

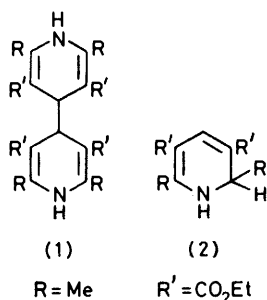
The Photoreactions of Pyridine and 2-Fluoropyridine with Aliphatic Amines

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Pyridine undergoes photochemical reaction with diethylamine, triethylamine, and diethyl ether to give 2- and 4-substituted pyridines which reflect attack at the α -CH₂ of the amine and the ether. Irradiation of 2-fluoropyridine with *t*-butylamine and diethylamine results solely in a nucleophilic displacement reaction and the formation of the 2-alkylaminopyridines but triethylamine and 2-fluoropyridine yield 2-(*N,N*-diethylamino)pyridine and a compound tentatively identified as 2-(*N*-ethyl-*N*-*n*-propylamino)pyridine. Mechanistic considerations are discussed in terms of pathways previously proposed for arene-amine photoreactions.

THE photochemistry of benzene and its simple derivatives is diverse and extensive and has been the subject of numerous publications.¹ In contrast there have appeared comparatively few accounts which describe photoinduced reactions of pyridine.² Photoisomerisation of pyridine,^{2,3} 2-fluoropyridine,² lutidine,² and perfluoroalkylpyridines^{4,5} to the *p*-bonded valence isomers and azaprismanes has been reported and in the presence of cyclohexane pyridine yields 2- and 4-cyclohexylpyridines⁶ and 2- and 4-picolines result from irradiation of pyridine and acidified methanol.⁷ Photo-substitution of some pyridine derivatives has been described⁸ but there is only one published account of the photoreaction of a pyridine, the 2,6-dimethyl-3,5-diethoxycarbonyl derivative, with an aliphatic amine.⁹ This reaction in contrast to those of amines and benzenoid compounds which give 1,2- and 1,4-acyclic 1:1 adducts and aniline derivatives,^{10,11} led solely to the reduction products (1) and (2). In view of the paucity of information on pyridine photochemistry and to complement our studies on the reaction of benzene¹⁰ and fluorobenzenes¹¹ with aliphatic amines, we have studied the photoreactions of pyridine and 2-fluoropyridine with *t*-butylamine, diethylamine, and triethylamine.¹²

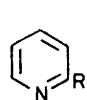
All solutions were nitrogen degassed before their irradiation in quartz tubes using low-pressure mercury-vapour lamps. Preparative experiments involved



equivolume solutions of the amine and heteroarene and the reaction was monitored by g.l.c.

The 254 nm irradiation of pyridine and diethylamine led to the slow formation of two products in a ratio of 0.85:1.0 (g.l.c. elution sequence). Both products had M^+ (m.s.-g.l.c.) of 150 m.u. which corresponds to an

amine substitution product of the pyridine. From the spectroscopic and analytical data (see Experimental section) of the separated components, the substitution was deduced to involve the α -CH₂ of the amine and to have occurred at the 2- and 4-positions of the pyridine; thus structures (3) and (4) were assigned to the major and



(3) $R = \text{CH}(\text{Me})\text{NHEt}$

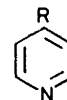
(5) $R = \text{CH}(\text{Me})\text{NEt}_2$

(11) $R = \text{CH}(\text{Me})\text{OEt}$

(17) $R = \text{NEt}_2$

(18) $R = \text{NHBU}^t$

(20) $R = \text{N}(\text{Et})\text{Pr}^n$



(4) $R = \text{CH}(\text{Me})\text{NHEt}$

(6) $R = \text{CH}(\text{Me})\text{NEt}_2$

(12) $R = \text{CH}(\text{Me})\text{OEt}$



(7) $R = \text{CH}(\text{Me})\text{NEt}_2$

(9) $R = \text{NEt}_2$

(13) $R = \text{CH}(\text{Me})\text{OEt}$

(14) $R = \text{NHBU}^t$

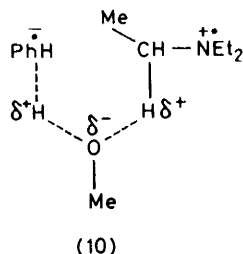


$\text{CH}(\text{Me})\text{NEt}_2$

(8)

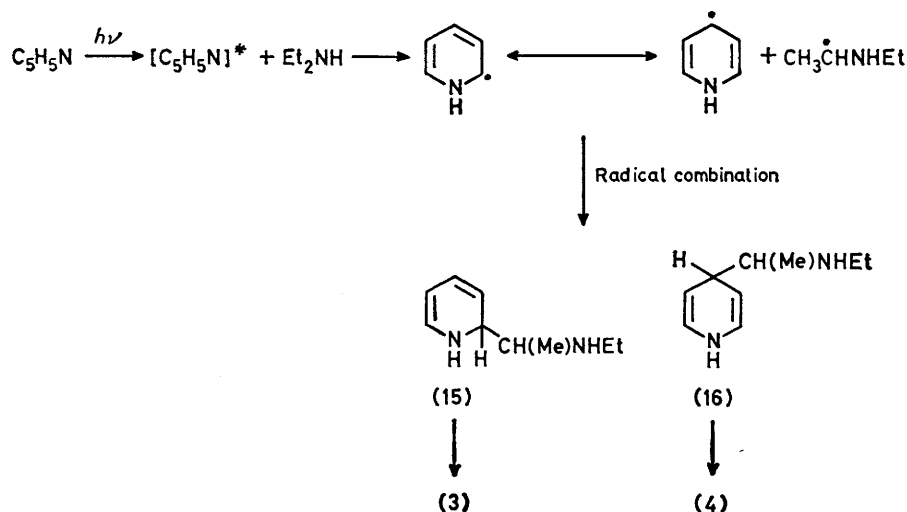
minor products respectively. Consistent with the formation of the α -C rather than *N*-substitution products from diethylamine and pyridine (contrast formation of *N,N*-diethylaniline from benzene and diethylamine¹⁰), *t*-butylamine gave no volatile products with pyridine and irradiation of triethylamine and the heteroarene gave the 2- and 4-substituted products (5) and (6) in a 0.8:1.0 ratio respectively. From the latter system, minor amounts [*ca.* 15% of (6)] of solely amine-derived products were also formed.¹³ Photoreaction at the amine α -CH₂ is reflected in the 1:1 adduct (7) from triethylamine and benzene¹⁰ and the substitution product (8) from 1,4-dicyanobenzene and the same amine,¹⁴ whereas diethylamine and benzene yield (9),¹⁰ so previous mechanistic proposals for arene-amine photoreactions

are relevant to the pathway for formation of the present compounds.* Formation of (7), (8), and (9) are considered to arise by electron transfer from the amine to the S_1 arene followed by proton transfer and radical combination: the adduct from dicyanobenzene was proposed to be unstable and to eliminate HCN. However



in contrast to the formation of (7) which is greatly accelerated by a proton source,¹⁰ that of the substitution product (8) was not formed in the presence of methanol.¹⁴ These observations were interpreted in terms of the trimolecular assembly (10) aiding the reaction in the former case but this species was not formed from the cyanoarene, and analogy was drawn with the trifluoroacetic acid inhibition of the photosubstitution of tetracyanobenzene by toluene which was explained by proton transfer from

heteroarene with the solvents. Thus in cyclohexane the products previously described were formed⁶ and in diethyl ether as solvent the 2- and 4-substituted products (11) and (12) were obtained: these have not previously been isolated although the quinoline analogues have been reported¹⁷ and (13) results from irradiation of the diethyl ether-benzene system but, in contrast to the present systems, was only formed in the presence of strong acids.¹⁸ Formation of the pyridine substitution products described here is not considered to involve a mechanism of electron transfer from the amine to the S_1 arene followed by proton transfer and radical combination. The reason for rejection of such a route is that the proton transferred would be that of the amine N-H as in the case of the photoaddition of *t*-butylamine and diethylamine to benzene which yields the N-substituted products (14) and (9) respectively and their 1,3-diene isomers.¹⁰ In contrast with pyridine as the arene, *t*-butylamine gave no substitution products and diethylamine reacted at the α -CH₂ to the nitrogen. On the other hand, there is ample precedent from the studies of Lablache-Combier and his co-workers² to suggest that the present photoamination products of pyridine arise *via* hydrogen abstraction by the photoexcited arene from the amine which would be expected to occur preferenti-



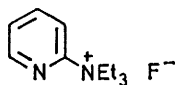
SCHEME

the acid to the arene radical anion followed by back electron transfer from the radical and deprotonation.¹⁶ The characteristics of the present photosubstitution reactions more resemble those of dicyanobenzene than of benzene in that the photosubstitution from both di- and tri-ethylamine and pyridine was inhibited in the presence of methanol or water whereas other solvents including acetonitrile had little effect on the efficiency of the process. Interpretation of the present results was, however, somewhat complicated by the competing reactions of the

allyl at the α -CH₂. This process is followed by radical combination to give the 1,2- and 1,4-dihydropyridines (15) and (16) respectively and these are fortuitously oxidised to the substitution products as shown in the Scheme. Even though we have been unable to detect such addition intermediates under carefully controlled anaerobic conditions, this mechanistic pathway is favoured as the route to the substitution products since (a) the alternative mechanism of homolytic substitution onto ground state pyridine by the derived amine radicals would also produce the 3-substituted isomer of (3) and (4) and of this there was no trace, and (b) dihydropyridines are extremely susceptible to oxidation.

* Subsequent to the preliminary account of the present work¹² similar products to (8) were also reported from irradiation of primary and secondary amines and 1,4-dicyanobenzene.¹⁵

The irradiation of fluorobenzene and the difluorobenzenes with primary and secondary aliphatic amines yields both 1 : 1 adducts and aniline derivatives and from the latter arenes, both cine and 'normal' substitution products are formed by an addition-elimination mechanism.¹¹ Irradiation of 2-fluoropyridine and diethylamine gave the insoluble amine hydrofluoride and an equivalent amount of 2-(*N,N*-diethylamino)pyridine (17) as the sole volatile product: similarly with *t*-butylamine as the amine, 2-(*N-t*-butylamino)pyridine (18) was produced. From neither system were the 3-substituted isomers detected and hence formation of (17) and (18) is deduced to arise by conventional photonucleophilic displacement of the fluorine¹⁹ rather than by an addition-elimination sequence.¹¹ Reaction of 2-fluoropyridine with triethylamine cannot, however, be so straightforward and irradiation of the system led to the slow formation of two major volatile products in a 0.65 : 1.0 ratio (elution sequence) and two minor products which together comprised *ca.* 10% of the mixture and which were not further investigated. The amounts of amine hydrofluoride from this system were very small in comparison to product formation. The shorter retention time major product was shown to be 2-(*N,N*-diethylamino)pyridine by comparison of its chromatographic and spectroscopic properties with those for authentic material:²⁰ it is noteworthy here that *N,N*-diethylaniline was a minor product from the irradiation of fluorobenzene and triethylamine.¹¹ Compound (17) does appear to be a primary photoproduct and not result from photolysis of an adduct or substituted product as occurred in the formation of ethyl benzonitriles from dicyanobenzenes and triethylamine.¹⁴ The formation of (17) in the present system may, however, be rationalised in terms of an addition-elimination mechanism related to that of the von Braun reaction²¹ and involving the intermediate (19), but from neither this system nor that



(19)

involving fluorobenzene has evidence yet been obtained which we consider to be conclusive and reliable for the presence of ethyl fluoride among the gaseous products of the reactions. Effective separation of the major product from triethylamine and fluorobenzene was only achieved by preparative g.l.c. but this was with low efficiency to give a yellow product containing typically 10% impurities. Analysis of this component by m.s.-g.l.c. showed that it had a molecular weight of 164 m.u. which indicates the formal loss of methyl fluoride from a 1 : 1 adduct of the starting materials. The ¹H n.m.r. spectrum of a 90% pure sample of the compound had resonances at 7.9–8.1 (1 H), 7.1–7.5 (1 H), and 6.2–6.6 p.p.m. (2 H) of multiplicities very closely resembling those of the 6-H, 4-H, and 3- and 5-H resonances respectively in 2-aminopyridines. The remainder of the

resonances in the spectrum comprised a quartet (*J* 7 Hz) and triplet (*J* 7 Hz) centred at 3.50 and 3.40 p.p.m. respectively of combined integral 4 H and a triplet (*J* 7 Hz) centred at 1.15 p.p.m. overlapping with less clearly resolved resonances between 0.8 and 1.4 p.p.m. (8 H). These data are consistent with this component being 2-(*N*-ethyl-*N*-*n*-propylamino)pyridine (20) but the small amounts of impure material realistically obtainable for this fraction rendered analytical data of little value and hence this structural assignment must be regarded as tentative particularly as the formation of such a compound is unprecedented from these systems. Quantum yields for total product formation from preparative experiments are low, being of the order of 0.01 for the pyridine irradiations and 0.05 for those with fluoropyridine. No ground-state complex formation between pyridine and 2-fluoropyridine with the aliphatic amines was detected by u.v. or n.m.r. spectroscopy and only weak quenching of the fluorescence of 2-fluoropyridine by the amines was observed: the involvement or otherwise of excited-state complexes in the present reactions is a matter for speculation.

EXPERIMENTAL

The irradiation source in all experiments comprised Hanovia 15-W low-pressure mercury-arc lamps. Degassed solutions (100 ml for pyridine experiments and 10 ml for those involving 2-fluoropyridine) of equivolumes of the reactants were irradiated for 24 h at 20 °C and monitored by g.l.c. using 10% Apiezon columns. Relative retention times of the substituted pyridines are given below. Starting materials were removed from the resulting brown solution by bubbling nitrogen through it for several hours: for experiments involving 2-fluoropyridine, the amine hydrofluoride was filtered off and the starting materials recovered by recycling by rotary evaporation at water-pump vacuum. The components of the viscous brown residues were isolated by preparative g.l.c. as colourless to pale yellow oils using 10% Apiezon L on Universal B support packed columns: this gave an overall separation efficiency from crude product mixture to substituted pyridine of *ca.* 25%.

The effect of solvent on the photosubstitution reactions was examined using relative concentrations of 1 : 1 : 2 (v/v) of pyridine : amine : solvent respectively.

The data relevant to the structural assignments of the substitution products are given below. I.r. spectra were recorded as liquid smears and ¹H n.m.r. spectra in CCl₄ solution (60 MHz).

Pyridine and Diethylamine.—These gave *ca.* 2.0 g of crude product from which (3) and (4) (relative retention times 1 : 1.4 respectively) were separated. Compound (3) (*M*⁺ = 150 m.u.) had δ values at 8.4–8.55 (1 H, m, pyridine 6-H), 7.4–7.8 (1 H, t of d, pyridine 4-H), 6.9–7.4 (2 H, m, pyridine 3-H and 5-H), 3.75 [1 H, q, *J* 7 Hz, NCH(R)Me], 2.40 (2 H, q, *J* 7 Hz, NCH₂Me), 1.5 (1 H, s, NH removed with D₂O), 1.3 (3 H, d, *J* 7 Hz), and 1.00 p.p.m. (3 H, t, *J* 7 Hz); and ν_{max} . at 3 300br, 3 060w, 3 010w, 2 970s, 2 930m, 2 895m, 2 870m, 2 840m, 1 590s, 1 570m, 1 135s, 785s, and 750s cm⁻¹ (Found: C, 71.55; H, 9.65; N, 19.05. C₉H₁₄N₂ requires C, 71.94; H, 9.40; N, 18.66%).

Compound (4) (*M*⁺ 150 m.u.) had δ values at 8.3–8.5 (2 H, d of d, pyridine 2-H and 6-H), 7.1–7.3 (2 H, d of d, pyridine 3-H and 5-H), 3.7 [1 H, q, *J* 7 Hz, NCH(R)Me],

2.45 (2 H, q, $J = 7$ Hz), NCH_2Me , 1.35 (1 H, s, NH removed with D_2O), 1.25 (3 H, d, J 7 Hz), and 1.05 p.p.m. (3 H, t, J 7 Hz); ν_{max} . 3 280br, 3 070w, 3 030w, 2 970s, 2 930m, 2 890m, 2 870m, 2 820m, 1 600s, 1 560w, 1 130s, 820s, and 780m cm^{-1} (Found: C, 71.65; H, 9.6; N, 18.95. $\text{C}_9\text{H}_{14}\text{N}_2$ requires C, 71.94; H, 9.40; N, 18.66%).

Pyridine and Triethylamine.—These gave 1.5 g of crude product which contained four products with relative retention times of 1:1.2:1.6:2.8. The former two products had δ values only in the 2.2–2.8 and 0.8–1.2 p.p.m. regions and are deduced to be amine-derived products previously described.¹³ The two major products were identified as the 2- and 4-substituted pyridines (5) and (6) respectively from the following data. Compound (5) (purity >99% by g.l.c. from repeat cycle preparative g.l.c. Found: M^+ , 178.147 8, $\text{C}_{11}\text{H}_{18}\text{N}_2$ requires M^+ , 178.146 9) had δ values at 8.40 (1 H, d of q, pyridine 6-H), 7.4–7.7 (2 H, m, pyridine 3-H and 4-H), 6.9–7.2 (1 H, m, pyridine 5-H), 3.95 (1 H, q, J 7 Hz), 2.5 (4 H, q, J 7 Hz), 1.3 (3 H, d, J 7 Hz), and 1.0 p.p.m. (6 H, t, J 7 Hz); ν_{max} . 3 080w, 3 060w, 3 010w, 2 970s, 2 930m, 2 900m, 2 870m, 2 810m, 1 590s, 1 570m, and 1 080m cm^{-1} .

Compound (6) (purity >99% by g.l.c. from repeat-cycle preparative g.l.c. Found: M^+ , 178.147 2; $\text{C}_{11}\text{H}_{18}\text{N}_2$ requires M^+ , 178.146 9) had δ values at 8.35–8.5 (2 H, d of d, pyridine 2-H and 6-H), 7.15–7.4 (2 H, d of d, pyridine 3-H and 5-H), 3.75 (1 H, q, J 7 Hz), 2.5 (4 H, q, J 7 Hz), 1.3 (3 H, d, J 7 Hz), and 1.0 p.p.m. (6 H, t, J 7 Hz); ν_{max} . 3 070w, 3 020w, 2 970s, 2 930m, 2 900m, 2 870m, 2 810m, 1 590s, 1 555w, 1 080m, and 825s cm^{-1} .

Pyridine and Diethyl Ether.—These gave 0.5 g of crude product: this was repeated twice and (11) and (12) (relative retention times 1:2) were separated from the combined products. Compound (11) ($M^+ = 151$ m.u.) had δ values of 8.3–8.5 (1 H, d of q, pyridine 6-H), 6.9–7.8 (3 H, m, pyridine 3-H, 4-H and 5-H), 4.45 (1 H, q, J 7 Hz), 3.40 (2 H, q, J 7 Hz), 1.35 (3 H, d, J 7 Hz), and 1.20 p.p.m. (3 H, t, J 7 Hz); ν_{max} . 3 080w, 3 060w, 3 010w, 2 970s, 2 930s, 2 880s, 2 870s, 2 850m, 1 590s, 1 570m, 1 470m, 1 435s, 1 370m and 1 110vs cm^{-1} (Found: C, 71.8; H, 8.4; N, 9.4. $\text{C}_9\text{H}_{13}\text{NO}$ requires C, 71.48; H, 8.67; N, 9.27%).

Compound (12) ($M^+ = 151$ m.u.) had δ values at 8.3–8.5 (2 H, d of d, pyridine 2-H and 6-H), 7.0–7.2 (2 H, d of d, pyridine 3-H and 5-H), 4.3 (1 H, q, J 7 Hz), 3.3 (2 H, q, J 7 Hz), 1.3 (3 H, d, J 7 Hz), and 1.15 p.p.m. (3 H, t, J 7 Hz); ν_{max} . 3 070w, 3 030w, 2 970s, 2 930m, 2 890m, 2 870s, 2 850s, 1 600s, 1 560m, 1 420s, 1 370m, and 1 105vs cm^{-1} (Found: C, 71.65; H, 8.95; N, 9.4. $\text{C}_9\text{H}_{13}\text{NO}$ requires C, 71.48; H, 8.67; N, 9.27%).

2-Fluoropyridine and Diethylamine.—These gave ca. 0.5 g of a brown oil which contained only one volatile product. The compound was identified as 2-(*NN*-diethylamino)-pyridine (17) from the identical spectroscopic (mass, n.m.r., and i.r. spectra) and chromatographic (g.l.c. 2 columns) properties with those of the authentic compound prepared by a published route.²⁰

*2-Fluoropyridine and *t*-Butylamine.*—These gave ca. 0.5 g of a brown oil containing essentially one volatile compound: this was identified as 2-(*N*-*t*-butylamino)pyridine (18) from the following data: $M^+ = 150$ m.u., δ values at 7.9–8.1 (1 H, m, pyridine 6-H), 7.0–7.4 (1 H, m, pyridine 4-H), 6.1–6.5 (2 H, m, pyridine 3-H and 5-H), 4.3 (1 H, br s removed with D_2O), and 1.4 p.p.m. (9 H, s) (Found: C, 71.75; H, 9.7; N, 18.9. $\text{C}_9\text{H}_{14}\text{N}_2$ requires C, 71.94; H, 9.40; N, 18.66%).

2-Fluoropyridine and Triethylamine.—These gave ca. 0.4 g of a brown oil which comprised four products with relative retention times of 1:1.2:1.7:2. The first and third product combined constituted ca. 10% of the mixture as judged by g.l.c. and were not further investigated. The shorter retention time major product was identified as 2-(*N,N*-diethylamino)pyridine (17) again from its identical spectroscopic and chromatographic properties with those of authentic compound. The major compound, tentatively identified as 2-(*N*-ethyl-*N*-*n*-propylamino)pyridine (20) had $M^+ = 164$ m.u., base ion of 135 m.u., and the only other abundant ion was at 78 m.u.: the ^1H n.m.r. spectrum of this product is given in the text and the i.r. spectrum had ν_{max} at 3 095w, 3 080w, 3 050w, 3 010w, 2 970s, 2 930s, 2 870m, 2 850m, 1 600s, 1 560m, and 1 490s.

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