A New Synthesis of 1-Arylpiperidin-4-ols

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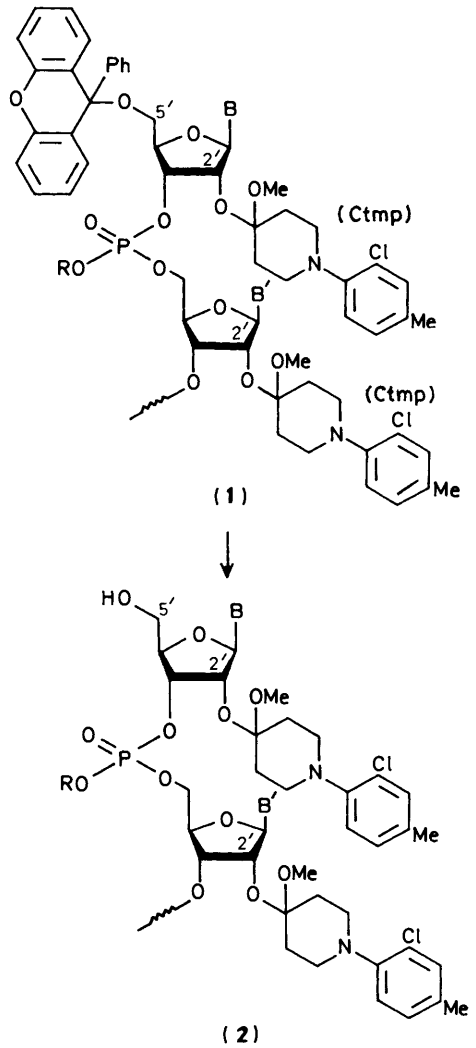
1,5-Dichloropentan-3-ol (**8**), which is readily prepared from the corresponding ketone (**7**), reacts with 2-fluoro-, 4-methyl-, 2-chloro-, 3-chloro-, 4-chloro-, and 3-chloro-4-methyl-anilines in the presence of potassium carbonate and sodium iodide in dimethylformamide at 100 °C to give 1-(2-fluorophenyl)-, 1-(4-tolyl)-, 1-(2-chlorophenyl)-, 1-(3-chlorophenyl)-, 1-(4-chlorophenyl)-, and 1-(3-chloro-4-tolyl)-piperidin-4-ols, respectively. The (2-fluorophenyl)-, (4-tolyl)-, and (4-chlorophenyl)-piperidin-4-ols are converted into the corresponding 1-arylpiperidin-4-ones. 1-(2-Fluorophenyl)piperidin-4-one (**10**; R^1 = F, R^2 = R^3 = H) is converted into its dimethyl acetal (**12**) and thence into the enol ether (**13**).

We have recently introduced the 1-(2-chloro-4-tolyl)-4-methoxypiperidin-4-yl (Ctmp) group[1,2] [as in (1)] for the protection of the 2′-hydroxy functions of ribonucleoside residues in rapid oligoribonucleotide synthesis.[3] The Ctmp group has been specially designed[1,2] so that it is virtually unaffected by the relatively drastic acidic conditions required to remove the 5′-terminal protecting group [as in the conversion of (**1**) into (**2**), Scheme 1] in rapid oligonucleotide synthesis,[3] and yet is easily removable under mild conditions of acidic hydrolysis [*e.g.* pH 2.0—2.5, room temperature] in the final unblocking step.

The possibility of being able to use the Ctmp protecting group depends on the availability and indeed accessibility of 1-(2-chloro-4-tolyl)piperidin-4-one (**6**; R = Me). Gallagher and Mann have reported[4] a three-step procedure for the synthesis of 1-phenylpiperidin-4-one (**5**; R = H) which involves (Scheme 2) the Cu^I-catalysed reaction between aniline and ethyl acrylate, Dieckmann cyclisation of the product (**4**; R = H) obtained, followed by hydrolysis and decarboxylation. As an aryl halogen substituent appears[1] to be required if a piperidinyl protecting group is to have the desired hydrolysis properties, attempts were made to convert 4- and 3-chloroanilines into 1-(4-chlorophenyl)piperidin-4-one (**5**; R = Cl) and the corresponding 3-chlorophenyl derivative. These attempts were unsuccessful as it proved possible[5] only to monoalkylate the presumably less nucleophilic chloroanilines with ethyl acrylate under the above conditions (Scheme 2, step i). 1-(2-Chloro-4-tolyl)piperidin-4-one (**6**; R = Me) was prepared[1] indirectly by the chlorination (Scheme 2) of 1-(4-tolyl)piperidin-4-one (**5**; R = Me), which was itself prepared from 4-toluidine by Gallagher and Mann's procedure.[4]

Although the Ctmp group has proved to be very satisfactory for the protection of the 2′-hydroxy functions of ribonucleoside residues in oligoribonucleotide synthesis,[3] the above procedure[1] (Scheme 2) for the preparation of 1-(2-chloro-4-tolyl)piperidin-4-one (**6**; R = Me) is rather long and not especially efficient. As it seemed likely to us that piperidinyl protecting groups, derived from other halogenated 1-arylpiperidin-4-ones, might be equally suitable for 2′-protection in rapid oligoribonucleotide synthesis, we believed that it was a matter of considerable importance to develop a general procedure for the conversion of primary aromatic amines (including halogeno anilines) into the corresponding 1-arylpiperidin-4-ones. Three separate reports in the literature encouraged us to undertake such a study. First, aniline and a variety of substituted primary aromatic amines were known[6] to react with 1,5-dibromopentane to give 1-arylpiperidines in good yields. Secondly, it was reported[7] that 1,5-dichloropentan-3-ol (**8**) could readily be prepared from crude 1,5-dichloropentan-3-one[8] (**7**). Finally, it was known[9] that 1-arylpiperidin-4-ols (**9**) could be converted into the corresponding ketones (**10**) by Moffatt oxidation.[10]

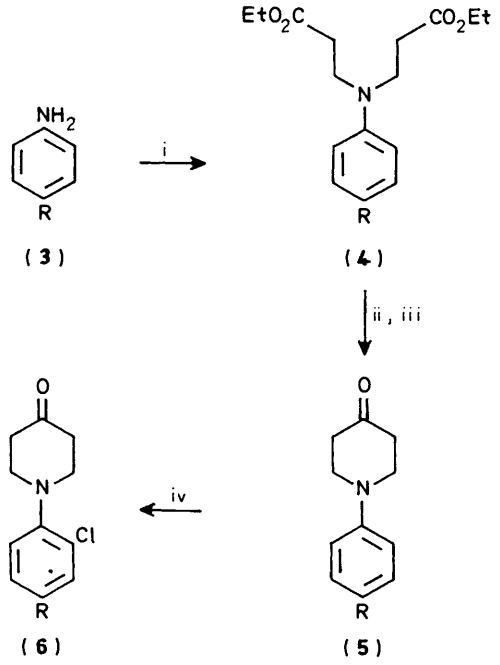


Scheme 1.

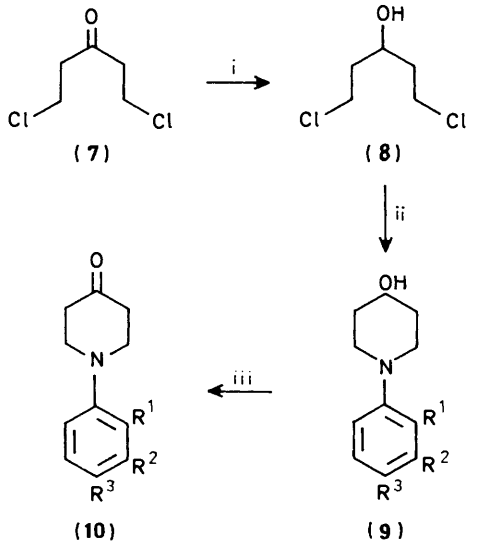
1,5-Dichloropentan-3-one (**7**) was obtained, as previously

Table. Preparation of 1-arylpiperidin-4-ols (**9**)

Entry no.	Substituent			Reaction time (h)	Yield (%)	M.p. (b.p.) (°C)
	R^1	R^2	R^3			
1	F	H	H	1.0	76	51
2	H	H	Me	1.5	82	83
3	Cl	H	H	5.0	48	(136—142/0.22 mmHg)
4	H	Cl	H	3.0	66	(148—152/0.07 mmHg)
5	H	H	Cl	1.0	77	99—101
6	H	Cl	Me	2.0	64.5	56—57



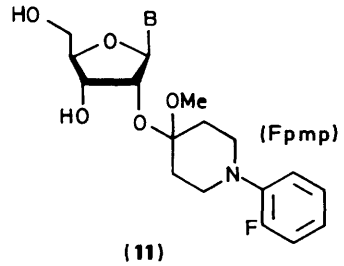
Scheme 2. *Reagents:* i, CH_2=$CHCO_2Et$, CuCl, AcOH; ii, NaH, benzene; iii, conc. HCl–water (1:4 v/v); iv, *N*-chlorosuccinimide, CH_2Cl_2



Scheme 3. *Reagents:* i, $NaBH_4$, EtOH, H_2O; ii, 2,3,4-$R^1R^2R^3C_6H_2NH_2$, K_2CO_3, NaI, Me_2NCHO, 100 °C; iii, $C_6H_{11}N$=C=NC_6H_{11}, CF_3CO_2H, C_5H_5N, Me_2SO, C_6H_6

reported,[8] as a dark brown oil in virtually quantitative yield, by the aluminium chloride-catalysed acylation of ethylene with 3-chloropropionyl chloride. The latter crude material (**7**) was reduced (Scheme 3) with sodium borohydride by a slight modification of Kelson and Robson's procedure[7] to give 1,5-dichloropentan-3-ol (**8**) in 76% overall yield, based on 3-chloropropionyl chloride. The reduction was carried out on a relatively large scale starting from crude (**7**) (200 g). When (**8**) was heated with 2-fluoroaniline (*ca.* 1.1 mol equiv.), potassium carbonate (*ca.* 2.2 mol equiv.), and sodium iodide (*ca.* 0.55 mol equiv.) in dimethylformamide (DMF) (Scheme 3 and Table, entry no. 1) under nitrogen at 100 °C for 1 h and the products worked up and distilled, 1-(2-fluorophenyl)piperidin-4-ol (9; R^1 = F, R^2 = R^3 = H) was obtained as a crystalline solid in 76% isolated yield. The *N*-(4-tolyl), *N*-(2-chlorophenyl), *N*-(3-chlorophenyl), *N*-(4-chlorophenyl), and *N*-(3-chloro-4-tolyl) derivatives of piperidin-4-ol (entries nos. 2–6, respectively) were all prepared in the same way. The reaction time for the preparation of the 2-chlorophenyl derivative (9; R^1 = Cl, R^2 = R^3 = H) (entry no. 3) was 5 h and the isolated yield was only 48%. Presumably this rather unsatisfactory result was due, at least in part, to steric hindrance. 1-(4-Tolyl)piperidin-4-one (9; R^1 = R^2 = H, R^3 = Me) was also prepared in 61% yield by allowing 4-toluidine to react with (**8**) in the presence of lithium di-isopropylamide in tetrahydrofuran (THF) at −70 °C. The latter procedure is less convenient and apparently less efficient than the above procedure involving potassium carbonate and sodium iodide in DMF.

1-(2-Fluorophenyl)-, 1-(4-tolyl)-, and 1-(4-chlorophenyl)-piperidin-4-ols [(9; R^1 = F, R^2 = R^3 = H), (9; R^1 = R^2 = H, R^3 = Me), and (9, R^1 = R^2 = H, R^3 = Cl), respectively] were converted into the corresponding 1-arylpiperidin-4-ones [(**10**; R^1 = F, R^2 = R^3 = H), (**10**; R^1 = R^2 = H, R^3 = Me), and (**10**, R^1 = R^2 = H, R^3 = Cl)] in 67.5, 80, and 82% isolated yields, respectively, by Moffatt oxidation[10] using a slight modification of Taylor and Skotnicki's procedure[9] (Scheme 3 and Experimental). The oxidation of the 2-fluorophenyl derivative (9; R^1 = F, R^2 = R^3 = H) was carried out on a *ca.* 0.26 mol scale using *N*,*N*′-dicyclohexylcarbodi-imide (DCC) (*ca.* 2.0 mol equiv.). It proved to be convenient during work-up to extract the products with 4M hydrochloric acid in order to destroy the excess of DCC. As indicated above, 1-(4-tolyl)-piperidin-4-one (**10**; R^1 = R^2 = H, R^3 = Me) is required in the preparation of 2′-*O*-(Ctmp)-protected ribonucleoside derivatives.[1] We have since found[11] that the 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl (Fpmp) [as in (11)] has virtually the same acidic hydrolysis properties as the Ctmp protecting group. As 1-(2-fluorophenyl)piperidin-4-one (**10**; R^1 = F, R^2 = R^3 = H) is more readily accessible than 1-(2-chloro-4-tolyl)-piperidin-4-one (**6**; R = Me), we intend in future to base our approach to rapid polyribonucleotide synthesis on the use of 2′-*O*-(Fpmp)-protected ribonucleoside derivatives (11). For this reason compound (**10**; R^1 = F, R^2 = R^3 = H) was heated, under reflux, with slight excesses of both trimethyl orthoformate



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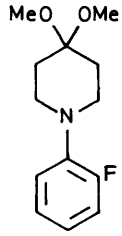

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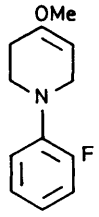

(13)

and toluene-4-sulphonic acid monohydrate in methanol solution, to give 1-(2-fluorophenyl)-4,4-dimethoxypiperidine (**12**). When the latter compound (**12**), which was isolated as a crystalline solid in 75% yield, was heated with a catalytic amount of toluene-4-sulphonic acid at 150 °C for 90 min under reduced pressure, 1-(2-fluorophenyl)-4-methoxy-1,2,5,6-tetrahydropyridine (**13**), the reagent required for the introduction of the Fpmp protecting group, was obtained. This enol ether (**13**) has since been used successfully[11] in the preparation of the protected ribonucleoside building blocks required in polyribonucleotide synthesis.

Experimental

^{1}H and ^{13}C N.m.r. spectra were measured with a Bruker WM 250 spectrometer; tetramethylsilane was used as an internal standard. DMF and dimethyl sulphoxide (DMSO) were dried by heating at 100 °C with calcium hydride and then distilled under reduced pressure; benzene was dried over sodium metal and then distilled.

1,5-*Dichloropentan*-3-*ol* (**8**).—A solution of sodium borohydride (24.73 g, 0.65 mol) in water (100 ml) was added dropwise to a stirred solution of crude 1,5-dichloropentan-3-one (**7**) (209.5 g, 1.35 mol) in ethanol (1 l), maintained below −5 °C (ice–salt bath). After the reaction had proceeded for a further period of 2 h, ice–water (1 l) was added, and the products were extracted with chloroform (3 × 700 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Distillation of the residual oil gave 1,5-*dichloropentan*-3-*ol* (162.2 g, 76% for the two steps starting from 3-chloropropionyl chloride), b.p. 62 °C/0.06 mmHg (lit.,[7] 64—70 °C/0.1 mmHg); $\delta_H(CDCl_3)$ 1.94 (4 H, m), 3.72 (4 H, m), and 4.14 (1 H, m); $\delta_C(CDCl_3)$ 39.59, 41.56, and 65.91.

1-(2-*Fluorophenyl*)*piperidin*-4-*ol* (**9**; R^1 = F, R^2 = R^3 = H).—2-Fluoroaniline (100 g, 0.90 mol), 1,5-dichloropentan-3-ol (128.5 g, 0.82 mol), anhydrous potassium carbonate (248.8 g, 1.80 mol), sodium iodide (67.45 g, 0.45 mol), and dry DMF (350 ml) were heated at 100 °C, in an atmosphere of nitrogen, for 1 h. The cooled products were partitioned between ether (500 ml) and water (200 ml), and the aqueous layer was back-extracted with ether (2 × 200 ml). The combined organic layers were then washed with saturated brine (5 × 200 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Distillation of the residue gave a pale yellow oil (122.3 g, 76%), b.p. 102—108 °C/0.02 mmHg. Recrystallization of this material from light petroleum (b.p. 40—60 °C) gave the *title compound* (**9**; R^1 = F, R^2 = R^3 = H) (Found: C, 67.4; H, 7.2; N, 7.2. $C_{11}H_{14}FNO$ requires C, 67.7; H, 7.2; N, 7.2%) as colourless crystals, m.p. 51 °C; $\delta_H[(CD_3)_2SO]$ 1.53 (2 H, m), 1.84 (2 H, m), 2.74 (2 H, m), 3.23 (2 H, m), 3.60 (1 H, m), 4.69 (1 H, d, *J* 4.0 Hz), and 6.9—7.15 (4 H, m); $\delta_C[(CD_3)_2SO]$ 34.39, 48.22, 48.27, 65.65, 115.61, 115.94, 119.37, 119.42, 121.67, 121.99, 124.64, 124.67, 140.30, 140.44, 153.01, and 156.69.

1-(4-*Tolyl*)*piperidin*-4-*ol* (**9**; R^1 = R^2 = H, R^3 = Me).—(a) 4-Toluidine (3.10 g, 28.9 mmol), 1,5-dichloropentan-3-ol (4.13 g, 26.3 mmol), potassium carbonate (8.0 g, 57.9 mmol), sodium iodide (2.17 g, 14.5 mmol), and DMF (10 ml) were heated together at 100 °C for 90 min and were then worked up as above. The crude products were not distilled but were crystallized from light petroleum (b.p. 40—60 °C) to give the *title compound* (**9**; R^1 = R^2 = H, R^3 = Me) (4.16 g, 82%) (Found: C, 75.2; H, 8.8; N, 7.3. $C_{12}H_{17}NO$ requires C, 75.35; H, 9.0; N, 7.3%) as colourless crystals, m.p. 83 °C; $\delta_H[(CD_3)_2SO]$ 1.45 (2 H, m), 1.80 (2 H, m), 2.18 (3 H, s), 2.75 (2 H, m), 3.43 (2 H, m), 3.59 (1 H, m), 4.65 (1 H, d, *J* 3.6 Hz), 6.81 (2 H, d, *J* 8.6 Hz), and 6.99 (2 H, d, *J* 8.4 Hz); $\delta_C[(CD_3)_2SO]$ 19.96, 33.87, 46.95, 66.05, 115.96, 127.00, 129.26, and 148.98.

(b) A hexane solution of butyl-lithium (2.6M; 12.25 ml, 31.9 mmol) was added to a cooled (acetone–solid CO_2), stirred anhydrous solution of di-isopropylamine (4.46 ml, 31.8 mmol) in THF (25 ml). A solution of 4-toluidine (1.50 g, 14.0 mmol) in THF (5 ml) was then added, and the resulting solution was allowed to cool to −70 °C. A solution of 1,5-dichloropentan-3-ol (1.00 g, 6.37 mmol) in THF (5 ml) was then added dropwise with stirring, and the products were allowed to warm to room temperature. After neutralization with glacial acetic acid, the resulting solution was evaporated under reduced pressure, the residue was dissolved in ether (50 ml), and the solution was extracted with saturated brine (2 × 50 ml). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the residue was chromatographed on silica gel to give 1-(4-tolyl)piperidin-4-ol (0.75 g, 61%), identical (t.l.c., n.m.r., and m.p. after recrystallization) with the material obtained as described above under (a).

1-(2-*Chlorophenyl*)*piperidin*-4-*ol* (**9**; R^1 = Cl; R^2 = R^3 = H).—2-Chloroaniline (20 g, 0.157 mol), 1,5-dichloropentan-3-ol (22.5 g, 0.143 mol), potassium carbonate (43.4 g, 0.314 mol), sodium iodide (11.84 g, 79 mmol), and DMF (100 ml) were heated together at 100 °C for 5 h and were then worked up as above. Distillation of the residue gave an orange oil (14.57 g, 48%), b.p. 136—142 °C/0.22 mmHg), Redistillation of this material gave the *title compound* (**9**; R^1 = Cl, R^2 = R^3 = H) (Found: M^+ at *m/z* 211.0768. $C_{11}H_{14}{}^{35}ClNO$ requires *M*, 211.0764) as a pale yellow liquid; $\delta_H[(CD_3)_2SO]$ 1.56 (2 H, m), 1.86 (2 H, m), 2.71 (2 H, m), 3.17 (2 H, m), 3.62 (1 H, m), 4.69 (1 H, d, *J* 4.1 Hz), and 6.95—7.45 (4 H, m); $\delta_C[(CD_3)_2SO]$ 34.53, 49.01, 65.62, 120.83, 123.46, 127.70, 127.86, 130.13, and 149.62.

1-(3-*Chlorophenyl*)*piperidin*-4-*ol* (**9**; R^1 = R^3 = H, R^2 = Cl).—3-Chloroaniline (20 g, 0.157 mol), 1,5-dichloropentan-3-ol (22.5 g, 0.143 mol), potassium carbonate (43.4 g, 0.314 mol), sodium iodide (11.84 g, 79 mmol), and DMF (70 ml) were heated together at 100 °C for 3 h and then worked up as above. Distillation of the residue gave the *title compound* (**9**; R^1 = R^3 = H, R^2 = Cl) (Found: M^+ at *m/z* 211.0772. $C_{11}H_{14}{}^{35}ClNO$ requires *M*, 211.0764) as a yellow oil (20.24 g, 66%), b.p. 148—152 °C/0.07 mmHg; $\delta_H[(CD_3)_2SO]$ 1.35—1.55 (2 H, m), 1.79 (2 H, m), 2.88 (2 H, m), 3.55 (2 H, m), 3.64 (1 H, m), 4.68 (1 H, d, *J* 3.8 Hz), 6.72 (1 H, dd, *J* 0.9 and 7.9 Hz), 6.88 (2 H, m), and

7.16 (1 H, t, *J* 8.0 Hz); δ_C[$(CD_3)_2SO$] 33.45, 45.74, 65.79, 113.71, 114.53, 117.27, 130.29, 133.77, and 152.01.

1-(4-*Chlorophenyl*)*piperidin*-4-*ol* (9; $R^1 = R^2 = H$, R^3 = Cl).—4-Chloroaniline (14.04 g, 0.11 mol), 1,5-dichloropentan-3-ol (15.7 g, 0.10 mol), potassium carbonate (0.22 mol), sodium iodide (8.24 g, 55 mmol), and DMF (50 ml) were heated together at 100 °C for 1 h and were then worked up as above. The crude products were not distilled but were crystallized from di-isopropyl ether to give the *title compound* (9; $R^1 = R^2 = H$, R^3 = Cl) (16.28 g, 77%) (Found: C, 62.2; H, 6.65; N, 6.6. $C_{11}H_{14}ClNO$ requires C, 62.4; H, 6.7; N, 6.6%) as colourless crystals, m.p. 99—101 °C; δ_H[$(CD_3)_2SO$] 1.43 (2 H, m), 1.80 (2 H, m), 2.83 (2 H, m), 3.47 (2 H, m), 3.62 (1 H, m), 4.68 (1 H, d, *J* 4.2 Hz), 6.92 (2 H, d, *J* 9.1 Hz), and 7.19 (2 H, *J* 9.0 Hz); δ_C[$(CD_3)_2SO$] 33.51, 46.14, 65.78, 116.94, 121.59, 128.50, and 149.65.

1-(3-*Chloro*-4-*tolyl*)*piperidin*-4-*ol* (9; $R^1 = H$, R^2 = Cl, R^3 = Me).—3-Chloro-4-methylaniline (30.0 g, 0.212 mol), 1,5-dichloropentan-3-ol (30.25 g, 0.193 mol), potassium carbonate (58.6 g, 0.424 mol), sodium iodide (15.89 g, 0.106 mol), and DMF (100 ml) were heated together at 100 °C for 2 h and were then worked up as above. The crude products were not distilled but were crystallized from di-isopropyl ether to give the *title compound* (9; $R^1 = H$, R^2 = Cl, R^3 = Me) (28.13 g, 64.5%) (Found: M^+, 225.0912. $C_{12}H_{16}{}^{35}ClNO$ requires *M*, 225.0920) as colourless crystals, m.p. 56—57 °C; δ_H[$(CD_3)_2SO$] 1.44 (2 H, m), 1.78 (2 H, m), 2.81 (2 H, m), 3.47 (2 H, m), 3.61 (1 H, m), 4.66 (1 H, d, *J* 4.1 Hz), 6.81 (1 H, dd, *J* 2.4 and 8.4 Hz), 6.90 (1 H, d, *J* 2.4 Hz), and 7.12 (1 H, d, *J* 8.5 Hz); δ_C[$(CD_3)_2SO$] 18.42, 33.57, 46.27, 65.86, 114.51, 115.42, 124.15, 131.22, 133.66, and 150.30.

1-(2-*Fluorophenyl*)*piperidin*-4-*one* (**10**; $R^1 = F$, $R^2 = R^3$ = H).—Dry trifluoroacetic acid (10 ml, 0.13 mol) was added dropwise over a period of 10 min to a cooled (ice–water bath), stirred anhydrous solution of 1-(2-fluorophenyl)piperidin-4-ol (50.56 g, 0.262 mol), DCC (107.3 g, 0.52 mmol), and pyridine (21.0 ml, 0.26 mol) in DMSO (150 ml) and benzene (400 ml), in an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature. After 24 h, the products were filtered and the residue was washed with a small volume of ether. The combined filtrate and washings were extracted with 4M hydrochloric acid (3 × 150 ml). After 30 min, the cooled (ice–salt) aqueous acidic extract was neutralized (to *ca.* pH 8) with 4M aqueous sodium hydroxide, and the resulting mixture was extracted with ether (3 × 200 ml). The combined ethereal extracts were washed with saturated brine (5 × 200 ml), then dried ($MgSO_4$), and evaporated under reduced pressure. The resulting yellow solid residue was recrystallized from di-isopropyl ether to give the *title compound* (**10**, $R^1 = F$, $R^2 = R^3 = H$) (33.8 g, 67.5%) (Found: C, 68.1; H, 6.2; N, 7.15. $C_{11}H_{12}FNO$ requires C, 68.4; H, 6.3; N, 7.25%) as colourless crystals, m.p. 64 °C; $\delta_H(CDCl_3)$ 2.63 (4 H, t, *J* 6.1 Hz), 3.41 (4 H, t, *J* 6.0 Hz), and 6.95—7.15 (4 H, m); $\delta_C(CDCl_3)$ 41.71, 50.78 (d), 116.35 (d), 119.72 (d), 123.15 (d), 124.54 (d), 139.20 (d), 155.75 (d), and 208.01.

1-(4-*Tolyl*)*piperidin*-4-*one* (**5**; R = Me) (*with the help of Mr. G. M. Porritt*).—This compound was prepared from trifluoroacetic acid (6.9 ml, 89.6 mmol), 1-(4-tolyl)piperidin-4-ol (33.79 g, 0.177 mol), DCC (74.3 g, 0.360 mol), and pyridine (14.6 ml, 0.181 mol) in DMSO (100 ml) and benzene (270 ml), according to the procedure described above in the preparation of 1-(2-fluorophenyl)piperidin-4-one. The products were worked up as above and distilled to give the *title compound* (**5**; R = Me) (27.0 g, 80%) (Found: C, 75.9; H, 7.8; N 7.6. $C_{12}H_{15}NO$ requires C, 76.2; H, 8.0; N, 7.4%) as a low melting (m.p. ~25 °C) colourless solid (b.p. 110 °C/0.05 mmHg); $\delta_H(CDCl_3)$ 2.29 (3 H, s), 2.55 (4 H, t, *J* 6.1 Hz), 3.55 (4 H, t, *J* 6.1 Hz), 6.90 (2 H, d, *J* 8.6 Hz), and 7.18 (2 H, d, *J* 9.3 Hz); $\delta_C(CDCl_3)$ 20.39, 40.77, 49.49, 116.34, 129.37, 129.91, 147.09, and 208.18.

1-(4-*Chlorophenyl*)*piperidin*-4-*one* (**5**; R = Cl).—This compound was prepared from trifluoroacetic acid (1.8 ml, 23.4 mmol), 1-(4-chlorophenyl)piperidin-4-ol (10.0 g, 47.2 mmol), DCC (14.55 g, 70.5 mmol), and pyridine (3.8 ml, 47.0 mmol) in DMSO (20 ml) and benzene (40 ml) according to the procedure described above in the preparation of 1-(2-fluorophenyl)-piperidin-4-one. A pale yellow solid (8.19 g, 82%) was obtained. A portion of this material was purified by Kugelrohr distillation, followed by recrystallization from di-isopropyl ether to give the *title compound* (**5**; R = Cl) (Found: C, 62.9; H, 5.7; N, 6.8. $C_{11}H_{12}ClNO$ requires C, 63.0; H, 5.8; N, 6.7%) as colourless crystals, m.p. 55—56 °C; $\delta_H(CDCl_3)$ 2.55 (4 H, t, *J* 6.0 Hz), 3.57 (4 H, t, *J* 6.0 Hz), 6.89 (2 H, d, *J* 8.9 Hz), and 7.24 (2 H, d, *J* 9.5 Hz); $\delta_C(CDCl_3)$ 40.58, 48.84, 117.13, 124.72, 129.30, 147.88, and 207.57.

1-(2-*Fluorophenyl*)-4,4-*dimethoxypiperidine* (**12**).—1-(2-Fluorophenyl)piperidin-4-one (15.42 g, 79.8 mmol), toluene-4-sulphonic acid monohydrate (16.91 g, 88.9 mmol), trimethyl orthoformate (10.6 ml, 97 mmol), and anhydrous methanol (50 ml) were heated under reflux for 10 min. The cooled products were basified with 30% methanolic sodium methoxide and filtered. Ether (300 ml) was then added and the resulting mixture was washed with water (2 × 100 ml) and saturated aqueous sodium hydrogen carbonate (2 × 100 ml). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure to give a colourless solid. The latter material was recrystallized from light petroleum (b.p. 60—80 °C) to give the *title compound* (**12**) (14.35 g, 75%) (Found: C, 65.2; H, 7.6; N, 5.8. $C_{13}H_{18}FNO_2$ requires C, 65.25; H, 7.6; N, 5.85%) as colourless crystals, m.p. 69—70 °C; $\delta_H(CDCl_3)$ 1.94 (4 H, t, *J* 5.7 Hz), 3.09 (4 H, t, *J* 5.6 Hz), 3.24 (6 H, s), and 6.99 (4 H, m); $\delta_C(CDCl_3)$ 32.68, 47.50, 47.88, 98.15, 115.90, 116.13, 119.34, 122.23, 122.32, 124.34, 140.26, 140.36, 154.37, and 157.08.

1-(2-*Fluorophenyl*)-4-*methoxy*-1,2,5,6-*tetrahydropyridine* (**13**).—A solution of 1-(2-fluorophenyl)-4,4-dimethoxypiperidine (22.28 g, 93.1 mmol) and toluene-4-sulphonic acid monohydrate (0.18 g, 0.95 mmol) in dichloromethane (200 ml) was evaporated and the residue was heated at 150 °C under reduced pressure (*ca.* 20 mmHg) for 90 min. The products were dissolved in dichloromethane (200 ml) and basified with methanolic sodium methoxide. The resulting mixture was washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Distillation of the residue under reduced pressure gave the crude enol ether (13.8 g, 72%), b.p. 94—96 °C/0.03 mmHg. Fractionation of this material on silica gel gave the *title compound* (**13**) (Found: M^+ at *m/z* 207.1059. $C_{12}H_{14}FNO$ requires *M*, 207.1059); $\delta_H(CDCl_3)$ 2.24 (2 H, m), 3.22 (2 H, t, *J* 5.8 Hz), 3.48 (3 H, s), 3.59 (2 H, m), 4.61 (1 H, m), and 6.8—7.0 (4 H, m); $\delta_C(CDCl_3)$ 28.41, 48.14, 54.16, 91.34, 115.92, 116.25, 122.13, 122.26, 124.36, 139.80, 153.60, 154.17, and 157.71.

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References

1 C. B. Reese, H. T. Serafinowska, and G. Zappia, *Tetrahedron Lett.*, 1986, **27**, 2291.

2 C. B. Reese, *Nucleosides, Nucleotides*, 1987, **6**, 121.
3 T. S. Rao, C. B. Reese, H. T. Serafinowska, H. Takaku, and G. Zappia, *Tetrahedron Lett.*, 1987, **28**, 4897.
4 M. J. Gallagher and F. G. Mann, *J. Chem. Soc.*, 1962, 5110.
5 C. B. Reese and G. Zappia, unpublished observations.
6 A. H. Sommers and S. E. Haland, *J. Am. Chem. Soc.*, 1953, **75**, 5280.
7 R. Kelson and R. Robson, *Coord. Chem.*, 1979, **6**, 235.
8 G. R. Owen and C. B. Reese, *J. Chem. Soc. C*, 1970, 2401.
9 E. C. Taylor and J. S. Skotnicki, *Synthesis*, 1981, 606.
10 K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, 1963, **85**, 3027.
11 S. V. Kelkar, C. B. Reese, H. T. Serafinowska, and E. A. Thompson, unpublished observations.

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