a corresponding amino group.[27] Thus in the case of the reaction of 2 there is initially a large excess of a very reactive substrate. In the azide decomposition the substrate is 4, which is formed during the course of the thermolysis, and never reaches a high concentration. It was subsequently found that the addition of one equivalent of 4 to the thermolysis substantially increased the yield of 3 (Table 3).

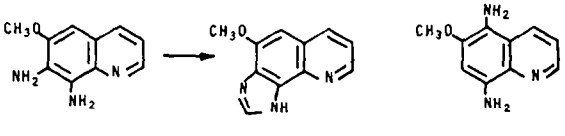
The deoxygenation of 6 - methoxy - 8 - nitroquinoline (1) at 160° in triethylphosphite in the presence of 4 resulted in a 16% yield of 3. It was also found that at 130° *ca.* 50% of 1 remained unreacted and the yield of 3 was only 5%, probably owing to too low a reaction temperature. This is the first example of intermolecular aromatic substitution by a nitrene generated by the deoxygenation of a nitro compound although similar reactions of nitroso compounds have recently been described.[26]

To obtain additional evidence to support the hypothesis of nitrene involvement in the formation of 3, other characteristics of nitrenoids from which their existence can be inferred were studied.

Reactions in amines. In dilute solution the formation of 3 from 2 and 5 was retarded,[24] and another interesting reaction was observed when these compounds were thermolyzed in amines under these conditions. When the azide 5 was heated in benzenemethanamine for 2·5 hr at 160°, TLC examination showed the clean reaction mixture to be composed of four products, in addition to a small amount of tar. The major product was 4 (R_f 0·46, orange); neither the azide 5 nor 3 were present and of the other three products, two were present in very small amounts (R_f 0·60, yellow; R_f 0·06, brown); the other component (R_f 0·22, green) was isolated by preparative TLC.

The compound with R_f 0·22, purified by crystallization from benzene-methanol, had a molecular ion *m/e* 189 which, with its elemental analysis, indicated a molecular formula of $C_{10}H_{11}N_3O$. Its NMR spectrum showed the usual ABC pattern for the nonbenzenoid quinoline ring as well as a singlet at δ 4·18 (4H, $2 \times NH_2$), a singlet at δ 3·91 (3H, OCH_3) and a singlet at δ 6·58 (1H). Compounds 7 and 8 are each consistent with these data. Preparation of the benzimidazole 9 confirmed the structure of the compound as being 7. The mass spectrum of 9 had M^+ *m/e* 199 with the most intense ion at *m/e* 172 (M–HCN), characteristic of benzimidazoles.

Compound 7 was clearly a decomposition product of some intermediate compound and a number of reactions was carried out under milder conditions in efforts to obtain the precursor. Heating the azide 5 at 140° for 2 hr resulted in no reaction; at 170° for 15 min a product distribution was obtained that was very similar to the reaction at 160° except that a new spot (R_f 0·44) appeared as a tail on the spot with the R_f value of 0·46 known to be 4 by TLC. Due to the large amount of 4, it was not possible to obtain a homogeneous sample of the material with R_f 0·44. However, a sample was obtained by preparative TLC which was a mixture of 4 and the desired



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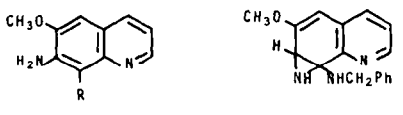


10a; R=NHCH$_2$Ph

b; R=NEt$_2$

c; R= 

11

compound. The mass spectrum of this mixture had an ion at *m/e* 279, corresponding to the parent ion expected for 7 - amino - 6 - methoxy - 8 - phenylmethylaminoquinoline (**10a**). It was found that on heating the reaction mixture longer, the spot corresponding to **10a** diminished. The loss of a phenylmethyl group is well known in catalytic reductions and photochemistry, and it is not surprising that the phenylmethyl group was lost in this thermolysis.

The formation of **7** may be rationalized in terms of a C–N bond cleavage of the aziridine intermediate **11** resulting in the diamine **10a**. This is in contrast to azepine formation which has often been observed in nitrene studies, but is consistent with the results recently reported by Iddon, Suschitzky and Taylor.[37] When **2** was thermolyzed under identical conditions, TLC examination revealed that the product distribution was very similar to that found in the azide reaction, except that a trace of **3** was present. Preparative TLC resulted in the isolation of pure **7**. That the hydroxylamine **2** and the azide **5** each give **7** is further evidence for the existence of a common intermediate in the reactions of these compounds.

When the hydroxylamine **2** was refluxed in N-ethylethanamine *o*-diamine formation again occurred giving 7 - amino - 8 - diethylamino - 6 - methoxyquinoline (**10b**) (10%). Again an aziridine intermediate can be invoked. When the azide **5** was heated in diethylamine no reaction occurred.

Thermolysis of **2** in morpholine gave mostly amine **4**, but the mass spectrum of the reaction mixture did contain an ion with *m/e* 259 corresponding to 7 - amino - 6 - methoxy - 8 - morpholinylquinoline (**10c**). Under the same conditions the azide **5** gave mostly **4** and no trace of **10c** was detected. As in the formation of **3** from **2**, the formation of **10a–c** can be readily rationalized in terms of nitrene generation.

Solvents effects. Heavy atom effects and singlet stabilization are phenomena which have often been utilized in nitrene studies.[38,39] A series of experiments was carried out in solvents containing heavy atoms to obtain additional evidence concerning the decomposition of **2**.

It is clear from Table 2 that the use of heavy atom solvents greatly decreases the formation of **3** from **2**, as well as the ratio of **3** to the "triplet product" **4**. Generally the reactions were carried out at 55–65°, and the reaction in tribromomethane at 130° is particularly interesting. The increased frequency of collisions at 130° would be expected to lead to increased deactivation of singlet nitrene to triplet nitrene, as was found to be the case. An identical reaction carried out in 1,4-dimethylbenzene shows that this is not merely a temperature effect but must involve the heavy atom. To demonstrate that the solvent effect was not due to solvent polarity, a reaction was carried out in heptane at 98°, giving a ratio of **3** to **4** greater than or equal to that obtained in the halogen containing solvents. (At 55°, **2** was too insoluble for reaction to occur). Since **3** is formed to a greater extent in both heptane and methanol than in the halo-compounds, the effect of the heavy atom solvents cannot be explained by solvent polarity. Table 3 lists the yields of **3** obtained in a variety of solvents. In general, solvents possessing a non-bonded pair of electrons gave better yields of **3** than those without. This may be rationalized by assuming that non-bonding electrons of the solvent coordinate with the empty p-orbital of the singlet nitrene, increasing the lifetime of the singlet, and thus increasing the probability that it encounter a suitable substrate before decaying to the triplet state.

Several similar reactions were carried out in which the azide **5** was thermolyzed to discover the effect of solvent on its reaction. The formation of **3** was favored by solvents in the order: DMSO > 2,2'-dihydroxydiethyl ether ≥ methoxybenzene ≥ N,N-dimethylbenzenamine > 1,4-dimethylbenzene. This order is generally the same as was found for **2**.

Nature of the reactive intermediate in the conversion of **2** *into* **3**. In the conversion of **2** into **3**, there are actually only two points which need be determined: when is the 8-amino group of **3** formed and when is the N–OH bond of the attacking species broken? The former is of minor significance since it is relatively unimportant whether the substrate is **2** or **4**. A comparison of the reactions of **2** and **5** in benzenemethanamine indicates that **2** is a better substrate than **4**. That is, in the decomposition of **2**, some **3** was formed, but in the decomposition of **5**, in which only **4** was available as substrate, no **3** was formed.

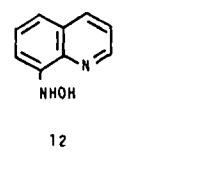
The most interesting question is in regard to the attacking species. Does the N–OH bond break prior to, simultaneous with, or after attack on substrate? If the nitrogen-oxygen bond breaks after or concerted with attack, then the reactive species must be either R–NHOH or R–N̈OH and these two possibilities clearly have little merit.

On the other hand, loss of –OH prior to attack would generate an electron-deficient species R–N̈H or R–N̈:. The nitrogen-oxygen bond is not a particularly strong one, and it has been shown[28] that in certain N,N-dialkylhydroxylamines, cleavage of the nitrogen-oxygen bond occurs by heating at 50° in methanol. In these reactions, which generated nitrenium ions, the OH group was converted into a variety of better leaving groups. Although good leaving groups enhance this type of bond breaking, they are not essential. For example, when benzhydroxamic acid is heated, nitrogen-oxygen bond cleavage occurs and benzenamine, carbon dioxide, and phenyl isocyanate are formed.[29]

In the present case there is no excellent leaving group to enhance N–O bond breaking, but there are other factors capable of enhancing this process. There most likely is considerable interaction between the nonbonded electrons of the heterocyclic N atom and the hydrogen attached to the exocyclic N in analogy to 8-hydroxyquinoline (oxine) in which there is strong internal H-bonding. Intramolecular H-bonding generates a partial positive charge on the ring N and a partial negative charge on the exocyclic N atom. The same effect could occur by the interaction of a weak base (another quinoline, for example) with the hydroxylamine. Each of the possible species generated would be an electrophile and would be expected to attack the benzenoid ring of a quinoline should such a reaction occur. Whether the active species is a nitrenium ion or a nitrene depends on the degree of removal of the hydrogen from the exocyclic N. It is generally agreed that when hydrogen is available in a reaction involving a nitrene, it is not possible to say *a priori* whether the active species is a nitrene or a nitrenium ion. It has been shown[30] that when aryl nitrenium ions are generated in methanol, one of the major products is an aryl methyl ether due to methanolysis. In the prexent case, if a nitrenium ion were involveld, a methanolysis product that would be a dimethoxybenzene derivative would be anticipated. In the thermolysis of **2** in methanol, no trace of *m/e* 204, corresponding to an 8 - amino - 6,x - dimethoxyquinoline, could be found in the mass spectrum of the product. This

is strong evidence against the involvement of a nitrenium ion.

In order to insure that the 6 - OMe group of 2 does not play some undetermined role in the generation of the active species in the reaction forming 3, 8 - hydroxylaminoquinoline (12) was prepared,[31] and its decomposition was studied. It is not as stable as 2 and cannot be stored for more than one day. However, after thermolysis of 12 in methanol, TLC examination revealed four major products and preparative TLC was used to isolate each of these products. These were identified as 8 - aminoquinoline (R_f 0·44), 8,8' - azobisquinoline (13) (2%, R_f 0·08, M^+ 284), and two additional products with R_f 0·36 (8%) and 0·16 (16%) to which the imino bis structures 14 and 15 were assigned. The mass spectrum of each showed an M^+ 286 and the NMR spectrum of each of these compounds contains signals corresponding to the six H atoms of the nonbenzenoid rings, indicating connection of the benzene rings by the NH function. The compound with the R_f value of 0·16 was identified as 15 by conversion into the benzimidazole 16. The mass spectrum of 16 had M^+ 296 with the most intense ion at m/e 269 (M–HCN). The hydroxylamino compound 12 thus forms the same type of product as does 2 on heating in methanol. It is interesting also that a good yield of the 7,8'-iminobis compound (15) is formed from 12. This type of product formation is sterically hindered in the reaction of 2.



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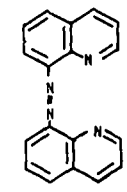

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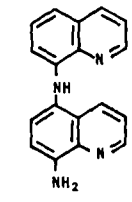

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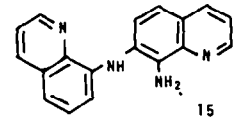

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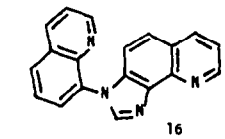

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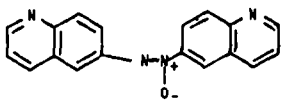
Having established that the methoxyl group is not essential for the formation of imino bis compounds, it was necessary to establish whether the nitrogen heteroatom was necessary for reaction to occur in the manner shown above. After considering the feasibility of using systems containing no ring N atom, a more suitable system to study was found to be 6-hydroxylaminoquinoline (17) in which there is no possibility for intramolecular hydrogen bonding between N_1 and the NHOH group and in which at the same time, the generated nitrene would be electrophilic due to the ring N atom.

This hydroxylamine was found to be a very unstable compound undergoing rapid conversion to 6,6'-azoxybisquinoline (18). In fact, it was not possible to obtain a pure sample of 17 for this reason, all preparations being contaminated to some extent with the azoxy compound 18. The compound thought to be impure 17 contained one impurity by TLC, the R_f value of which corresponded to that of 18. The mass spectrum of the compound had as its most intense ion m/e 144 (160–16) and also had m/e 160 (60%). The parent ion of the spectrum



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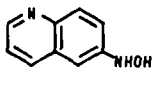

17

was m/e 300 (55%). Since the mass spectrum of pure 18 contains less than 1% m/e 160, it can be concluded that this ion is due to 17 (parent ion). The ion with m/e 144 also provides strong support for this conslusion.[23]

The thermolysis of 17 gave no detectable amount of imino bis compound. Even when 4 was added as substrate, no diquinolylamines could be found. It has thus been shown that moving the hydroxylamino function from the 8 to the 6 position of quinoline drastically alters its mode of reaction. Since 17 did not behave as did the 8-hydroxylaminoquinolines, it is indicated that the ring nitrogens do play a role in the formation of the active species in the thermolysis of 2 and 12-probably by an intramolecular process.

EXPERIMENTAL*

In this present study a unique, quantitative TLC procedure was developed for investigation of reaction products. This is described below.

Thin layer chromatography

I. Materials and apparatus. Silica Gel F-254 (EM Labs Inc.) and Silica Gel F 254/366 (Woelm) precoated 0·25 mm plates were used. Preliminary experiments were carried out using 5 × 10 cm plates, and for final determinations 20 × 20 cm plates were used, utilizing standard developing chambers (30 × 27 × 9 cm) lined with filter paper (Reeve Angel, Grade 250). Samples were applied with a "Pressure Lok" microsyringe (Pierce Chem. Co.) and spots were developed under a long-wave and short-wave UV light.

II. General procedure. The following is typical of the TLC procedure normally employed.

Determination of the amount of 3 formed in the thermolysis of 2 in methanol

(a) *Sample application.* The crude mixture (theoretically containing 1·3 mmoles of 2) was concentrated to dryness and

*All m.ps were determined in capillaries using a Thomas–Hoover Capillary Melting Point Apparatus, Model No. 6406H and are uncorrected. Catalytic reductions were carried out using Parr Series 3910 and 3920 Hydrogenation Apparatus. Spectral characteristics were determined on the following instrumentation: IR spectra, Perkin-Elmer 337 and 137 spectrophotometers; NMR spectra, Varian T-60 and HA-100 spectrometers, using TMS as an internal standard; mass spectra, JEOL JMS-01SC mass spectrometer, utilizing the direct inlet probe with a source temperature of *ca.* 150°. All evaporations were done under reduced pressure and microanalysis were performed by Instranal Laboratories, Inc., Rensselaer, New York.

Table 1. Thin layer chromatographic characteristics of various quinolines

Compound	Rf, Solvent System A[a]		Rf, Solvent System B[b]	
	EM (Color)	Woelm	EM	Woelm
5	0.54 (red-rust)	-	0.84	0.92
1	0.51 (pale yellow)	0.57	0.61	0.70
4	0.46 (orange-rust)	0.50	0.68	0.77
3	0.41 (purple)	0.45	0.71	0.81
2	0.24 (tan, pale)	0.27	0.23-.46	0.53-.67
7	0.22 (green)	-	-	-
10	0.44 -	-	-	-
9	0.44 (rust)	-	0.78	0.85
14	0.35 (purple)	-	0.82	0.91
15	0.16 (orange)	-	0.62	0.66
12	0.20 (tan, pale)	-	-	-
16	0.23 (gray)	-	0.70	0.75

[a]Benzene:trichloromethane:methanol::49:47:4. [b]tetrachloromethane: isopropanol:methanol:acetic acid::68:20:8:4. [c]8-Aminoquinoline.

dissolved in chloroform. A small amount of black solid was removed, and the volume of the soln was adjusted to 50·00 ml. Meanwhile, a standard soln of 3 was prepared (45 mg, 0·13 mmoles, in 50·00 ml chloroform). A starting line was traced across the thin layer plate (EM) 2 cm from the bottom, and a finish line was scored through the adsorbent 15 cm above the lower line. The adsorbent (2–3 mm width) was removed from the vertical edges of the plate to insure even migration of the solvent front. Two samples (5 and 10 μl) of the mixture were spotted using the "touch and dry" technique. By applying the sample under a gentle steam of N_2, spots no more than 3–4 mm in diam. were obtained. Standard samples were applied in the same manner (5, 10, 15, 20, 30 and 40 μl).

(*b*) *Development.* It was found that pre-equilibration of the chamber gave poorer separations, therefore, the following procedure was used. The dry development tank was lined with filter paper, the solvent (200 ml; benzene : trichloromethane : methanol : :49:47:4) was introduced. The plate was immediately put in place and the chamber was covered. When the solvent front had risen 15 cm the plate was removed and the spot at R_f 0·41 was yellow with a pink fluorescence under long-wave UV light. After a short time the spot slowly turned purple. The yield of 3 was determined to be 35 ± 5% of theory.

As a further check, a second chromatogram was run in a different solvent system (tetrachloromethane : isopropanol : methanol : acetic acid : :68:20:8:4). The sample (5 μl) and 3 standard spots (15, 17·5, 20 μl) were applied to the plate (Woelm) as above. After development, analysis showed a 35 ± 5% yield of 3 having an R_f value of 0·81. Table 1 contains a summary of the chromatographic characteristics of compounds in the quinoline series.

8 - *Hydroxylamino* - 6 - *methoxyquinoline* (2). 6 - Methoxy - 8 - nitroquinoline[32] (20·4 g, 0·100 mole) was treated with 5% Pd–C (0·50 g, 50% wet) as supplied by Engelhard Ind. Inc., and ammonium hydroxide (0·20 g of 28% soln) in MeOH (90 ml). The mixture was reduced at 25–30° and 30 psi of H_2. The reduction was discontinued after *ca.* 0·2 mole of H_2 had been consumed (30 min). The insolubles were filtered off, then dissolved in THF (500 ml) at 35° and after filtering off the THF insolubles, the filtrate was concentrated *in vacuo* at 15° until precipitation occurred. The product was filtered off at 0°, washed with cold THF and dried at 35° *in vacuo* giving bright yellow needles: 13·0 g (68%); m.p. 128–129°; IR (KBr) 3180, 2850, 1154 cm^{-1}; NMR (DMSO-d_6, 20%) δ 8·80–8·87 (2, NH, OH), 8·62 (dd, 1, C_2–H; $J_{2,3}$ = 4·0 Hz; $J_{2,4}$ = 2·0 Hz), 8·20 (dd, 1, C_4–H; $J_{3,4}$ = 8·0 Hz), 7·54 (dd, 1, C_3–H), 7·02 (d, 1, C_5–H; $J_{5,7}$ = 2·0 Hz), 6·82 (d, 1, C_7–H), 3·88 (s, 3, OCH_3); mass spectrum *m/e* (rel intensity), M^+ 190 (68), 174 (100); TLC no 4 or 1. (Found: C, 62·92; H, 5·26; N, 14·59. Calcd for $C_{10}H_{10}N_2O_2$: C, 63·15; H, 5·30; N, 14·73%).

Reductions carried out in the absence of ammonia proceeded very slowly. Reduction at higher temps or pressure gave mostly 4.[33]

Reactions of 8 - *hydroxylamino* - 6 - *methoxyquinoline* (2) *in methanol in the presence of* 8 - *amino* - 6 - *methoxyquinoline* (4). 4 (26·0 g, 0·15 mole), Pd–C (12·0 g, 5%, 50% wet, Engelhard), 2 (15·0 g, 0·079 mole) and MeOH (250 ml) were stirred at 25° for 20 hr under N_2. The mixture was filtered at −5° and the filter cake was then slurried in 10% HCl and filtered. The acidic soln was adjusted to pH 9 by the dropwise addition of 10% NaOH aq and the green solid that separated was collected, washed with water, and dried *in vacuo* to give crude 3: 12·0 g (44% based on 4 as substrate, 88% based on 2 as substrate; mass spectrum, *m/e* (rel

Table 2. Effect of heavy atom solvents on the decomposition of 2

Solvent	Temp, °C/Time, hr	% 3	% 4	Ratio 3:4
MeOH	65/22	35	5	7.0
$CHCl_3$	55/22	15	10	1.5
$CHBr_3$	55/22	10	15	0.67
$CHBr_3$	130/22	5	15	0.33
1,4-dimethyl-benzene	130/22	15	10	1.5
Heptane	98/22	20	7.5	2.7
$(CH_2)_2Cl_2$	60/22	20	7.5	2.7
$(CH_2)_2Br_2$	60/22	15	10	1.5

intensity) 346 (100); TLC 3 major impurities, amount of **3**, 50 ± 10%. After a number of unsuccessful recrystallizations and regenerations, a pure sample of **3** was obtained by preparative TLC. From 500 mg of crude product was obtained 222 mg of **3**, the physical and spectral properties of which were identical with an authentic sample: m.p. 220–221° IR(Nujol) 3520, 3410, cm^{-1}; NMR (DMSO-d_6 10%) δ 8·65–7·15 (m, 7, NH and pyridine protons), 6·92 (s, 1, C_7–H), 6·55 (d, 1, C_5–H), 5·68 (d, 1, C_7–H), 6·18 (s, 2, NH_2), 3·82 (s, 3, OCH_3), 3·69 (s, 3, OCH_3); mass spectrum, *m/e* (rel intensity) M^+ 346 (100) TLC pure. (Found: C, 69·17; H, 5·27; N, 16·09. Calcd for $C_{20}H_{18}N_4O_2$: C, 69·35; H, 5·24; N, 16·18%).

8 - *Azido* - 6 - *methoxyquinoline* (**5**). 8 - Amino - 6 - methoxyquinoline (35·0 g, 0·20 mole) was dissolved in 10% HCl (300 ml) and an orange solid formed as ice (50 g) was added. A soln of $NaNO_2$ (15·6 g, 0·23 moles) in water (50 g) was added at 0–5° over 15 min. After stirring for an additional 15 min, soln occurred and urea (5·0 g) was added. The soln was stirred for 10 min, then poured into a soln of NaOAc (15·0 g) and sodium azide (15·0 g, 0·22 mole) in water (400 ml). After stirring for 15 min the soln was charcoaled and adjusted to pH 8·5 with ammonium hydroxide (70 ml of a 28% soln) to give a light-green solid. This was filtered, washed free of ammonia, and recrystallized from 92% EtOH. After drying at 40° *in vacuo* there was obtained light yellow needles: 29·0 g (73%); m.p. 82–83°; IR (KBr) 2120 (N_3) cm^{-1}; mass spectrum, *m/e* (rel intensity) M^+ 200 (45), 172 (69); NMR ($CDCl_3$, 20%) δ 8·61 (dd, 1, C_2–H; $J_{2,3}$ = 4·0 Hz, $J_{2,4}$ = 1·5 Hz), 7·92 (dd, 1, C_4–H; $J_{3,4}$ = 8·0 Hz), 7·26 (q, 1, C_3–H), 6·90 (d, 1, C_5–H; $J_{5,7}$ = 2·5 Hz), 6·72 (d, 1, C_7–H), 3·80 (s, 3, OCH_3); TLC pure. (Found: C, 59·67; H, 3·77; N, 27·98. Calcd for $C_{10}H_8N_4O$: C, 59·99; H, 4·03; N, 27·99%).

Decomposition of 8 - *azido* - 6 - *methoxyquinoline* (**5**) *in Dowtherm.* The azide **5** (2·00 g, 0·0100 mole) was heated in Dowtherm (3 ml) and at 170° N_2 evolution began. The reaction was quite exothermic, the temp rising to 190°. After a very short time N_2 evolution ceased and after 30 min at 170° the brown soln was cooled to 50° and 10% HCl (32 ml) was added. Then water (50 ml) was added, and the Dowtherm was removed by extraction with chloroform. The aqueous part was made slightly basic, then in turn extracted with chloroform. The chloroform soln was washed with water, dried over Na_2SO_4 and concentrated to dryness to give a brown solid (1·92 g). This solid contained 7·5 ± 2·5% of **3** by TLC, which corresponds to an 8% yield of **3**. The solid also contained 15 ± 5% of **4**. Preparative TLC resulted in the isolation of pure **3** (102 mg, 6%); IR, mass spectrum and TLC data identical to that of an authentic sample.

Decomposition of 8 - *azido* - 6 - *methoxyquinoline in benzenemethanamine*

(a) *At* 160° *for* 2·5 *hr.* The azide **5** (1·5 g, 7·5 mmole) was heated for 2·5 hr at 160° in benzenemethanamine (125 ml) under N_2. After this time the benzenemethanamine was removed *in vacuo*. The residue was dissolved in benzene except for a small amount of tar which was filtered off. The benzene was washed well with water, then concentrated to an oil. Examination of the oil by TLC (solvent system A) showed only four spots. The major product was **4** (R_f 0·46, orange-rust). The second most intense spot was green and had an R_f value of 0·22. The other two spots were weak with R_f values of 0·06 and 0·60. No **3** or unreacted **5** was present.

The amounts of the compounds with R_f values of 0·06 and 0·60 were too small to allow their isolation by preparative TLC, but the compound with R_f 0·22 was obtained in a pure state. Crystallization from benzene-methanol afforded **7** as yellow irregular prisms: 50 mg (4%); m.p. 94–95°, NMR ($CDCl_3$, 10%), δ 8·61 (dd, 1, C_2–H, $J_{2,3}$ = 4·0 Hz, $J_{2,4}$ = 1·5 Hz), 7·90 (dd, 1, C_4–H, $J_{3,4}$ = 8·0 Hz), 7·13 (q, 1, C_3–H), 6·58 (s, 1, C_5–H), 4·18 (s, 4, 2 × NH_2), 3·91 (s, 3, OCH_3); mass spectrum, *m/e* (rel intensity) M^+ 189 (100); TLC pure. (Found: C, 63·45; H, 5·84; N, 22·30. Calcd for $C_{10}H_{11}N_3O$: C, 63·49; H, 5·82; N, 22·22%).

(b) *At* 170° *for* 15 *min.* The azide **5** (500 mg, 2·5 mmoles) was added to benzenemethanamine (35 ml) at 140°. The mixture was rapidly heated to 170° under N_2, and maintained at this temp. for 15 min. After concentration *in vacuo*, TLC analysis of the products showed: a small amount of unreacted **5**; **4** as the major; **7** as a minor product; and a new spot at R_f 0·44 (solvent system A) which appeared as a tail on the spot corresponding to **4**. Preparative TLC afforded an oil (85 mg), which contained only R_f 0·46 (major) and R_f 0·44 (tail on R_f 0·46) by TLC. The mass spectrum of the oil also showed it was composed mostly of **4** (*m/e* 174, 100%); however, there was a peak at *m/e* 279 (3%) corresponding to **10**. After a similar reaction at 170° for 30 min the spot at R_f 0·44 had diminished in intensity; and in another reaction at 170° for 1 hr, the spot at R_f 0·44 was not visible upon TLC examination.

Decomposition of 8 - *hydroxylamino* - 6 - *methoxyquinoline* (**2**) *in benzenemethanamine.* The hydroxylamino compound **2** (1·5 g, 7·9 mmoles) was heated for 15 min at 170° in benzenemethanamine

Table 3. Effect of solvent on the formation of **3** from the hydroxylamine **2** and the azide **5**

Reactant	Solvent	Additive	Temp, °C	% Yield of 3
2	N,N-diethylethanamine	-	90	10
2	1,4-dimethylbenzene	-	130	15
2	methylbenzene	-	110	20
2	heptane	-	98	20
2	methoxybenzene	-	130	20
2	benzenamine	-	130	20
2	N,N-diMe-benzenamine	-	130	20
2	ethanol	-	78	30
2	methanol	-	65	35
2	dimethyl sulfoxide	-	130	40
2	2,2'-dihydroxydiethyl ether	-	130	50
5	1,4-dimethylbenzene	-	130	0
5	N,N-diMe-benzenamine	-	130	0
5	N,N-diMe-benzenamine	4	130	5
5	methoxybenzene	-	130	1
5	2,2'-dihydroxydiethyl ether	-	130	2
5	2,2'-dihydroxydiethyl ether	4	130	10
5	dimethyl sulfoxide	-	130	5

(125 ml) under N_2. After concentration *in vacuo* the residue was taken up in benzene, filtered, washed with water, and dried (Na_2SO_4). The TLC of the benzene soln showed: **4** (major), **7** (minor), **3** (trace). Preparative TLC afforded **7**; 35 mg (3%); m.p. 95°; mass spectrum, *m/e* (rel intensity) M^+ 189 (100); TLC, R_f 0·22 (green).

4 - *Methoxy* - 1H - *pyrido*[3,2 - g]*benzimidazole* (**9**). The compound **7** (35 mg, 0·18 mmole) was heated for 2 hr at 98° in 45% formic acid (1 ml). A brown soln formed. After cooling, the soln was adjusted to *ca.* pH 8, whereupon a brown oil separated. The oil was removed from the aqueous phase by filtration through a bed of Solka-Floc using gentle vacuum. The filter cake was washed with water until the cake was no longer alkaline. The cake was then heated at 90–95° in water (100 ml) and Darco-X (1 g). After hot filtration, the aqueous soln was cooled at 5° for 18 hr giving colorless irregular prisms of **9**: 5 mg (14%); m.p. 185°; mass spectrum, *m/e* (rel intensity) M^+ 199 (60), 172 (100, M–HCN). (Found: C, 65·88; H, 4·06; N, 20·96. Calcd for $C_{11}H_9N_3O$: C, 66·32; H, 4·55; N 21·10%).

Decomposition of **2** *in* N-*ethylethanamine.* The compound **2** (0·95 g, 5·0 mmoles) was refluxed for 18 hr in N-ethylethanamine (100 ml) under N_2. After concentration *in vacuo* TLC analysis showed two major products, one of which was **4**. The other was isolated by preparative TLC and crystallization from benzene-ethanol afforded **10b** as orange irregular prisms: 0·12 g (10%) m.p. 103–108° (dec); NMR ($CDCl_3$, 5%), δ 8·61 (dd, 1, C_2–H, $J_{2,3}$ = 4·0 Hz, $J_{2,4}$ = 1·5 Hz), 7·92 (dd, 1, C_4–H, $J_{3,4}$ = 8·0 Hz), 7·18 (q, 1, C_3–H), 6·55 (s, 1, C_5–H), 4·05 (s, 2, NH_2), 3·93 (s, 3, OCH_3), 2·85 (q, 4, $2\times CH_2$, J = 7·0 Hz), 1·80 (t, 6, $2\times CH_3$, J = 7·0 Hz); mass spectrum, *m/e* (rel intensity) M^+ 245 (100). (Found: C, 68·62; H, 7·66; N, 17·21. Calcd for $C_{14}H_{19}N_3O$: C, 68·57; H, 7·76; N, 17·14%).

When the azido compound **5** was heated at reflux for 18 hr in N-ethylethanamine no reaction occurred.

Reactions of **2** *and* **5** *in morpholine.* The compound **2** (0·50 g, 2·6 mmoles) was heated at reflux for 2 hr in morpholine (50 ml) under N_2. After concentration *in vacuo* TLC analysis showed **4** as the major product along with a large amount of unreacted **2** and several minor products: mass spectrum, *m/e* (rel intensity) M^+ 259 (10), 174 (100).

The azido compound **5** (1·0 g, 5·0 mmoles) was refluxed for 2 hr in morpholine (100 ml) under N_2. After concentration *in vacuo* TLC analysis showed **4** and only trace amounts of other compounds; mass spectrum, *m/e* (rel intensity) M^+ 174 (100).

Deoxygenation of 6 - *methoxy* - 8 - *nitroquinoline* (**1**). The compound **1** (500 mg, 2·4 mmoles) was heated for 22 hr at 130° in redistilled triethylphosphite (10 ml) in the presence of **4** (1·0 g, 5·7 mmoles). After this time the solvent was removed *in vacuo* and the residue was dissolved in warm chloroform. TLC examination revealed *ca.* 50% unreacted **1**. Repeated preparative TLC resulted in the isolation of **3**: 41 mg (5%); IR superimposable with that of an authentic sample. When the reaction was run at 160°, 130 mg (16%) of **3** was obtained by repeated preparative TLC and no unreacted **1** was detected.

Thermolysis of 8 - *hydroxylaminoquinoline* (**12**) *in methanol.* The compound **12**[31] (500 mg, 3·1 mmole) was refluxed in MeOH (10 ml) for 22 hr under N_2. The mixture was concentrated to dryness *in vacuo*, and the residue was dissolved in chloroform and filtered. TLC examination of the chloroform soln showed a number of spots, the most intense of which had R_f values of 0·44, 0·36, 0·16 and 0·08 (solvent system A).

The compound with the R_f value of 0·44 was identified as 8-aminoquinoline by comparison of its IR spectrum and chromatographic charactestics with those of an authentic sample: R_f 0·44 (solvent system A), R_f 0·78 (solvent system B).

The other three major products were isolated by preparative TLC. The compound with the R_f value of 0·08 was tentatively identified as **13**. It was obtained as a red powder after crystallization from 92% EtOH: 8·5 mg (2%); m.p. 241–242°, mass spectrum, *m/e* (rel intensity) M^+ 284 (100).

Isolation of the compound with the R_f value of 0·16 gave, after crystallization from benzene-ethanol, **15**: 69 mg (16%); IR (KBr) 3300 (b) cm^{-1}; mass spectrum, *m/e* (rel intensity) M^+ 286 (100); NMR ($CDCl_3$, 10%), δ 8·73–8·77 (m, 2, C_2–H, $C_{2'}$–H), 7·22–7·92 (m, 4, pyridine protons), 6·20 (s, 1, NH), 6·12–6·88 (m, 5, aromatics), 4·05 (s, 2, NH_2). (Found: C, 75·53; H, 4·90; N, 19·58. Calcd for $C_{18}H_{14}N_4$: C, 75·50; H, 4·93; N, 19·57%).

Isolation of the compound with the R_f value of 0·36 gave, after crystallization from benzene-ethanol, **14**: 34 mg (8%); IR (KBr) 3320 (b) cm^{-1}; mass spectrum, *m/e* (rel intensity) M^+ 286 (100); NMR ($CDCl_3$, 10%) δ 8·74–8·77 (m, 2, C_2–H $C_{2'}$–H), 7·20–7·90 (m, 4, pyridine protons), 7·80 (s, 1, NH), 6·05–6·90 (m, 5, aromatic), 5·88 (s, 2, NH_2). (Found: C, 75·41; H, 4·86; N, 19·62. Calcd for $C_{18}H_{14}N_4$: C, 75·50; H, 4·93; N, 19·57%).

3 - (8' - *Quinolyl*) - 3H - *pyrido*[3,2 - g]*benzimidazole* (**16**). The iminobisquinoline **15** (50 mg, 0·17 mmole) was heated for 2 hr in 45% formic acid (1 ml). The soln was adjusted to pH 8 whereupon an oil separated which was collected. Preparative TLC and crystallization from pyridine-ether afforded 3 - (8' - quinolyl) - 3H - pyrido[3,2-g]benzimidazole; 8 mg (16%); m.p. 150–160° (dec); mass spectrum, *m/e* (rel intensity) M^+ 296 (45), 269 (100, M–HCN). (Found: C, 77·40; H, 3·68; N, 18·77. Calcd for $C_{19}H_{12}N_4$: C, 77·03; H, 4·05; N, 18·92%).

6-*Hydroxylaminoquinoline* (**16**). 6-Nitroquinoline[34] (5·0 g, 0·03 mole) and platinum oxide (50 mg) in a soln of MeOH (5 ml) and EtOAc (25 ml) were subjected to 50 psi of H_2 at 25–30°. After shaking for 8 hr *ca.* 0·06 mole of H_2 was absorbed. THF was added until all organic material was in sol and, after filtration, hexane was added to the filtrate until it became cloudy. After several minutes, a solid formed. It was filtered and washed well with hexane. It was dried *in vacuo* under N_2 at 25° to give crude **16**: 1·7 g (35%); TLC 2 spots, R_f 0·32 orange, R_f 0·23 gray; mass spectrum, *m/e* (rel intensity) M^+ 300 (55), 282 (60), 160 (60), 144 (100).

Use of MeOH in the above reaction gave **17**; 2·5 g (56%); m.p. 210° (lit[35] m.p. 212°); IR (KBr) 3220, 1310 (NO) cm^{-1}; mass spectrum, *m/e* (rel intensity) M^+ 300 (94), 282 (100), 272 (13, M–CO), 160 (0·07); TLC 1 orange spot R_f 0·32 (solvent system A). When EtOAc above was used as solvent no reduction occurred.

Thermolysis of 6-*hydroxylaminoquinoline* (**16**). Crude **16** (500 mg) was heated at reflux in MeOH (10 ml) for 22 hr under N_2. The mixture was then concentrated to an oil. The mass spectrum of the oil contained no ion at *m/e* 286. An identical reaction was carried out, except that 8 - amino - 6 - methoxyquinoline (500 mg) was added initially. The mass spectrum of the product mixture had no ions at *m/e* 286 or 316.

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