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AN N → N'-BENZYL MIGRATION DURING THE FORMATION OF SOME (TRIFLUOROMETHYL)IMIDAZO[4,5-h]QUINOLINES

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SUMMARY

Photolysis of 8-azidoquinoline in dioxan-benzylamine followed by cyclisation of the resulting 7-amino-8-benzylaminoquinoline (1a) in hot trifluoroacetic acid gave a mixture of isomeric 2-(trifluoromethyl)imidazoquinolines. The structures of these isomers have been established by spectroscopic data and by alternative synthesis from unambiguously prepared 7-amino-8-benzylamino- (1a) and from 8-amino-7-benzylamino-quinoline (4c) respectively, as the expected 1-benzyl-2-(trifluoromethyl)imidazo[4,5-h]quinoline (2a) (6%) and the unexpected and rearranged 1-benzyl-2-(trifluoromethyl)imidazo[5,4-h]quinoline (3a) (52%). Examples of this N → N' alkyl rearrangement in the presence of acetic and formic acid, and with other alkylamino-groups are noted.

INTRODUCTION

The formation of o-diamines by photolysis and by thermolysis of aryl and heteroaryl azides in amine solution is well documented [1,2]. As part of a programme aimed at the synthesis of (trifluoromethyl)imidazoquinolines [3] we were interested in the photolysis of 8-azidoquinoline as a preparative route to 7,8-diaminoquinolines, and hence, by acid-cyclisation, the desired heterocycles.

Photolysis of 8-azidoquinoline in 1:1 dioxan-benzylamine solution yielded the air-sensitive diamine (1a) which, surprisingly, on cyclisation in hot trifluoroacetic acid gave two products in 6% and 51% yield. From spectroscopic and analytical data it was obvious that these products were isomeric 2-(trifluoromethyl)imidazoquinolines to which structures (2a) and (3a) were assigned provisionally.

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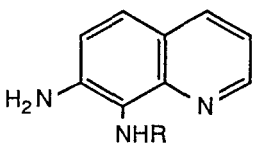
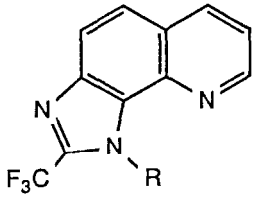
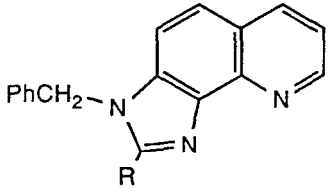
Imidazo[4,5-h]quinoline (2a) is the product arising from cyclisation of the 7,8-diamine (1a) expected [4] from decomposition of 8-azidoquinoline in benzylamine. However, the imidazo[5,4-h]quinoline (3a) must be produced from the isomeric diamine (4c), or by a benzyl rearrangement at some stage of the cyclisation. The isolation of pairs of isomeric o-diamines during azide decomposition has been reported previously [1], and their formation has mechanistic implications for the mode of decomposition of aryl azides. In fact, their occurrence has been cited [1] as evidence for the transient existence of isomeric benzazirines during azide decompositions. However, we find that in this present work, the imidazoquinoline (3a) arises not from an isomeric diamine but by an N → N'-benzyl migration during cyclisation of diamine (1a) under acid conditions.



1 a) R = CH_2Ph
b) R = n-Bu
c) R = t-Bu



2 a) R = CH_2Ph
b) R = n-Bu
c) R = H



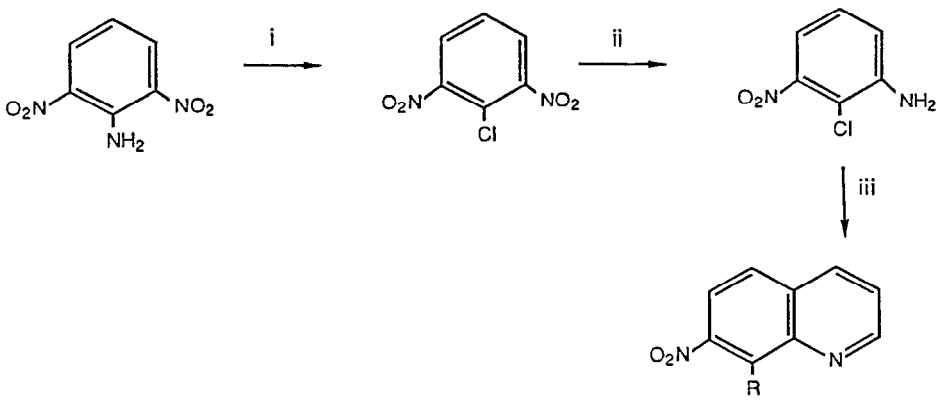
3 a) R = CF_3
b) R = H
c) R = Me

RESULTS AND DISCUSSION

In order to establish the structures of the imidazoquinolines (2a) and (3a) the parent quinoline diamines were synthesised unambiguously and their cyclisation in trifluoroacetic acid investigated. Diamine (4c) was obtained by condensing 7-chloro-8-nitroquinoline (4a) with benzylamine in hot pyridine solution followed by reduction of the nitro-amine (4b) with palladium charcoal and hydrazine. Surprisingly, 8-chloro-7-nitroquinoline (7a) had not been described previously and was synthesised as indicated in the Scheme. Condensation with benzylamine followed by reduction as before, gave the required diamine (1a), identical, by ^1H n.m.r. and i.r. spectra, to the product obtained from photolysis of 8-azidoquinoline in dioxan-benzylamine.

The ease of condensation of 8-chloro-7-nitroquinoline with benzylamine contrasted strongly with that experienced for the 7-chloro-8-nitro-isomer. The former condenses readily in boiling ethanol whereas the latter requires heating in pyridine for 24 h, there being no reaction in boiling ethanol even after 8 h. This marked difference in reactivity presumably reflects the decreased activation of halogen by the o-nitro-group which, at the 8-position, is twisted out of the ring-plane and hence is not able to stabilise successfully the transition state for nucleophilic substitution.

Analogous effects are well known for nucleophilic displacements in peri-chloronitro-naphthalenes [5] and with 8-halogenoquinolines [6].



i, $NaNO_2$, AcOH, H_2SO_4, CuCl; ii, $Ti_2(SO_4)_3$ 1 equiv.;
iii, Skraup Reaction

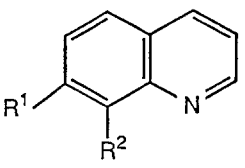
Scheme

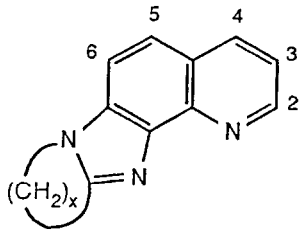
7 a) R = Cl
b) R = $NHCH_2Ph$
c) R = n-BuNH
d) R = t-BuNH

Cyclisation of the 7,8-diaminoquinoline (4c) in hot trifluoroacetic acid produced a single product which was identical (i.r., ^1H n.m.r., and mass spectrum) with the major isomer (3a) obtained previously and hence, was assigned as the 2-(trifluoromethyl)imidazo[5,4-h]quinoline. In contrast, cyclisation of 7-amino-8-benzylaminoquinoline (1a) under similar conditions, as on cyclisation of the photolysate from 8-azidoquinoline, yielded a 10:1 mixture of isomeric products, the major product being the rearranged imidazo[5,4-h]quinoline (3a) and the minor product the expected unrearranged imidazo[4,5-h]quinoline (2a).

Assignment of structure to these isomers has been made on the basis of ^1H n.m.r. and mass spectral data. Distinct differences are apparent in their proton magnetic resonance spectra. In particular, the CH_2 in the 8-benzyl[4,5-h]isomer (2a) lies close to the pyridine nitrogen lone pair and, as expected, resonates at much lower field (6.5 δ) than the corresponding CH_2-group (5.65 δ) of the -[5,4-h]quinoline (3a). In addition, chemical shift differences between the 2- and 4-, and between the 5- and 6-, protons (Table) of model imidazo[5,4-h]quinolines prepared previously, [7] appear to be diagnostic, and strongly support assignment of the imidazo[5,4-h] structure to the major product (3a). The mass spectra of isomers (2a) and (3a) are also informative. It would appear that the loss of Ph· from the [4,5-h] isomer and formation of $(M-77)^+$ as the base peak is indicative of a stabilised fragment, possibly tetracyclic ion (6). The [5,4-h] isomer, in contrast, shows an initial loss of both Ph· and $PhCH_2$· in approximately equal amounts.

We find that benzyl migration also occurs during cyclisation of the 8-(benzylamino)-quinoline (1a) in formic and in acetic acid. 1-Benzylimidazo[5,4-h]quinoline (3b), and its 3-methyl derivative (3c) respectively, are the sole products. As before, identity was established by synthesis from 8-amino-7-benzylaminoquinoline (4c) and confirmed by comparison of ^{1}H n.m.r. data (Table). The benzyl rearrangement has also been observed during cyclisation of 7-amino-8-benzylamino-6-methoxy-quinoline (9) [8] which in hot trifluoroacetic acid furnished a single product. Comparison of spectral data (Table) confirmed the structure as 1-benzyl-9-methoxy-2-(trifluoromethyl)imidazo[5,4-h]quinoline (8b).





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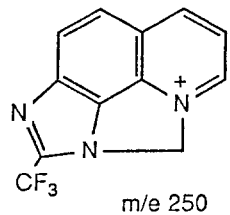


m/e 250

(6)

4 a) $R^1 = Cl$, $R^2 = NO_2$
b) $R^1 = PhCH_2NH$, $R^2 = NO_2$
c) $R^1 = PhCH_2NH$, $R^2 = NH_2$
d) $R^1 = n\text{-}BuNH$, $R^2 = NO_2$
e) $R^1 = n\text{-}BuNH$, $R^2 = NH_2$
f) $R^1 = R^2 = NHCOCF_3$

The cyclisation of the 7-(n-butylamino)- (4e), 8-(n-butylamino)- (1b) and the 8-(t-butylamino)- (1c) derivatives, prepared from the respective amines and chloronitroquinolines followed by catalytic reduction, were also studied. Cyclisation of 8-amino-7-n-butylamino-quinoline (4e) in hot trifluoroacetic acid was rapid and yielded only one product which was identified (Table) as 1-(n-butyl)-2-(trifluoromethyl)imidazo[5,4-h] quinoline (8a). Cyclisation, under similar conditions of the 8-n-butylamino- derivative (1b), however, was very slow (36 h) and gave a major product (64%), identified subsequently from spectroscopic data (Table) as unrearranged 1-n-butylamino-2-(trifluoromethyl)imidazo[4,5-h]quinoline (2b), together with a small amount (1%) of the rearranged [5,4-h] isomer (8a). In contrast, the t-butylamino derivative (1c) in hot trifluoroacetic acid under-went dealkylation and formation of the bis-trifluoroacetyl derivative (4f), which on treatment with aqueous sodium carbonate cyclised to the known [3] 2-(trifluoromethyl)imidazo[4,5-h]quinoline (2c).

Alkyl group migrations from N → N' are rare. A related example, however, has been noted [9] during attempts to benzylate 9-benzyltheophylline with benzyl bromide in DMF. Only the isomeric 7-benzyltheophylline could be isolated and the authors have demonstrated conclusively the acid-catalysed nature of the rearrangement. More recently [10] Lewis-acid catalysed benzyloxy-methyl (but not benzyl) migrations have been observed with 1,2,3-triazoles.

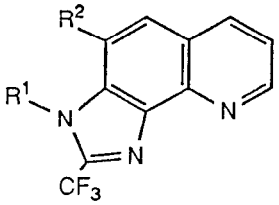
TABLE

^{1}H N.m.r. spectra of Imidazo[5,4-h]- and Imidazo[4,5-h]-quinolines
δ_H ($CDCl_3$; 60 MHz)

Compound	2-H*	4-H	5-H	6-H	δ_{2H-4H}	δ_{5H-6H}	CH_2
	(dd)	(dd)	(d)	(d)			
(5; X = 3)	8.94	8.11	7.45	7.35	0.83	0.1	-
(5; X = 4)	8.91	8.09	7.42	7.31	0.82	0.11	-
(5; X = 5)	8.94	8.12	7.50	7.38	0.82	0.12	-
(3a)[a]	9.1	8.25	7.7	7.51	0.85	0.19	5.65
(2a)[b]	8.79	8.24	7.98	7.65	0.55	0.33	6.5
(3b)[c]	9.05	8.17	7.61	7.45	0.88	0.16	5.41
(3c)[d]	9.0	8.2	7.66	7.5	0.80	0.16	5.46
(8a)[e]	9.0	8.25	7.75	7.54	0.75	0.21	4.36
(8b)[f]	8.91	8.05	6.87	-	0.86	-	5.8
(2b)[g]	8.95	8.32	7.97	7.64	0.63	0.33	5.1

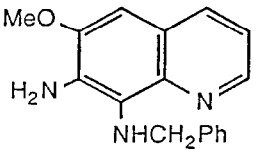
*Numbering of hydrogens for convenience only and not for nomenclature purposes. (See diagram 5).

Other resonances; [a] 7.35-6.9 (6H, m, 3-H + Ph); [b] 7.17 (5H, m, Ph), 7.4 (1H, dd, 3-H); [c] 7.31 (6H, m, 3-H + Ph), 8.1 (1H, s, CH); [d] 2.7 (3H, s, Me), 7.3 (6H, m, 3-H + Ph); [e] 7.35 (1H, dd, 3-H), 2.2 (2H, m, β-CH_2), 1.15 (2H, m, γ-CH_2), 0.95 (3H, t, Me); [f] 7.37 (1H, dd, 3-H), 3.86 (3H, s, OMe), 7.3-6.88 (7H, m, 5-H, 6-H, + Ph); [g] 7.43 (1H, dd, 3-H), 2.2 (2H, m, β-CH_2), 1.15 (2H, m, γ-CH_2), 0.97 (3H, t, Me).



8 a) R^1 = n-Bu, R^2 = H

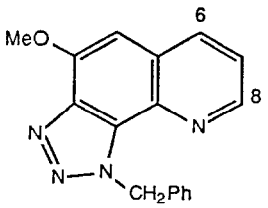
b) R^2 = $PhCH_2$, R^2 = MeO



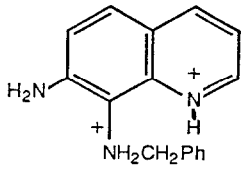
(9)

The mechanism of our alkyl migrations, however, is not yet clear. The possibility of an acid-catalysed isomerism between the two imidazoquinolines was discounted as both isomers are recovered unchanged even after prolonged (24 h) boiling in trifluoroacetic acid. It would appear, therefore, that benzyl migration is occurring during acylation/cyclisation of diamine (1a) and, presumably, involves benzyl cation migration from the initially acylated (more basic) and sterically crowded secondary 8-amino group to the less hindered (and less basic) primary 7-amino group. Such a shift will be facilitated by the proximity of the protonated pyridine ring-nitrogen.

Benzyl migration via the diprotonated species (11), either by an inter- or intra-molecular process to the less basic 7-amino group would also relieve the considerable steric and 'electronic' crowding in the dication. However, attempts to isomerise the 8-benzylamino-isomer (1a) to the 7-benzylamino-isomer (4c) in hot dilute hydrochloric acid failed. The slow cyclisation of the 8-n-butylamino derivative (1b) to the sterically congested and unrearranged product (2b) probably reflects the poorer migratory aptitude of the n-butyl cation. The opposite argument can of course explain the behaviour of the t-butyl derivative (1c).



(10)



(11)

Interestingly, the methoxydiamine (9) on diazotisation with sodium nitrite and dilute hydrochloric acid cyclised to a triazolo[4,5-h] quinoline which displayed ^1H n.m.r. data (CH_2, δ 6.40; δ H_6-δ H_8 = 0.57 p.p.m.) in close agreement with the imidazo[4,5-h] quinolines (2a, 2b) (Table) and hence was assigned the unrearranged structure (10).

EXPERIMENTAL

All compounds described herein are new unless indicated otherwise.

Photolysis of 8-Azidoquinoline in Benzylamine-dioxan

8-Azidoquinoline [4] (3 g) in a 1:1 (v/v) mixture of redistilled benzylamine and dry dioxan (300 ml) was irradiated in a Pyrex vessel using a 125 W medium pressure mercury lamp until azide decomposition, as measured by disappearance of $\nu(N_3)$ at 2120 cm^{-1}, (ca. 20 h.) was complete. The solvent mixture was removed under reduced pressure and the resultant oily residue chromatographed on alumina (Type H). Elution with light petrol (b.p. 60-80°C) - toluene (4:1 v/v) gave 7-amino-8-benzylaminoquinoline (1a) (0.58 g; 53%) as an orange oil b.p. 160°C/12 mm; ν_{max} (liquid film), 3380-3100 (NH and NH_2) cm^{-1}; δ_H $CDCl_3$; 90 MHz) 8.7 (1H, dd, 2-H), 7.9 (1H, dd, 4-H), 7.2 (8H, m, 3-H, 5-H, 6-H and C_6H_5) 5.7-5.2 (1H, bs, NH), 4.2 (2H, s, N-CH_2), 4.08 (2H, bs, NH_2).

Further elution with methanol gave only tar.

1-Benzyl-2-(trifluoromethyl)imidazo[4,5-h]quinoline (2a) and 1-benzyl-2-(trifluoromethyl)-imidazo[5,4-h]quinoline (3a)

The diamine (1a) obtained from the photolysis mixture was heated under reflux in trifluoroacetic acid (25 ml) for 2 h. The mixture was cooled, neutralised by addition of solid sodium carbonate, and then extracted with chloroform (3 x 20 ml). The chloroform extracts were combined dried over $MgSO_4$ and evaporated to give a solid residue. Chromatography of the residue on alumina (type H) using light-petrol (b.p. 60-80°)-toluene (5:1; v/v) as eluant gave 1-benzyl-2-(trifluoromethyl)imidazo[4,5-h]quinoline (2a) (0.26 g; 6%) which crystallised as white granules from light petrol (b.p. 60-80°C), m.p. 112°C. (Found; C, 66.0; H, 3.6; N, 12.6. $C_{18}H_{12}F_3N_3$ requires C, 66.05; H, 4.0; N, 12.9%); ν_{max} (nujol) 1200-1100 (CF_3) cm^{-1}; For NMR data see Table; m/e 327 (M^+) (78%), 250 (100%), 236 (2%), 141 (3%), 114 (5%), 71 (1%).

Further elution with toluene-ethyl acetate (4:1 v/v) gave 1-benzyl-2-(trifluoromethyl)-imidazo[5,4-h]quinoline (3a) (1.86 g; 51%), which crystallised as white granules from ethanol, m.p. 226°C. (Found: C, 66.05; H, 3.7; N, 12.85. $C_{18}H_{12}F_3N_3$ requires C, 66.05; N, 4.0; N, 12.9%); ν_{max} (nujol) 1200-1100 (CF_3) cm^{-1}; (For NMR data see Table); m/e 327 (M^+) (28%), 250 (28%), 236 (20%), 141 (18%), 114 (20%), 71 (100%).

Further elution with MeOH-EtOAc (1:1; v/v) gave only tars.

7-Benzylamino-8-nitroquinoline (4b)

A solution of 7-chloro-8-nitroquinoline [11] (4.17 g; 0.02 mol) and benzylamine (4.5 g; 0.042 mol) in pyridine (80 ml) was heated under reflux for 24 h. The excess of pyridine (60 ml) was removed under reduced pressure and the residue poured onto ice-water to yield the nitroaminoquinoline as an orange solid. Filtration of the aqueous mixture and crystallisation of the residue from ethanol gave 7-benzylamino-8-nitroquinoline (3.75 g; 71%) as orange needles, m.p. 188°C (Found: C, 68.7; H, 4.5; N, 14.9. $C_{16}H_{13}N_3O_2$ requires C, 68.8; H, 4.7; N, 15.05%); ν_{max} (nujol) 3400 (NH), 1530 and 1350 (NO_2) cm^{-1}; δ_H (d^6-DMSO; 60 MHz) 8.8 (1H, dd, 2-H), 8.25 (1H, dd, 4-H), 7.9 (1H, d, 6-H), 7.37 (7H, m, 3-H, 5-H, C_6H_5), 4.6 (2H, d, NCH_2).

Prepared similarly was 7-n-butylamino-8-nitroquinoline (4d) (89%) orange needles from ethanol, m.p. 82°C. (Found: C, 64.0; H, 6.1; N, 17.1. $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.2; N, 17.1%). δ_H ($CDCl_3$; 60 MHz) 8.98 (H, dd, 2-H), 8.0 (1H, dd, 4-H), 7.76 (1H, d, 5-H), 7.17 (1H, dd, 3-H), 7.13 (1H, d, 6-H), 7.0 (1H, bs, NH), 3.4 (2H, q, NCH_2-), 1.8-1.1 (4H, m, CH_2CH_2), 0.84 (3H, t, CH_3).

8-Amino-7-benzylaminoquinoline (4c)

To a solution of 7-benzylamino-8-nitroquinoline (2.63 g; 0.01 mol) in ethanol (250 ml) containing 10% Pd-C (0.2 g) under reflux, was added dropwise, over 15 min. hydrazine hydrate (0.64 g, 0,01 mol). The solution was boiled for a further 0.5 h. then cooled, filtered and the filtrate evaporated to dryness. 8-Amino-7-benzylaminoquinoline was obtained as a yellow solid (2.0 g; 87%), m.p. 95-97°C; ν_{max} (nujol) 3100-3080 (NH, NH_2); δ_H ($CDCl_3$; 90 MHz) 8.7 (1H, dd, 2-H), 7.95 (1H, d, 4-H), 7.2 (8H, m, 3-H, 5-H, 6-H, and C_6H_5), 4.45 (2H, s, NCH_2), 4.08 (3H, bs, NH and NH_2).

8-Chloro-7-nitroquinoline (7a)

A mixture of 2-chloro-3-nitroaniline [12] (4 g), arsenic pentoxide (3 g), glycerol (5 ml) and sulphuric acid (d, 1.84; 4 ml) contained in two-necked flask fitted with thermometer and condenser were heated at 135°C (oil-bath) for 4 h. The reaction mixture was cooled, water (100 ml) added, and the mixture extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried ($MgSO_4$), boiled with decolourising carbon (2 min.) then filtered: Evaporation of the filtrate gave 8-chloro-7-nitroquinoline (3.14 g; 65%) which crystallised from ethyl acetate - light petrol (b.p. 60-80°C) (1:4, v/v) as pale-yellow needles, m.p. 170°C. (Found: C, 55.7; H, 2.5; N, 7.1. $C_9H_5ClN_2O_2$ requires C, 55.55; H, 2.6; N, 7.2%) δ_H ($CDCl_3$, 60 MHz) 9.3 (1H, dd, 2-H), 8.73 (1H, dd, 4-H), 8.33 (1H, d, 6-H), 7.94 (1H, d, 5-H), 7.75 (1H, dd, 3-H).

8-Benzylamino-7-nitroquinoline (7b)

A solution of 8-chloro-7-nitroquinoline (1.04 g; 0.005 mol) and benzylamine (1.12 g; 0.0105 mol) in ethanol (100 ml) was heated under reflux for 6 h. The solvent was removed under reduced pressure, the residue washed with water and dried. 8-Benzylamino-7-nitroquinoline crystallised from ethanol (1.2 g, 92%) as orange plates, m.p. 119°C. (Found: C, 68.6; H, 4.55; N, 15.0. $C_{16}H_{13}N_3O_2$ requires C, 68.8; H, 4.7; N, 15.05%); ν_{max} (nujol) 3230 (NH), 1530 and 1350 cm^{-1} (NO_2); δ_H (d^6-acetone; 60 MHz) 8.8 (1H, dd, 2-H); 8.3 (1H, dd, 4-H), 8.03 (1H, d, 6-H), 7.68 (1H, d, 3-H), 7.13 (1H, d, 5-H), 5.24 (2H, d, CH_2).

Prepared similarly were a) 8-n-butylamino-7-nitroquinoline (7c) (87%) which crystallised from ethanol as an orange solid, m.p. 67°C (Found: C, 63.5; H, 6.15; N, 17.2. $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.2; N, 17.1%) δ_H ($CDCl_3$; 60 MHz) 9.2 (1H, t, NH), 8.69 (1H, dd, 2-H), 7.97 (1H, d, 6-H), 7.92 (1H, dd, 4-H), 7.4 (1H, dd, 3-H), 6.75 (1H, d, 5-H), 3.98 (2H, q, N-CH_2), 1.8-1.1 (4H, m, -CH_2CH_2-), 0.98 (3H, t, CH_3); b) 8-t-butylamino-7-nitroquinoline (7d) (89%) orange crystals from ethanol, m.p. 95°C. (Found: C, 63.8; H, 6.2; N, 17.1 $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.2; N, 17.1%); δ_H ($CDCl_3$; 60 MHz) 9.17 (1H, s, NH), 9.14 (1H, dd, 2-H), 8.47 (1H, dd, 4-H), 8.21 (1H, dd, 6-H), 7.84 (1H, dd, 3-H), 7.38 (1H, d, 5-H), 1.71 (9H, s, Me_3C).

7-Amino-8-benzylaminoquinoline (1a)

To a rapidly and efficiently stirred solution of 8-benzylamino-7-nitroquinoline (2.79 g; 0.1 mol) in acetic acid (100 ml) was added portionwise over 1 h, reduced iron powder (3 g). During addition the reaction temperature was maintained at 10°C, and the mixture was then left to stir at room temperature for 1 h. Neutralisation of the reaction mixture with sodium carbonate followed by extraction with chloroform (3 x 25 ml) gave, after drying ($MgSO_4$) and evaporation of the combined extracts, 7-amino-8-benzylaminoquinoline (1.8 g, 72%) which was identical (i.r. and ^1H n.m.r.) to the product obtained from photolysis of 8-azidoquinoline.

Cyclisation of 7-amino-8-benzylaminoquinoline (1.25 g; 0.05 mol) in hot trifluoroacetic acid (12 ml) gave a mixture of the imidazo[4,5-h]quinoline (2a) (0.11 g; 7%) and the imidazo[5,4-h]quinoline (3a) (0.99 g, 60%) (separated, as previously, by column chromatography).

Cyclisation of 8-amino-7-benzylaminoquinoline in hot trifluoroacetic acid gave imidazo[5,4-h]quinoline (3a) as the sole product. Similarly by heating 7-amino-8-benzylaminoquinoline (0.5 g) in formic acid (6 ml) for 2 h., and in acetic acid (6 ml) for 2 h., were obtained respectively. a) 1-Benzylimidazo[5,4-h]quinoline (3b) (0.51 g; 91%) as white granules from aqueous ethanol, m.p. 185°C (Found: C, 78.7; H, 5.0; N, 16.2. $C_{17}H_{13}N_3$ requires C, 78.7; H, 5.05; N, 16.2%); (see

Table for NMR data), and b) 1-Benzyl-2-methylimidazo[5,4-h]quinoline (3c) (0.58 g; 91%), as white needles from aqueous ethanol m.p. 84°C (Found: C, 79.6; H, 5.55; N, 15.1. $C_{18}H_{15}N_3$ requires C, 79.1; H, 5.5; N, 15.4%) - (see Table for NMR data).

Diaminoquinolines (4e), (1b), and (1c)

A solution of the aminonitroquinoline (0.002 mol) in ethanol (ca. 80 ml) was reduced at atmospheric pressure with hydrogen and 10% Pd-C (0.1 g). The reduction mixture was filtered and the solvent evaporated to give the diamines [4] as dark oils which were purified by vacuum distillation.

1-n-Butyl-1-(trifluoromethyl)imidazo[5,4-h]quinoline (8a)

The imidazoquinoline was prepared and isolated as directed for the 1-benzyl derivative by heating in trifluoroacetic acid for 2 h. 1-n-Butyl-2-(trifluoromethyl)imidazo[5,4-h]quinoline (87%), after chromatography, crystallised from ethanol, m.p. 164°C, (Found: C, 61.7; H, 4.7; N, 14.2. $C_{15}H_{14}F_3N_3$ requires C, 61.4; H, 4.8; N, 14.3%). (see Table for NMR data).

Treatment of 7-amino-8-n-butylaminoquinoline in boiling trifluoroacetic acid for 36 h gave a mixture of imidazoquinolines which were separated by column chromatography as directed previously for the benzyl isomers. 1-n-Butyl-2-(trifluoromethyl)imidazo[4,5-h]quinoline (2b) was obtained in 64% yield, m.p. 164°C, along with 1-n-Butyl-2-(trifluoromethyl)imidazo[5,4-h]-quinoline (8a) (2%) which crystallised from light petrol (b.p. 60-80°C) m.p. 88°C (Found: C, 61.7; H, 4.8; N, 14.3. $C_{15}H_{14}F_3N_3$ requires, C, 61.4; H, 4.8; N, 14.3%) (See Table for NMR data).

1-Benzyl-9-methoxy-2-(trifluoromethyl)imidazo[5,4-h]quinoline (8b)

A solution of 7-amino-8-benzylamino-6-methoxyquinoline (0.56 g; 0.002 mol) in trifluoro-acetic acid (8 ml) was heated under reflux for 10 h. The solution was cooled, neutralised with sodium carbonate, and the mixture extracted with chloroform (3 x 20 ml). The combined chloroform extracts were dried ($MgSO_4$), and evaporated to give the product as a grey residue which was purified by column chromatography on alumina (type H). Elution with light petrol (b.p. 60-80°C) - ethyl acetate afforded 1-benzyl-9-methoxy-2-(trifluoromethyl)imidazo[5,4-h]quinoline (0.37 g; 53%), as white granules from aqueous ethanol, m.p. 190°C. (Found: C, 63.6; H, 4.0; N, 11.85. $C_{19}H_{14}F_3N_3O$ requires C, 63.9; H, 3.9; N, 11.8%) (See Table for NMR data); m/z 357 (M^+).

Cyclisation of 8-t-butylamino-7-aminoquinoline

The diamine was heated under reflux in trifluoroacetic acid for 6 h. Work-up as in the previous example gave 7,8-bis-(trifluoroacetylamino) quinoline [3] (4f) in 71% yield.

1-Benzyl-4-methoxytriazolo[4,5-h]quinoline (10)

To a cooled (0 °C) solution of 7-amino-8-benzylamino-6-methoxyquinoline in concentrated hydrochloric acid (10 ml) and water (15 ml) was added dropwise with stirring a solution of sodium nitrite (0.13 g) in water (10 ml).

The solution was stirred for 30 min., then neutralised with sodium carbonate, and the mixture extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give 1-benzyl-4-methoxytriazolo[4,5-h]quinoline (0.18 g, 58%) as a solid residue which crystallised from light petrol (b.p. 80-100°C), m.p. 141°C (Found: C, 70.3; H, 5.0; N, 19.2. $C_{17}H_{14}N_4O$ requires C, 70.3; H, 4.9; N, 19.3%); δ_H ($CDCl_3$: 60 MHz) 8.94 (1H, dd, 8-H), 8.34 (1H, dd, 6-H), 7.67-7.1 (6H, m, 7-H + Ph), 6.63 (1H, s, 5-H), 6.37 (2H, s, CH_2), 3.05 (3H, s, OMe).

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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.*, **18** (1979) 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 I.G. Moores, R.K. Smalley, and H. Suschitzky, *J. Fluorine Chem.*, **20**. (1982) 573.

4 F. Hollywood, B. Nay, E.F.V. Scriven, H. Suschitzky, Z.V. Khan, and R. Hull, *J. Chem. Soc., Perkin Trans. 1*, (1982). 421.

5 E. Berliner, M.J. Quinn, and P.J. Edgerton, *J. Am. Chem. Soc.*, 72 (1950) 5305.

6 R.K. Smalley 'Chemistry of Heterocyclic Compounds', ed., G. Jones, J. Wiley and Sons, London, **32**. (1977) 531.

7 H. Suschitzky and M.E. Sutton, *J. Chem. Soc.*, (C) (1968) 3058. Unfortunately, these compounds were named erroneously (Table 5) as the [4,5-h] isomers.

8 D.I. Patel, E.F.V. Scriven, R.K. Smalley, H. Suschitzky, and D.I.C. Scopes, *J. Chem. Soc., Perkin Trans. 1*, (1985) 1911.

9 J.H. Lister, *Heterocycles*, **6**, (1977) 383.

10 J.H. Jones and P.B. Wyatt, *J. Chem. Research* (M), (1987) 3173; (S) p. 396.

11 A.K. Sen, N.K Ray, and U.P. Basu, *J. Sci. Ind. Res. India*, **11B** (1952) 322.

12 F.D. Gunstone and S.H. Tucker, *J. Appl. Chem.*, **2** (1952) 204.