Formation, Dealkylation, and Nucleophilic Substitution of Some Mono- and Di-alkoxypyridoazepines

Dalpat I. Patel, Eric F. V. Scriven,† Robert K. Smalley,* and Hans Suschitzky
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford M5 4WT
David I. C. Scopes
Glaxo Group Research Ltd., Ware, Herts. SG12 0DJ

The photo-induced ring-expansions of 5-azido-, 8-azido-, 6-azido-8-methoxy, and 8-azido-6-methoxy-quinolines to alkoxypyridoazepines in alcohol–alkoxide–dioxane solution containing 18-crown-6 are reported, although in some instances azepinone and/or azepine ring-contraction products are noted. In addition, ring-expansions in the presence of phenoxide ion have been achieved for the first time. ^{1}H N.m.r. spectra indicate that some of the pyrido-azepines and -azepinones are formed as mixtures of the 5*H*- and 7*H*-isomers.

Dealkylations and nucleophilic substitutions of the alkoxypyridoazepines are discussed, the latter in some instances being accompanied by ring-contraction to diaminoquinolines.

2-Amino-3*H*-azepines are available by photo- and thermal ring-expansions of aryl azides in amine solution.[1] However, in some cases, particularly with bicyclic aryl and heteroaryl azides, *e.g.* quinolyl azides, ring-expansion fails and only triplet nitrene derived and/or azepine ring-contraction products, *i.e.* amines or diamines, are obtained.[1,2] Therefore, as an alternative approach to the synthesis of aminopyridoazepines, and pyridoazepinones, several mono- and di-alkoxypyridoazepines have been prepared and their reactivity towards nucleophilic displacement of the alkoxy group, and their dealkylation, examined.

Ring-expansions of the azidoquinolines were carried out in strong base,[3] consisting of a solution of the alkoxide in a 1:1 mixture of the corresponding alcohol and dioxane. As noted previously,[2] the yields of pyridoazepines were improved in some cases (Table 1) by the presence of a crown-ether in the photolysate.

Of particular interest are the phenoxy derivatives (**2d**) and (**3b**), prepared by photolysing 8- and 5-azidoquinoline respectively, in a solution of sodium phenoxide in dioxane containing 15-crown-5, since, as far as we are aware, these represent the first examples of the ring-expansion of an aryl azide in the presence of an aryloxide. Previous attempts[4] to bring about ring-expansion of *o*-azidobenzoates in phenol–THF solutions have failed.

Nucleophilic displacement of alkoxide from 2-alkoxyazepines is to be expected on account of their imidate nature, although only a few examples have been recorded.[5a] Recent work[6] from these laboratories has shown that 7-methoxy-5*H*-pyrido-[3,2-*c*]azepine (**1**), prepared by photolysis of 6-azidoquinoline in methanol–potassium methoxide–dioxane mixture, readily undergoes displacement of the methoxy-group by primary and secondary amines.

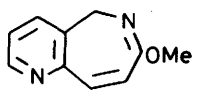
In contrast it is now found that 9-methoxy-5*H*-pyrido[2,3-*c*]-azepine (**2a**), obtained by the photolysis of 8-azidoquinoline in a similar mixture, fails to react with cyclohexylamine, diethylamine, or benzylamine, either in neat amine or in hot dimethyl sulphoxide or ethanol solution. Likewise, 5-methoxy-9*H*-pyrido[3,2-*c*]azepine (**3a**), prepared by ring-expansion of 5-azidoquinoline, is unaffected by diethylamine, benzylamine, or ammonia in a range of solvents (ethanol, dimethyl sulphoxide, acetonitrile, and dimethylformamide). The phenoxy derivatives (**2d**) and (**3b**) were also unreactive.

† *Present address*: Reilly Tar and Chemical Corporation, 1510 Market Square Center, 151 North Delaware St., Indianapolis, Indiana 46204, U.S.A.

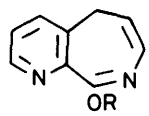
Table 1. 9-Alkoxy-5*H*-pyrido[2,3-*c*]azepines (**2**) by photolysis of 8-azidoquinoline (8-N_3-Q) in potassium alkoxide, alcohol–dioxane solution[a] containing a crown-ether.

Reactants	Product % yield[b]
8-N_3-Q; KOMe (3M), MeOH, dioxane[c]	(**2a**); 70 (72)
8-N_3-Q; KOEt (3M), EtOH dioxane[c]	(**2b**); 71 (47)
8-N_3-Q; KOPr^i (3M), Pr^{i}OH, dioxane[c]	(**2c**); 70 (61)
8-N_3-Q; $NaOCH_2CH{=}CH_2$ (0.86 M),[d] $CH_2{=}CHCH_2OH$, dioxane	(**2e**); 43

[a] A 1:1 dioxane–alcohol solution was used in every case. [b] Figures in brackets refer to yields in the absence of crown-ether. [c] 18-crown-6 present. [d] 15-crown-5 present.



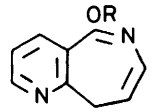
(1)



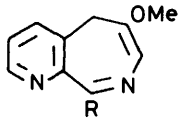
(2) a; R = Me
b; R = Et
c; R = Pr^i
d; R = Ph
e; R = $CH_2CH{=}CH_2$

More successful were the nucleophilic displacements of the dimethoxypyridoazepines (**4a**) and (**5a**). In hot (140 °C) dimethyl sulphoxide, the 5*H*-pyrido[3,2-*c*]azepine (**5a**) with isopropylamine, pyrrolidine, or cyclohexylamine, gave the bis-s-alkylaminopyridoazepines (**5b**—**d**) in high yields. In contrast, the action of amines in hot dimethyl sulphoxide on the isomeric dimethoxypyridoazepine (**4a**) was unpredictable. For example, with propylamine the 6-methoxy-9-propylamine derivative (**4b**) was the only product (35%), whereas with cyclohexylamine formation of the monocyclohexylamino derivative (**4c**) (65%) was accompanied by the *o*-diamine (**6b**). The *o*-diamine (**6a**) was the sole product when the reaction was carried out in hot benzylamine. The ring-contraction of bicyclic azepines to *o*-diamines under basic conditions is well documented.[1,2]

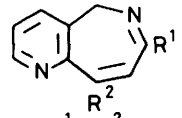
The structures of these mono- and di-aminopyridoazepines were established by ^{1}H n.m.r. spectroscopy. In the case of the dipyrrolidinyl derivative (**5c**), the 5-H_2 group showed geminal coupling and appeared as a doublet of doublets, which



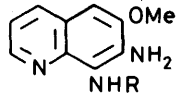
(3) a; R = Me
b; R = Ph



(4) a; R = OMe
b; R = PrNH
c; R = $C_6H_{11}NH$
d; R = OBu^t



(5) a; R^1 = R^2 = OMe
b; R^1 = R^2 = PrNH
c; R^1 = R^2 = C_4H_9N
d; R^1 = R^2 = $C_6H_{11}NH$
e; R^1 = OCH_2Ph, R^2 = OMe
f; R^1 = OBu^t, R^2 = OMe

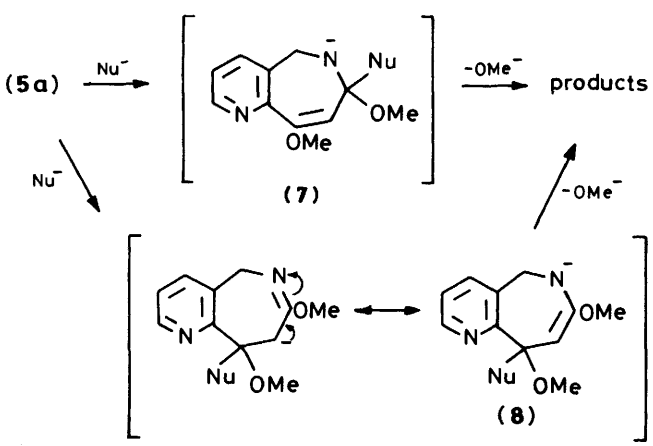


(6) a; R = CH_2Ph
b; R = C_6H_{11}

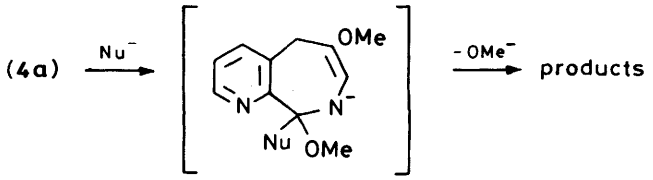
coalesced to a sharp singlet at *ca.* 120—125 °C. The observation of non-equivalence in this system is probably due to steric crowding between the pyridine lone pair and the adjacent pyrrolidine ring, which prevents ring-flipping of the non-planar azepine ring. Similar results have been noted with monocyclic aminoazepines.[5b]

The difference in reactivity between the 5- and 9-alkoxypyridoazepines (**3**) and (**2**) and the 7-methoxy isomer (**1**) may be due to inhibition of nucleophilic attack by unfavourable *peri*-interactions between, in the former case, the 4-proton, and in the latter case the pyridine lone pair, and the alkoxy group undergoing substitution. However, on this basis it is not at all clear why the 9-methoxy group in the dimethoxypyridoazepine (**4a**) is so readily displaced.

The ease of disubstitution of the dimethoxyazepine (**5a**) compared with monosubstitution of its isomer (**4a**) presumably is related to the relative stability of the transition states for nucleophilic substitution. In the former isomer stabilisation of the negative charge onto the azepine ring-nitrogen is possible for substitution at the 7- and 9-positions (**7**) and (**8**), (Scheme 1), whereas with the 6,9-dimethoxy isomer (**4a**) such stabilisation is possible only for substitution at the 9-alkoxy site (**9**), (Scheme 2).



Scheme 1.



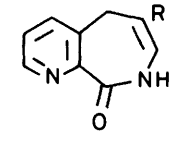
Scheme 2.

Alternatively, it can be argued that both the dimethoxypyridoazepines can undergo base-catalysed hydrogen shifts (see later), which in the case of the 7,9-dimethoxy derivative (**5a**) would locate both methoxy groups at a reactive allylic carbon centre. For the 6,9-dimethoxy derivative, however, a similar hydrogen shift imparts allylic reactivity to the 9-methoxy group only.

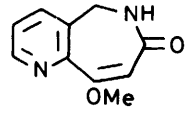
Attempts to add hydrogen bromide to the allyloxypyridoazepine (**2e**) in dichloromethane, acetonitrile, or hot (< 100 °C) acetic acid, were unsuccessful and the pyridoazepine was recovered unchanged. However, with hydrogen bromide in boiling acetic acid, quantitative dealkylation to the pyridoazepinone (**10a**) occurred. The ethoxypyridoazepinone (**2b**) behaved similarly. The relative ease of these dealkylations raised the possibility of carrying out bis-dealkylations, and more interestingly selective mono-dealkylations of the dialkoxypyridoazepines (**4**) and (**5**), particularly with more readily cleaved alkyl ethers, *e.g.* t-butyl and benzyl.

7-Benzyloxy-9-methoxy-5*H*-pyrido[3,2-*c*]azepine (**5e**), was prepared by photolysis of 6-azido-8-methoxyquinoline in a mixture of benzyl alcohol, its sodium salt, dioxane, and 15-crown-5 but proved to be difficult to separate from the excess of benzyl alcohol. The t-butyl ether (**5f**) was prepared by photolysis of the azidomethoxyquinoline in a mixture of potassium t-butoxide, t-butyl alcohol, dioxane, and 18-crown-6. However, acidification of the reaction mixture with methanol–hydrochloric acid (1:1, v/v) unexpectedly gave the 7,9-dimethoxypyridoazepine (**5a**). The transetherification had occurred during work-up. Repetition of the photolysis and work-up using t-butyl alcohol–hydrochloric acid (1:1, v/v) gave two products, namely 9-methoxy-7-t-butoxy-5*H*-pyrido[3,2-*c*]azepine (**5f**), (25%) and the corresponding 9-methoxypyridoazepin-7-one (**11**), (42%).

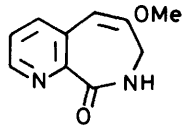
Photolysis of 8-azido-6-methoxyquinoline under the same conditions was more complex. The major component (70%) was a mixture of the isomeric 5*H*- (**10b**) and 7*H*-azepin-9-ones (**12**).



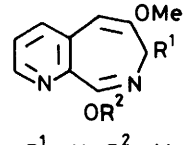
(10) a; R = H
b; R = OMe



(11)



(12)

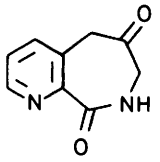


(13) a; R^1 = H, R^2 = Me
b; R^1 = H, R^2 = Bu^t
c; R^1 = OMe, R^2 = Ph

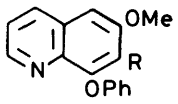
Similarly, the minor component (2%) proved to be a mixture of the corresponding 5*H*- (**4d**) and 7*H*-6-methoxy-9-t-butoxypyridoazepines (**13b**). In addition, 8-amino-6-methoxyquinoline was obtained in 10% yield.

The structures of the isomeric pairs were determined by ^{1}H n.m.r. spectroscopy, which indicated for the t-butoxy derivative an isomer ratio (5*H*:7*H*) of 3:1, whereas for the azepinone this ratio is reversed. Isomeric mixtures of 5*H*- and 7*H*-pyridoazepines have been obtained on other occasions,[2,7] and the parameters which determine their relative stability are being investigated. It appears that isomerisation is promoted by strong base as we have found that with sodamide in liquid ammonia, the 6,9-dimethoxy-5*H*-pyridoazepine (**4a**) is isomerised quantitatively to the 7*H*-derivative (**13a**), most likely as the result of a base-catalysed allylic shift of the benzylic 5-proton to the more acidic 7-position.

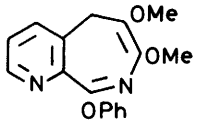
Treatment of the dimethoxypyridoazepine (**5a**) with hydrogen bromide in hot acetic acid resulted in selective monodemethoxylation to the 7-azepinone (**11**), which was identical with the product obtained from the photolysis of 6-azido-8-methoxyquinoline in t-butyl alcohol. In contrast, the 6,9-dimethoxypyridoazepine (**4a**) suffered bis-demethoxylation to the ketoazepinone (**14**).



(**14**)



(**15**) a; R = NH_2
b; R = H
c; R = N_3



(**16**)

Photolysis of 8-azido-6-methoxyquinoline in sodium phenoxide and dioxane gave 7-amino-6-methoxy-8-phenoxyquinoline (**15a**), (41%) as the sole identifiable product. Conversion of the amine into the azide (**15c**) followed by photolysis in potassium methoxide–methanol–dioxane furnished 6,7-dimethoxy-9-phenoxypyrido[2,3-*c*]azepine as a mixture of the 5*H*- (**16**) and 7*H*-isomers (**13c**). The alternative cyclisation of the nitrene onto the adjacent phenoxy group[8] was not detected.

Experimental

I.r. and mass spectra were measured on a Perkin-Elmer 257 and an AEI MS12 or MS9 spectrometer, respectively. ^{1}H and ^{13}C N.m.r. spectra were recorded on a Perkin-Elmer R32 90 MHz and Varian EM 390 (90 MHz) (at Glaxo by Dr. J. Hunt and his staff) and a Varian Associates CFT20 spectrometer, and were calibrated with reference to tetramethylsilane and deuteriochloroform, respectively, as internal standards.

Dioxane (**1l**) was purified by being heated under reflux with concentrated hydrochloric acid (15 ml) and water (100 ml) for 6 h. The cold mixture was then kept overnight over potassium hydroxide pellets (100 g). The decanted solvent was heated under reflux with sodium shavings for 3 h and finally distilled off from the sodium under dry nitrogen. THF was purified by being heated under reflux with benzophenone over sodium wire until the solution became blue.

The 9-alkoxy-5*H*-pyrido[2,3-*c*]azepines listed in Table 1 were prepared by photolysing 8-azidoquinoline in a mixture of sodium or potassium alkoxide, alcohol, and dioxane as described previously.[2]

5-Phenoxy-9H-pyrido[3,2-c]*azepine* (**3b**).—Photolysis of 5-azidoquinoline in a mixture of sodium phenoxide (1.5 M) in dioxane (80 ml) containing 15-crown-5 (0.2 g) was carried out as for 8-azidoquinoline. *5-Phenoxy-9H-pyrido*[3,2-c]*azepine* (0.2 g, 32%) was obtained by column chromatography [light petroleum (b.p. 60—80 °C) as eluant], followed by crystallisation from the same solvent, as white prisms, m.p. 85 °C (Found: C, 76.0; H, 5.1; N, 12.0. $C_{15}H_{12}N_2O$ requires C, 76.2; H, 5.1; N, 11.9%); $\nu_{max.}$(Nujol) 1 605 cm^{-1} (C=N); δ_H (90 MHz, $CDCl_3$) 8.7 (1 H, dd, 2-H), 8.1 (1 H, q, 3-H), 7.3 (6 H, m, 4-H and ArH), 6.5 (1 H, d, 7-H), 5.3 (1 H, q, 8-H), and 3.4 (2 H, d, 9-H_2); *m/z* 236 (M^+).

9-Phenoxy-5H-pyrido[2,3-c]*azepine* (**2d**), m.p. 91 °C was obtained (8.6%) in a like manner from 8-azidoquinoline (see Table 2 for data).

Attempted Nucleophilic Substitutions of 9-Methoxy-5H-pyrido[2,3-c]*azepine* (**2a**) *and 5-Methoxy-9H-pyrido*[3,2-c]*azepine* (**3a**).—The azepines (0.35 g) were heated under reflux either as neat amine, or as a solution of the amine in ethanol or an aprotic solvent, for several h. In every case a t.l.c. investigation of the reaction mixture showed in most cases unchanged pyridoazepine (subsequently recovered), and occasionally (with $PhCH_2NH_2$ and $PhNH_2$) complex mixtures.

Nucleophilic Substitution of 7,9-Dimethoxy-5H-pyrido[3,2-c]*azepine*[2] (**5a**).—(*a*) *By propylamine.* The dimethoxypyridoazepine (0.5 g) in a solution of dry DMSO (10 ml) and propylamine (5 ml), containing acetic acid (5 drops) was heated under reflux for 7 h, after which time t.l.c. (Al_2O_3–EtOAc) indicated the disappearance of the dimethoxypyridoazepine. The reaction mixture was poured into water (60 ml) and extracted with dichloromethane (3 × 50 ml), to give after drying ($MgSO_4$) and evaporation of the solvent, the product as a brown oil. Bulb-to-bulb distillation gave *7,9-dipropylamino-5H-pyrido*[3,2-c]*azepine* (**5b**) (0.25 g, 40%) as a colourless oil, b.p. 162—165 °C/0.5 mmHg (Found: C, 69.6; H, 8.55; N, 21.5. $C_{15}H_{22}N_4$ requires C, 69.7; H, 8.6; N, 21.7%); $\nu_{max.}$(Nujol) 3 320 (NH) and 1 610 cm^{-1} (C=N); δ_H (90 MHz; $CDCl_3$) 8.48 (1 H, dd, 2-H), 7.7 (1 H, dd, 4-H), 7.3 (1 H, dd, 3-H); 5.1 (1 H, s, 7-H), 4.18 (2 H, s, 5-H_2), 3.1 (4 H, t, 2 × NCH_2), 1.75—1.5 (4 H, m, 2 × NCH_2CH_2), and 1.02—0.88 (6 H, t, 2 × NCH_2CH_2Me).

(*b*) *By cyclohexylamine.* A similar reaction with cyclohexylamine (4 ml) in dry DMSO (20 ml) gave, after 10 h, *7,9-dicyclohexylamino-5H-pyrido*[3,2-c]*azepine* (**5d**) (0.35 g, 35%) which was crystallised from light petroleum as a pale-yellow solid, m.p. 177 °C (Found: C, 74.3; H, 9.2; N, 16.3. $C_{21}H_{30}N_4$ requires C, 74.5; H, 8.9; N, 16.55%); $\nu_{max.}$(Nujol) 3 320 (NH) and 1 605 cm^{-1} (C=N); δ_H (90 MHz, $CDCl_3$) 8.53 (1 H, dd, 2-H), 7.7 (1 H, dd, 4-H), 7.37 (1 H, dd, 3-H), 5.18 (1 H, s, 8-H), 4.18 (2 H, s, 5-H_2), 4.0—3.1 (4 H, br, 2NH and 2 × NCH), and 2.5—0.7 (20 H, m, cyclohexyl-CH_2); Found M^+, 338.2479. $C_{21}H_{30}N_4$ requires *M*, 338.2470.

(*c*) *By pyrrolidine.* A similar reaction of the dimethoxypyridoazepine (0.5 g) with pyrrolidine (4 ml) in DMSO (10 ml) and acetic acid (3 drops) gave after 14 h under reflux *7,9-dipyrrolidin-1-yl-5H-pyrido*[3,2-c]*azepine* (**5c**) as an oil (0.26 g, 46%). The *hydrochloride monohydrate*, m.p. 174 °C [Found: C, 61.1; H, 7.45; N, 16.7. $C_{17}H_{22}N_4 \cdot H_2O \cdot HCl$ requires C, 60.6; H, 7.5; N, 16.6%]. Free base; $\nu_{max.}$ 1 605 cm^{-1} (C=N); δ_H (90 MHz; $CDCl_3$) 8.52 (1 H, dd, 2-H), 7.7 (1 H, dd, 4-H), 7.22 (1 H, dd, 3-H), 5.2 (1 H, s, 8-H), 4.3 and 3.87 (2 H, dd, 5-H_2), 3.8—2.9 (8 H, m,

2 × CH_2NCH_2), and 2.2—1.7 (8 H, m, 2 × CH_2CH_2); *m/z* 282 (M^+).

Nucleophilic Substitution of 6,9-*Dimethoxy*-5H-*pyrido*[2,3-c]*azepine*[2] (**4a**).—(*a*) *By propylamine.* The pyridoazepine (0.4 g) was heated under reflux for 14 h with propylamine (4 ml) in dry DMSO (10 ml) and acetic acid (4 drops). On evaporation of the reaction mixture 6-methoxy-9-propylamino-5*H*-pyrido[2,3-*c*]-azepine (**4b**) was obtained as a yellow oil (0.16 g, 35%), b.p. 124 °C/0.2 mmHg; which solidified with time, m.p. 58 °C (lit.,[2] 59 °C).

(*b*) *By benzylamine.*—The dimethoxypyridoazepine (0.5 g) was heated under reflux in benzylamine (10 ml) for 8 h. Removal of the excess of amine under reduced pressure gave a residual oil, which on chromatographic separation on alumina, eluting with EtOAc–light petroleum (b.p. 60—80 °C) (4:1, v/v), gave 7-*amino*-8-*benzylamino*-6-*methoxyquinoline* (**6a**) (0.62 g, 91%) as a rapidly darkening unstable oil; $\nu_{max.}$(film) 3 450—3 400 cm^{-1} (NH and NH_2); δ_H (90 MHz; $CDCl_3$) 8.8 (1 H, dd, 2-H), 7.95 (1 H, dd, 4-H), 7.7—7.3 (5 H, m, ArH), 7.2 (1 H, dd, 3-H), 6.75 (1 H, s, 5-H), 4.35 (3 H, br s, NH and CH_2), and 4.0 (3 H, s, OMe).

(*c*) *With cyclohexylamine.* The dimethoxypyridoazepine was treated with cyclohexylamine as in reaction (*a*). Chromatographic separation of the reaction mixture on alumina gave 9-cyclohexylamino-6-methoxy-5*H*-pyrido[2,3-*c*]azepine (**4c**) (65%), m.p. 67 °C (lit.,[2] 67 °C) and 7-amino-8-cyclohexylamine-6-methoxyquinoline (**6b**) (25%), m.p. 135 °C (lit.,[2] 135 °C).

Dealkylation of 9-*Allyloxy*-5*H*-*pyrido*[2,3-c]*azepine* (**2e**).—After dry hydrogen bromide had been bubbled through a solution of 9-allyloxy-5*H*-pyrido[2,3-*c*]azepine (0.2 g) in acetic acid (10 ml) the latter was heated under reflux for 30 min. Removal of the excess of acid (Kugelrohr) gave a solid residue of 8,9-*dihydro*-5H-*pyrido*[2,3-c]*azepine*-9-*one* (**10a**) as its *hydrobromide* (0.18 g, 90%), m.p. 180 °C (Found: C, 44.6; H, 3.8; N, 11.45. $C_9H_8N_2O$·HBr requires C, 44.8; H, 3.8; N, 11.6%), $\nu_{max.}$(Nujol) 3 200—3 100 (NH^+) and 1 620 cm^{-1} (C=O); δ_H (90 MHz; [$^2H_6$]-DMSO) 12.3 (1 H, br, NH), 8.8 (1 H, dd, 2-H), 8.5 (1 H, dd, 4-H), 8.2 (1 H, dd, 3-H), 6.2 (1 H, d, 7-H) 5.6 (1 H, m, 6-H), and 3.3 (2 H, d, 5-H_2); *m/z* 240 (M^+).

The pyridoazepinone was also obtained under the same conditions from 9-ethoxy-5*H*-pyridoazepine (**2b**).

7-*Benzyloxy*-9-*methoxy*-5H-*pyrido*[3,2-c]*azepine* (**5e**).—6-Azido-8-methoxyquinoline[2] in a solution of sodium benzyl oxide (0.5 M) in dioxane and benzyl alcohol (1:1, v/v) containing 15-crown-5 (0.2 g) was photolysed under the conditions described previously. Work-up as before, gave a residual oil which on chromatographic separation [Al_2O_3; toluene–EtOAc (9.5:0.5 v/v) as eluant] gave a mixture of benzyl alcohol and the pyridoazepine (**5e**), which was separated by repeated distillation (bulb-to-bulb) to yield 7-*benzyloxy*-9-*methoxy*-5H-*pyrido*[3,2-c]*azepine* (**5e**) (0.18 g, 42%), m.p. 116 °C (Found: C, 74.6; H, 5.9; N, 8.6. $C_{17}H_{16}N_2O_2$ requires C, 74.7; H, 5.9; N, 8.6%); δ_H (90 MHz; $CDCl_3$) 8.7 (1 H, dd, 2-H), 7.74 (1 H, dd, 4-H), 7.7—7.5 (6 H, m, 3-H and ArH), 5.8 (1 H, s, 8-H), 5.04 (2 H, s, 7-OCH_2Ar), and 5.94 (3 H, s, 9-OMe); *m/z* 280 (M^+).

9-*Methoxy*-7-*t*-*butoxy*-5H-*pyrido*[3,2-c]*azepine* (**5f**).—6-Azido-8-methoxyquinoline (1.5 g) was photolysed in a solution of potassium t-butoxide (6.8 g) in t-butyl alcohol–dioxane (1:1, v/v) as described previously.[2] After irradiation (4 h) the photolysate was allowed to stand at room temperature overnight and then neutralised with t-butyl alcohol–hydrochloric acid (1:1). Chromatographic separation of the resulting oily product, using ethyl acetate–light petroleum (b.p. 60—80 °C) (1:4 v/v) as eluant gave the title *compound* (**5f**) (0.5 g, 25%) as white crystals, m.p. 137 °C (Found: C, 68.1; H, 7.3; N, 11.2. $C_{14}H_{18}N_2O_2$ requires C, 68.3; H, 7.4; N, 11.4%); δ_H (90 MHz; $CDCl_3$) 8.67 (1 H, dd, 2-H), 7.62 (1 H, dd, 4-H), 7.32 (1 H, dd, 3-H), 5.64 (1 H, s, 8-H), 4.12 (2 H, s, 5-H_2), 3.9 (3 H, s, 9-OMe), and 1.44 (9 H, s, Bu^t); *m/z* 246 (M^+).

Further elution with ethyl acetate–light petroleum (b.p. 60—80 °C) (1:1, v/v) gave 6-amino-8-methoxyquinoline (0.19 g, 7%), m.p. 168 °C (lit.,[2] 168 °C). Elution with EtOAc–EtOH (3:1, v/v) gave 6,7-*dihydro*-9-*methoxy*-5H-*pyrido*[3,2-c]*azepine*-7-*one* (**11**) (0.6 g, 42%), m.p. 194 °C (Found: C, 63.3; H, 5.2; N, 14.5. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.3; N, 14.7%) $\nu_{max.}$(Nujol) 3 250 (NH) and 1 650 cm^{-1} (CO); δ_H (90 MHz; [$^2H_6$]-DMSO) 8.68 (1 H, dd, 2-H), 8.05 (1 H, br, 6-NH), 7.88 (1 H, dd, 4-H), 7.5 (1 H, dd, 3-H), 5.68 (1 H, s, 8-H), 4.1 (2 H, d, 5-H_2), and 3.8 (3 H, s, 9-OMe); δ_C (20 MHz; [$^2H_6$]-DMSO) 167.73 (s, C-7), 159.67 (s, C-9), 149.17 (s, C-9a), 148.56 (d, C-2?), 135.39 (d, C-4?), 134.89 (s, C-4a), 124.62 (d, C-3?), 101.55 (d, C-8), and 55.67 (q, OMe). The triplet signal for the 5-CH_2 group overlapped with the solvent signal.

Photolysis of 8-*Azido*-6-*methoxyquinoline in the Presence of Potassium t-Butoxide.*—The methoxyazidoquinoline[2] (4.5 g) was photolysed for 4 h in a solution of potassium t-butoxide (6.5 g) in t-butyl alcohol–dioxane (300 ml, 1:1, v/v) containing 18-crown-6 (0.2 g) using a 400 W lamp and a Pyrex filter. The reaction mixture was then treated as in the previous experiment. Chromatographic separation on alumina, using EtOAc–light petroleum (b.p. 60—80 °C) (7:3, v/v) as eluant gave 6-*methoxy*-9-*t*-*butoxypyrido*[2,3-c]*azepine* (0.12 g, 2%) as a mixture of the 5H- (**4d**) and 7H-isomers (**13b**) in the ratio (by ^1H n.m.r.) of 3:1; δ_H (90 MHz; $CDCl_3$) 5*H*-isomer, 8.64 (dd, 2-H), 5.94 (s, 7-H), 3.1 (s, 5-H_2), and 1.64 (s, Bu^t); 7*H*-isomer, 8.33 (dd, 2-H), 5.5 (s, 5-H), 3.65 (s, 7-H_2) (5*H*- and 7*H*-isomers) 7.5 (1 H, dd, 4-H), 7.27 (1 H, dd, 3-H), and 3.5 (1 H, s, OMe).

Elution with EtOAc–light petroleum (b.p. 60—80 °C) (1:1, v/v) gave 8-amino-6-methoxyquinoline[2] (0.4 g, 10%). Elution with EtOAc–MeOH (1:1, v/v) gave 8,9-*dihydro*-6-*methoxypyrido*[2,3-c]*azepine*-9-*one* (3 g, 70%), m.p. 224 °C as a mixture of the 5*H*- (**10b**) and 7*H*-isomers (**12**) in the ratio (by ^1H n.m.r.) of 1:3 (Found: C, 63.0; H, 5.3; N, 14.7. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.3; N, 14.7%); $\nu_{max.}$(Nujol) 3 150 (NH) and 1 650 cm^{-1} (CO); δ_H (90 MHz; [$^2H_6$]-DMSO) 5*H*-isomer, 8.34 (dd, 2-H), 7.47 (dd, 4-H), 7.2 (dd, 3-H), 5.67 (d, 7-H), 3.2 (s, 5-H_2); 7*H*-isomer, 8.27 (dd, 2-H), 7.54 (dd, 4-H), 7.18 (dd, 3-H), 5.34 (s, 5-H), 3.5 (d, 7-H_2): 5*H*- and 7*H*-isomers 9.03 (1 H, br, NH), 3.67 (3 H, s, OMe).

On addition of D_2O, the NH absorption disappeared with concomitant collapse of the doublets at 5.67 [5*H*-isomer, 7-H] and 3.5 (7*H*-isomer, 7-H_2) to singlets.

Isomerisation of 6,9-*Dimethoxy*-5H-*pyrido*[2,3-c]*azepine with Potassium Amide.*—The dimethoxyazepine (0.5 g) was added to a solution of potassium (0.2 g) in an excess of liquid ammonia (25 ml) contained in a Dewar flask. The solution was stirred (magnetically) at room temperature until all the ammonia had evaporated whereupon water (25 ml) was added to the residue and the solution adjusted to pH 7 by addition of 50% hydrochloric acid. The mixture was extracted with ethyl acetate (3 × 40 ml) and the combined extracts dried ($MgSO_4$). Removal of the solvent gave an oily residue of 6,9-dimethoxy-7*H*-pyrido[2,3-*c*]azepine (**13a**) (0.48 g, 80%) identical (i.r., ^1H n.m.r., and ^{13}C n.m.r.) with a sample prepared previously.[2]

Monodemethoxylation of 7,9-*dimethoxy*-5H-*pyrido*[3,2-c]*azepine* (**5a**).—The pyridoazepine (0.5 g) was stirred at room temperature with a saturated solution of hydrogen bromide in acetic acid (10 ml). After 30 min a precipitate of 6,7-*dihydro*-9-*methoxy*-5H-*pyrido*[2,3-c]*azepin*-7-*one hydrobromide* (0.6 g,

Table 2. Analytical and spectroscopic data for 9-alkoxy- and 9-aryloxy-5*H*-pyrido[2,3-*c*]azepines

Azepine	B.p. (°C)/mmHg [m.p. °C)]	Molecular formula	Elemental analysis Required (Found) C	H	N	*m/z* (M^+)
(**2a**)	Ref. 2					
(**2b**)	112/0.5[a]	$C_{11}H_{12}N_2O$	70.2 (70.1)	6.4 (6.5)	14.9 (14.6)	(188)
(**2c**)	(63)[b]	$C_{12}H_{14}N_2O$	71.3 (71.7)	7.0 (6.9)	13.8 (13.5)	(202)
(**2d**)	(91)[c]	$C_{15}H_{12}N_2O$	76.2 (76.0)	5.1 (5.1)	11.9 (11.7)	(236)
(**2e**)	103/0.2[d]	$C_{12}H_{12}N_2O$	72.0 (72.0)	6.0 (6.1)	14.0 (14.0)	(200)

δ_H (90 MHz, $CDCl_3$) [a] 8.6 (1 H, dd, 2-H), 7.4 (2 H, m, 3- and 4-H), 6.5 (1 H, d, 7-H), 5.3 (1 H, m, 6-H), 4.5 (2 H, q, Et), 3.0 (2 H, d, 5-H_2), 1.4 (3 H, t, Et); [b] 8.67 (1 H, dd, 2-H), 7.4 (2 H, m, 3- and 4-H), 6.6 (1 H, d, 7-H), 5.4 (2 H, m, 6-H and C*H*Me_2), 2.9 (2 H, d, 5-H_2), 1.33 (6 H, d, CH*Me*$_2$); [c] 8.7 (1 H, dd, 2-H), 7.4 (7 H, m, 3- and 4-H, and ArH), 6.5 (1 H, d, 7-H), 5.3 (1 H, m, 6-H), 3.1 (2 H, d, 5-H_2); [d] 8.6 (1 H, dd, 2-H), 7.5 (2 H, m, 3-and 4-H), 6.6 (1 H, d, 7-H), 6.4 (1 H, m, OCH_2CH=CH_2), 5.4 (3 H, m, 6-H, and OCH_2CH=C*H*$_2$), 4.95 (2 H, d, OC*H*$_2$CH=CH_2), 3.0 (2 H, d, 5-H_2).

90%), m.p. 218 °C was produced. The free base (**11**), m.p. 194 °C was identical with the product from the photolysis of 6-azido-8-methoxyquinoline in t-butyl alcohol.

Demethoxylation of 6,9-*Dimethoxy*-5H-*pyrido*[2,3-c]*azepine* (**4a**).—The dimethoxypyridoazepine (0.44 g) was treated as in the previous experiment to give 5,6,7,8-*tetrahydro*-9H-*pyrido*-[2,3-c]*azepine*-6,9-*dione* (**14**) as its *hydrobromide* (0.45 g, 82%), m.p. 268—271 °C (Found: C, 42.1; H, 3.4; N, 10.85. $C_9H_8N_2O_2$·HBr requires C, 42.0; H, 3.5; N, 10.9%); $\nu_{max.}$(Nujol) 3 220 (NH), 1 720 (ketone CO), and 1 660 cm^{-1} (lactam CO); δ_H (90 MHz; [$^2H_6$]-DMSO) 8.7 (1 H, dd, 2-H), 8.62 (1 H, br, NH) 7.87 (1 H, dd, 4-H), 7.54 (1 H, dd, 3-H), 3.95 (2 H, s, 5-H_2), and 3.78 (2 H, d, 7-H_2). On deuteriation the NH absorbance at δ 8.62 disappeared and the doublet at δ 3.78 collapsed to a singlet.

Photolysis of 8-*Azido*-6-*methoxyquinoline in the Presence of Sodium Phenoxide*.—The photolysis and work-up were carried out as described in the general procedure. The residual oil so obtained (from 2 g of azide) was chromatographed on alumina using EtOAc–light petroleum (b.p. 60—80 °C) (8:1, v/v) as eluant to give firstly 8-amino-6-methoxyquinoline (0.3 g), followed by 7-*amino*-6-*methoxy*-8-*phenoxyquinoline* (**15a**) (1.3 g, 49%), m.p. 185 °C (Found: C, 72.1; H, 5.4; N, 10.5. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%); $\nu_{max.}$(Nujol) 3 370 and 3 470 cm^{-1} (NH_2); δ_H (90 MHz; $CDCl_3$) 8.63 (1 H, dd, 2-H), 8.0 (1 H, dd, 4-H), 7.33—6.63 (7 H, m, 3-H, 5-H and ArH), 4.7 (2 H, br, NH_2), and 3.97 (3 H, s, OMe); *m/z* 266 (M^+).

6-*Methoxy*-8-*phenoxyquinoline* (**15b**).—To a cold diazotised [$NaNO_2$ (0.31 g) and 4M-hydrochloric acid (20 ml)] solution of 7-amino-6-methoxy-8-phenoxyquinoline (0.51 g) was added 50% hypophosphorous acid (10 ml). The solution was stirred at room temperature for 2 h and then quenched with 4M-sodium hydroxide (25 ml). The alkaline solution was extracted with chloroform (3 × 40 ml) and the combined extracts were dried ($MgSO_4$) and evaporated to dryness to give 6-*methoxy*-8-*phenoxyquinoline* (**15b**) (0.2 g, 41%), m.p. 108 °C [light petroleum (b.p. 60—80 °C)–ethyl acetate] (Found: C, 76.3; H, 5.2; N, 5.5. $C_{16}H_{13}NO_2$ requires C, 76.5; H, 5.2; N, 5.6%); δ_H (90 MHz; $CDCl_3$) 8.83 (1 H, dd, 2-H), 8.03 (1 H, dd, 4-H), 7.5—7.07 (6 H, m, 3-H and ArH), 6.8 (1 H, d, 5-H), 6.7 (1 H, d, 7-H, $J_{5,7}$ 2 Hz), and 3.83 (3 H, s, 6-OMe); *m/z* 251 (M^+).

6,7-*Dimethoxy*-9-*phenoxy*-5H- (**16**) *and* 7H-*pyrido*[2,3-c]-*azepine* (**13c**).—7-Azido-6-methoxy-8-phenoxyquinoline (**15c**) (0.62, 60%) [$\nu_{max.}$(Nujol) 2 100 cm^{-1} (N_3); *m/z* 292 (M^+)] was prepared from the 7-amino compound (0.8 g), by diazotisation, followed by azidation with sodium azide in the presence of a sodium acetate buffer, as described previously.[2] After purification [(Al_2O_3 column with light petroleum (b.p. 40—60 °C) as eluant], the azide (0.58 g) was irradiated as in the general procedure. Work-up as previously described gave a semi-solid residue, which on chromatographic separation on Al_2O_3 [EtOAc–light petroleum (b.p. 60—80 °C) 4:1, v/v as eluant] gave 6,7-*dimethoxy*-9-*phenoxypyrido*[2,3-c]*azepine* (0.22 g, 37%), m.p. 134 °C as a 1:1 (by ^1H n.m.r.) mixture of the 5*H*- (**16**) and 7*H*-isomers (**13c**) (Found: C, 68.95; H, 5.35, N, 9.55. $C_{17}H_{15}N_2O_3$ requires C, 69.1; H, 5.1; N, 9.5%); δ_H (90 MHz; $CDCl_3$) 8.6 (1 H, dd, 2-H), 7.65 (1 H, dd, 4-H), 7.3—7.1 (6 H, m, 3-H and ArH), 6.4 (1 H, s, 7-H), 3.9 (1 H, s, 5-H), 3.86—3.76 (6 H, s, 6- and 7-OMe), and 3.65 (2 H, s, 5-H_2).

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References

1 B. Iddon, O. Meth-Cohn, E. F. V. Scriven, H. Suschitzky, and P. T. Gallagher, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 900.
2 Z. U. Khan, D. I. Patel, R. K. Smalley, E. F. V. Scriven, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2495.
3 J. Rigaudy, C. Igier, and J. Barcelo, *Tetrahedron Lett.*, 1979, 1837.
4 R. Purvis, R. K. Smalley, W. A. Strachan, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1978, 191.
5 (*a*) R. K. Smalley, 'Azepines' in 'Comprehensive Heterocyclic, Chemistry,' ed. W. Lwowski, Pergamon Press, Oxford, 1984, vol. 7, p. 514; (*b*) p. 495.
6 F. Hollywood, Z. U. Khan, E. F. V. Scriven, R. K. Smalley, H. Suschitzky, D. R. Thomas, and R. Hull, *J. Chem. Soc., Perkin Trans. 1*, 1982, 431.
7 D. I. Patel and R. K. Smalley, unpublished results.
8 P. A. S. Smith, B. B. Brown, R. K. Putney, and R. F. Reinisch, *J. Am. Chem. Soc.*, 1953, **75**, 6335.

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