Unexpected perimidine formation in the ring opening of 1,2-dihydro-2-piperidinomethylperimidines with di-*iso*-butylaluminium hydride to 1-amino-8-(2-piperidinoethyl)aminonaphthalenes

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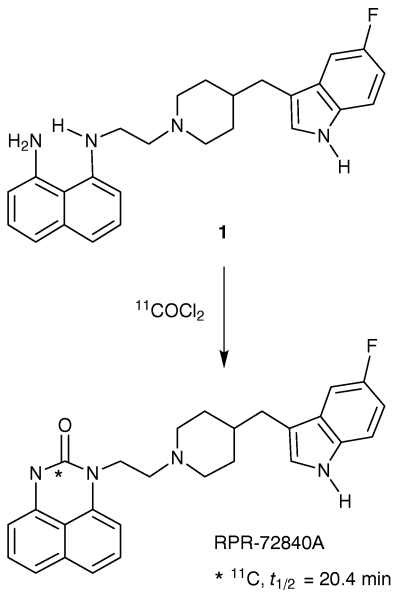
This paper describes the synthesis of 1-amino-8-(2-piperidinoethyl)aminonaphthalenes. The key step in our synthesis is the ring opening of 1,2-dihydro-2-piperidinomethylperimidines with di-*iso*-butylaluminium hydride. Unusually high amounts of DIBAL-H and long reaction times were needed to effect the reaction. Unexpected perimidine formation could be demonstrated in more or less important quantities, depending on the amount of hydride used. This observation is remarkable since it constitutes a formal oxidation in a powerful reducing medium.

Ouverture de cycles de type 1,2-dihydro-2-pipéridinométhylpérimidines par le DIBAL-H. Obtention de dérivés 1-amino-8-(2-pipéridinoéthyl)aminonaphthalènes et formation de périmidines inattendues. Ce manuscrit décrit la synthèse chimique de dérivés 1-amino-8-(2-pipéridinoéthyl)aminonaphthalènes. L'étape clef dans cette synthèse est l'ouverture de cycles de type 1,2-dihydro-2-pipéridinométhylpérimidine à l'aide d'hydrure de di-*iso*-butylaluminium. Des quantités inhabituelles de DIBAL-H et des longs temps de réaction ont été nécessaires pour effectuer cette réaction. De plus, nous avons pu démontrer la formation en quantité plus ou moins importante d'une périmidine inattendue, en fonction du nombre d'équivalents de DIBAL-H utilisés. Cette observation est remarquable et constitue formellement une étape d'oxydation dans un millieu fortement réducteur.

In the course of a program on ^{11}C-labelled neuroreceptor ligands, we needed to synthesize the mono-*N*-substituted 1,8-diaminonaphthalene derivative **1** as a precursor of the labelling step, that is cyclization with ^{11}C-phosgene (Scheme 1). We decided to focus first on the synthesis of 1-amino-8-(2-piperidinoethyl)aminonaphthalene (**2**), chosen as a model, and secondly, to apply our selected successful approach to the synthesis of the desired fluoroindole derivative **1**. The present paper discusses some aspects of the synthesis of the model compound **2** as well as its application to the synthesis of 1-amino-8-[2-{4-[(5-fluoro-1*H*-indol-3-yl)methyl]piperidino}-ethyl]aminonaphthalene (**1**). The ring opening of 1,2-dihydro-2-piperidinomethylperimidine (**7**) with di-*iso*-butylaluminium hydride (see Scheme 4 below), the key step in our synthesis, in particular will be discussed, since an unexpected perimidine formation, thus a formal oxidation in a powerful reducing medium, could be demonstrated.



Scheme 1 Cyclization of **1** with ^{11}C-phosgene, radiosynthesis of [^{11}C]RPR-72840A

Results and Discussion

Only a few direct mono-*N*-alkylations of 1,8-diaminonaphthalene (**3**) are described in the literature.[1,2] Yields are usually poor and when the mono-substituted derivative is formed, it is accompanied by a mixture of polyalkylation products, which have to be separated. Nevertheless, we applied some strategies, based on the alkylation of simple aromatic amines such as aniline, to 1,8-diaminonaphthalene.

Initial attempts to mono-alkylate 1,8-diaminonaphthalene (**3**) with 2-piperidinoethanol using Raney nickel and $(Bu^tO)_3Al$, as described by Botta *et al.*[3] for aniline and simple alkyl alcohols, were unsuccessful (Scheme 2). The starting materials were recovered unchanged. Similarly, **3** could not be converted into the desired **2** using 1-bromo-2-piperidinoethane. The latter in its acid-free form is probably unstable under the reaction conditions. *N*-Tosylaniline and simple alcohols can be condensed under Mitsunobu conditions.[4,5] However, our application of this reaction to 1-amino-8-tosylaminonaphthalene (**4**) and 2-piperidinoethanol failed.

We finally succeeded in synthesizing **2** by ring opening of the easily accessible 1,2-dihydro-2-piperidinomethylperimidine

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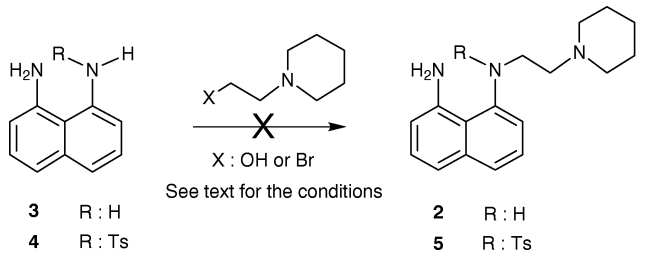
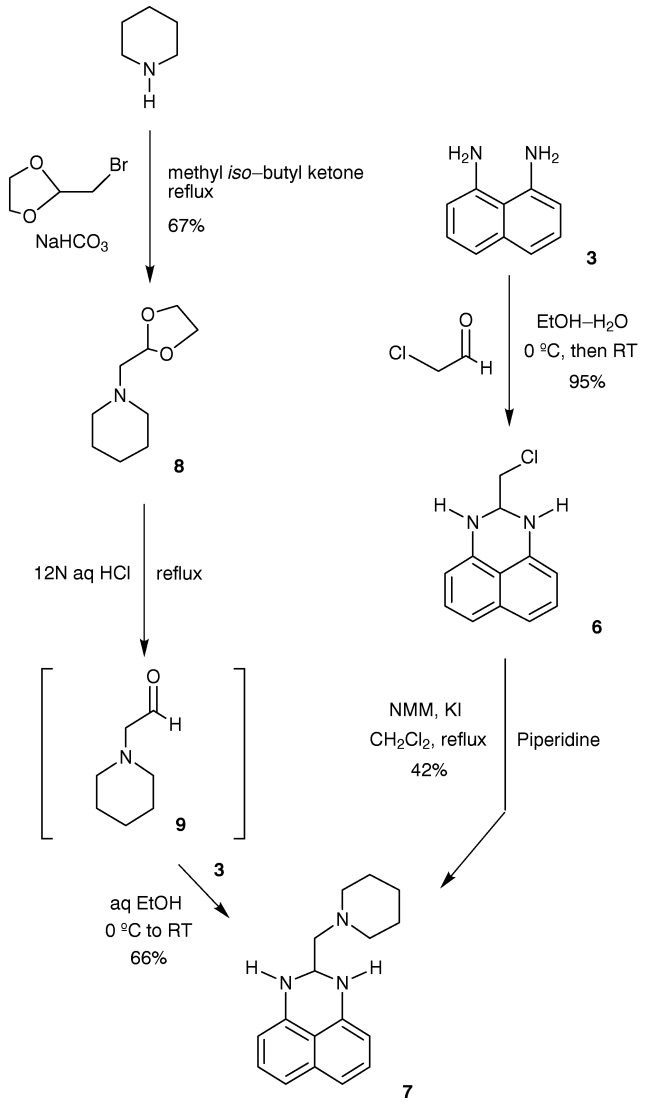


Scheme 2 Attempted mono-alkylation of 1,8-diaminonaphthalene

(**7**) with di-*iso*-butylaluminium hydride (DIBAL-H) according to the method of Yamamoto and Maruoka.[2] For this, **3** was easily converted into the derivative **6** using chloroacetaldehyde in a mixture of water and ethanol (95% yield). Condensation with piperidine in refluxing dichloromethane containing 1 equiv. of both *N*-methylmorpholine and potassium iodide afforded compound **7** in 42% isolated yield (Scheme 3). In an alternative route, **7** was synthesized in 66% isolated yield from piperidinoacetaldehyde [**9**, generated[6] from 2-piperidinomethyl-1,3-dioxolane (**8**)] and **3** in aqueous ethanol. Care must be taken not to expose the aldehyde, which is unstable in its acid-free form, to basic or even neutral conditions. Derivative **9** could not be synthesized *via* partial oxidation of 2-piperidinoethanol using pyridinium chlorochromate (PCC), even when mild conditions were applied, such as PCC adsorbed on alumina. This is also in agreement with observations by others.[6] Compound **8** was synthesized from



Scheme 3 Synthesis of 1,2-dihydro-2-piperidinomethylperimidine (**7**)

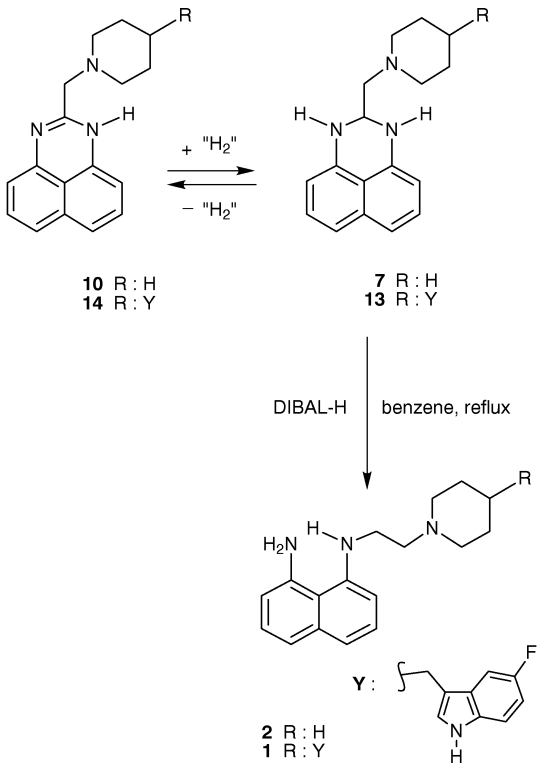
commercially available 2-bromomethyl-1,3-dioxolane and piperidine in refluxing methyl *iso*-butyl ketone in 67% yield.

According to Yamamoto and Maruoka,[2] the ring opening reaction of 2-alkyl-1,2-dihydroperimidines with DIBAL-H proceeds smoothly and rapidly. For example, 1,2-dihydro-2-hexylperimidine requires 5–6 equiv. DIBAL-H for 2 h in benzene at 0 °C for conversion to *N*-heptyl-1,8-diaminonaphthalene. In our case, at least 20 h of reflux in benzene and a very large excess of DIBAL-H (12 equiv.) were required to achieve ring opening of **7** to **2** in 36% yield (Scheme 4).

Unexpectedly, a considerable amount of 2-piperidinomethylperimidine (**10**) was also isolated from the reaction mixture (16% yield). The relative isolated yields of **2** and **10** depended on the amount of DIBAL-H used. After the addition of only 6 equiv.[2] of the reducing agent, derivative **10** was the only product isolated (53% yield) while no **2** was found. When more equivalents of DIBAL-H were added, we were able to show by TLC that **7** rapidly forms **10**, the latter being the predominant product within 15 min. after the DIBAL-H addition; **10** is then slowly converted into **2**, most likely *via* **7**. Irrespective of the total amount of DIBAL-H added, the total conversion of **10** into **2** could never be achieved. A minimum of a twelvefold excess of DIBAL-H was needed to obtain **2** in excess of **10**. However, DIBAL-H is required for the formation of either derivative **2** or **10**, as shown by a control experiment in which **7** was refluxed in benzene alone; at the same concentration no reaction could be detected by TLC after 3 h.

Yamamoto and Maruoka[2] showed that 2-substituted perimidines are equally well opened with DIBAL-H as the corresponding 1,2-dihydroperimidines. Thus, we subjected the isolated derivative **10** again to DIBAL-H (12 equiv.) Once more, TLC revealed that **10** is slowly converted to **2**, most likely *via* **7**, which was detected. Product **2** was isolated from the reaction mixture in 31% yield. Neither starting material **10** nor the possible intermediate **7** were isolated in this case.

The formation of **10** is remarkable as it constitutes an oxidation of **7** in a reducing medium. Possibly, ring opening is hampered by the formation of a chelate of an aluminium



Scheme 4 Reaction of DIBAL-H with **7** (respectively **13**): synthesis of perimidine **10** (respectively **14**) and the desired ring-opened **2** (respectively **1**)

species involving the piperidine nitrogen and a perimidine nitrogen, causing steric strain at ring opening (*peri* interaction[7]). It is noteworthy in this respect that Yamamoto and Maruoka[2] reported that 1,2-bis(2-tetrahydropyrimidyl) ethane could not be ring-opened to spermine, even under vigorous conditions.

A mechanism that might be proposed to explain the formation of **10** involves a hydride transfer from a bis(di-*iso*-butylaluminium amide) complex of **7** to another DIBAL-H, forming an ion pair having the partial structure (*iso*-butyl)$_2$ Al—N—C$^+$—N—Al(*iso*-butyl)$_2$ · (*iso*-butyl)$_2$Al$^-$H$_2$, in accordance with the immediate intense bright yellow colouring of the reaction mixture upon DIBAL-H addition. Hydride transfer of this type in structurally related *ortho*-amides such as 3a,6a,9a-triazaphenalene[8–11] has been ascribed to a weakening of the C—H bond and an increase of negative charge on the hydrogen atom by mixing of the σ^*_{CH} orbital with the nitrogen lone pairs that are anti *peri*-planar to the C—H bond. Addition of a second DIBAL-H to the bis(di-*iso*-butylaluminium amide) complex of **7** leads, after hydrolysis, to the ring-opened derivative **2**, as described by Yamamoto and Maruoka,[2] while the ion pair leads to the perimidine **10**.

An alternative mechanism for the formation of **10** could be the elimination of DIBAL-H from its complex with **7** by a cyclic transition state involving an additional DIBAL-H molecule, along the lines of a mechanism that was proposed for the reduction of ketones by di-*iso*-butylaluminium-1,2-dihydroquinoline.[12] It is conceivable that the hydride loss as suggested above is generally present when treating a 2-substituted 1,2-dihydroperimidine with DIBAL-H, although the perimidine derivatives are not found. In this case, ring opening is much faster, drawing the mentioned reaction completely towards ring-opened products.

The findings for the above model reactions were then applied to the synthesis of the more complex compound **1**. For this, derivative **13** was synthesized in 31% yield from the chloro intermediate **6**, using the same procedure as described above for **7**. Piperidine was replaced in this case by the following amine: 5-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole. We selected this route rather than the alternative one *via* 4-[(5-fluoro-1*H*-indol-3-yl)methyl]piperidinoacetaldehyde (analogue of **9**). The latter approach gave a better yield with the model reaction (**9** to **7**), but is experimentally somewhat difficult. The chosen method also avoids a two-step derivatization of our 5-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole to the corresponding 1,3-dioxolane.

Ring opening of 1,2-dihydroperimidine (**13**) with DIBAL-H followed a similar pathway of the one described for **7** (Scheme 4). Derivative **14** was also formed and could be isolated and characterized. Treatment of **13** with 13 equiv. DIBAL-H in refluxing benzene gave perimidine **14** in 47% isolated yield at the expense of the desired **1** (only 25%). The latter could be obtained as the predominant product (34% yield) only when no less than 20 equiv. DIBAL-H were applied. Again, isolated **14** could be partially converted into **1** by addition of DIBAL-H (27% yield) with neither starting material nor intermediate recovered.

Conclusions

This paper describes the synthesis of 1-amino-8-(2-piperidinoethyl)aminonaphthalenes. The key step in our synthesis is the ring opening of 1,2-dihydro-2-piperidinomethylperimidines with di-*iso*-butylaluminium hydride. Unusually high amounts of DIBAL-H and long reaction times were needed to effect the reaction. Unexpected perimidine formation could also be demonstrated in more or less important quantities, depending on the amount of hydride used. This observation is remarkable since it constitutes a formal oxidation in a powerful reducing medium.

Experimental

Chemicals were purchased from Aldrich, France and were used without further purification. 5-Fluoro-3-[(4-piperidinyl) methyl]-1*H*-indole was kindly donated by Rhône-Poulenc Rorer (Vitry-Alfortville, France). This product can be synthesized according to a literature procedure.[13] Benzene was dried by distillation from CaH_2. TLC were run on pre-coated plates of 0.2 mm neutral alumina 60F254 (Merck) or 0.2 mm silica gel 60F254 (Merck). The compounds were visualized using both a UV lamp at 254 nm and iodine staining. Flash chromatography was run on silica gel (various granulometry, Merck). All solvent mixtures for TLC and flash chromatography were treated with 1 vol.% of concentrated ammonia. Melting points (mp) were measured on a 9200 Electrothermal instrument and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AMX (300 MHz) apparatus at room temperature using the hydrogenated residue of the deuteriated solvents (CD_2Cl_2, $\delta = 5.32$ or DMSO-d_6, $\delta = 2.49$) and/or TMS as internal standards. The chemical shifts are reported in ppm, downfield from TMS. Abbreviations used are: s, d, t, m, br, $w_{1/2}$, J_{app} for singlet, doublet, triplet, multiplet, broad, width at half-height and $J_{apparent}$, respectively. Mass spectra were obtained with a Nermag R10-10 instrument at 70 eV. Air- or moisture-sensitive reactions were conducted in oven-dried glassware and under an argon atmosphere.

Reactions with DIBAL-H: synthesis of perimidines and 1-amino-8-(2-piperidinoethyl)aminonaphthalenes, representative examples

Ring opening of 1,2-dihydroperimidines with DIBAL-H. 1,2-Dihydroperimidine **7** (0.135 mmol) in 1.5 mL of dry benzene was placed in a reaction vessel under an argon atmosphere and equipped with a magnetic stirrer and a reflux condenser. DIBAL-H (290 μL, 1.63 mmol, 12 equiv.) was added at once. The reaction mixture turned instantaneously bright yellow under brief vigorous gas development. After 20 h of reflux, TLC (alumina) showed the ring-opened product **2** as the one major product whilst a minor amount of perimidine **10** could be detected as well. The reaction mixture was diluted with benzene to 5 mL and NaF (272 mg, 6.50 mmol) and H_2O (87 μL, 4.90 mmol) were added under vigorous stirring. Stirring was continued for 20 min while the colour of the mixture changed from white to pink. The precipitate was filtered off and was washed with benzene. The combined filtrate and washings were concentrated with a rotary evaporator. The residue was purified using flash chromatography (EtOAc–heptane gradient) giving **2**, a pink solid/oil and **10**, a yellow solid.

Ring opening of perimidines with DIBAL-H. Perimidine **10** (0.075 mmol) was treated as described above for **7** (12 equiv. DIBAL-H, 160 μL, 0.90 mmol in refluxing benzene for 20 h). TLC (alumina) revealed that **10** is slowly converted to **2**, most likely *via* **7**, which was detected. Workup and purification by flash chromatography was as described above. Neither starting material **10** nor possible intermediate **7** were isolated in this case.

Oxidation of 1,2-dihydroperimidines into perimidines with DIBAL-H. 1,2-Dihydroperimidine **7** (0.64 mmol) was treated as described above, differing only in the amount of DIBAL-H (680 μL, 3.84 mmol, 6 equiv.) and reaction time (36 h). TLC (alumina) showed that considerably more of the yellow perimidine **10** was formed at the expense of **2**. Workup and purification by flash chromatography was as described above.

Selected analytical data for compounds 2, 7, 10 and 1, 13, 14

1-Amino-8-(2-piperidinoethyl)aminonaphthalene, 2. TLC, silica (EtOAc–heptane, 1 : 1) $R_f = 0.19$; TLC, alumina

(EtOAc–heptane, 1 : 1) $R_f = 0.88$; ^{1}H NMR (CD_2Cl_2): δ 7.23–7.06 (4H, naphth. CH), 6.59–6.49 (2H, naphth. CH), 6.13 (1H, br, $w_{1/2} = 17$ Hz, NH), 4.74 (2H, br, $w_{1/2} = 23$ Hz, NH_2), 3.17 (2H, br d, $J_{app} = 4.8$ Hz, CH_2), 2.63 (2H, t, $J = 5.9$ Hz, CH_2), 2.42 (4H, br, $w_{1/2} = 16$ Hz, piperidine CH_2), 1.65–1.39 (6H, piperidine CH_2); microanalysis: calcd for $C_{17}H_{23}N_3$ (269.39) C: 75.80, H: 8.60, N: 15.60, found C: 75.74, H: 8.88, N: 15.33.

1,2-Dihydro-2-piperidinomethylperimidine, 7. TLC, silica (EtOAc–heptane, 1 : 1) $R_f = 0.43$; TLC, alumina (EtOAc–heptane, 1 : 1) $R_f = 0.82$; ^{1}H NMR (CD_2Cl_2): δ 7.21–7.08 (4H, naphth. CH), 6.46 (2H, d, $J = 7.2$ Hz, naphth. CH), 4.74 (2H, br, $w_{1/2} = 13$ Hz, NH), 4.45 (1H, t, $J = 6.3$ Hz, CH), 2.47–2.42 [(2 + 4)H, CH_2 + piperidine CH_2], 1.59–1.42 (6H, piperidine CH_2); microanalysis: calcd for $C_{17}H_{21}N_3$ (267.37) C: 76.37, H: 7.92, N: 15.72; found C: 76.75, H: 8.03, N: 15.51.

2-Piperidinomethylperimidine, 10. TLC, silica (EtOAc–heptane, 1 : 1) $R_f = 0.15$; TLC, alumina (EtOAc–heptane, 1 : 1) $R_f = 0.74$; ^{1}H NMR (DMSO-d_6): δ 10.19 (1H, br, $w_{1/2} = 15$ Hz, NH), 7.15–6.94 (4H, naphth. CH), 6.50 (2H, d, $J = 6.9$ Hz, naphth. CH), 3.07 (2H, s, CH_2), 2.43 (4H, br, $w_{1/2} = 15$ Hz, piperidine CH_2), 1.61–1.34 (6H, piperidine CH_2); MS: 266 $[M + H]^+$; microanalysis: calcd for $C_{17}H_{19}N_3$ (265.36) C: 76.95, H: 7.22; N: 15.84; found 76.76; H: 7.31; N: 15.92.

1-Amino-8-[2-{4-[(5-fluoro-1*H*-indol-3-yl)methyl]piperidino}ethyl]aminonaphthalene, 1. TLC, silica (EtOAc–heptane, 1 : 1) $R_f = 0.15$; TLC, alumina (EtOAc–heptane, 1 : 1) $R_f = 0.64$; mp 49 °C; ^{1}H NMR (CD_2Cl_2): δ 8.11 (1H, br, $w_{1/2} = 11$ Hz, indole NH), 7.29–7.02 (7H, naphth. + indole CH), 6.90 (1H, td, $J = 9.2$ Hz and 2.4 Hz, indole CH), 6.57 (1H, m, naphth. CH), 6.50 (1H, d, $J = 7.2$ Hz, naphth. CH), 6.10 (1H, br, $w_{1/2} = 17$ Hz, NH), 4.70 (2H, br, $w_{1/2} = 23$ Hz, NH_2), 3.17 (2H, br t, $w_{1/2} = 14$ Hz, piperidine CH), 2.89 (2H, br d, $J_{app} = 11.4$ Hz, CH_2), 2.66–2.61 (4H, CH_2), 1.94 (2H, br d, $J_{app} = 10.8$ Hz, piperidine CH), 1.69–1.53 [(2 + 1) H, piperidine CH], 1.38–1.20 (2H, br q, $J_{app} = 12.0$ Hz, piperidine CH); microanalysis: calcd for $C_{26}H_{29}FN_4$(416.54) C: 74.97, H: 7.02, N: 13.45; found C: 75.02, H: 7.37, N: 13.65.

2-{4-[(5-Fluoro-1*H*-indol-3-yl)methyl]piperidinomethyl}-1,2-dihydroperimidine, 13. TLC, silica (EtOAc–heptane, 1 : 1) $R_f = 0.30$; TLC, alumina (EtOAc–heptane, 1 : 1) $R_f = 0.60$; ^{1}H NMR (CD_2Cl_2): δ 8.15 (1H, br, $w_{1/2} = 13$ Hz, indole NH), 7.23–7.10 (6H, naphth. + indole CH), 6.97 (1H, br, $w_{1/2} = 3$ Hz, indole CH), 6.89 (1H, td, $J = 9.3$ Hz and 2.4 Hz, indole CH), 6.49 (2H, d, $J = 7.2$ Hz, naphth. CH), 4.74 (2H, br d, $w_{1/2} = 6$ Hz, NH), 4.48 (1H, t, $J = 6.3$ Hz, CH), 2.87 (2H, br d, $J_{app} = 11.1$ Hz, piperidine CH), 2.62 (2H, d, $J = 6.6$ Hz, CH_2), 2.49 (2H, d, $J = 6.3$ Hz, CH_2), 2.02 (2H, br t, $J_{app} = 11.1$ Hz, piperidine CH), 1.70–1.50 [(2 + 1)H, piperidine CH], 1.34 (2H, br q, $J_{app} = 11.7$ Hz, piperidine CH); microanalysis: calcd for $C_{26}H_{27}FN_4$ (414.52) C: 75.34, H: 6.57, N: 13.52; found C: 75.01, H: 6.38, N: 13.72.

2{4-[(5-Fluoro-1*H*-indol-3-yl)methyl]piperidinomethyl}perimidine, 14. TLC, silica (EtOAc–heptane, 1 : 1) $R_f = 0.10$; TLC, alumina (EtOAc–heptane, 1 : 1) $R_f = 0.46$; ^{1}H NMR (CD_2Cl_2): δ 8.23 (1H, br, $w_{1/2} = 16$ Hz, indole NH), 7.35–7.00 (9H, naphth. + indole CH), 6.91 (1H, t, $J = 8.8$ Hz, indole CH), 6.27 (1H, br, $w_{1/2} = 18$ Hz, NH), 3.15 (2H, s, CH_2), 2.87 (2H, br d, $J_{app} = 11.4$ Hz, piperidine CH), 2.66 (2H, d $J = 6.6$ Hz, CH_2), 2.14 (2H, t, $J = 10.1$ Hz, piperidine CH), 1.78–1.54 [(2 + 1)H, piperidine CH], 1.43–1.20 (2H, piperidine CH); microanalysis: calcd for $C_{26}H_{25}FN_4$ (412.51) C: 75.70, H: 6.11, N: 13.58; found C: 75.92, H: 6.23, N: 13.59.

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