SYNTHESIS OF VARIOUS SUBSTITUTED NITROISOQUINOLINES BY $S_{RN}1$ METHODOLOGY

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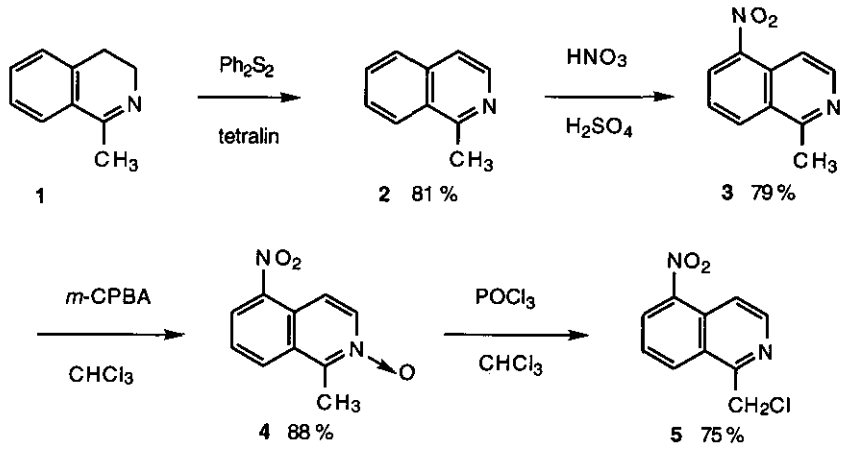
Abstract- The versatile $S_{RN}1$ methodology allows straightforward access to new 1-substituted 5-nitroisoquinolines from an original heterocyclic reductive alkylating agent, 1-chloromethyl-5-nitroisoquinoline, with various nitronate anions. By base-promoted nitrous acid elimination, trisubstituted olefins are prepared from the C-alkylation derivatives.

Kornblum[1] and Russell[2] have described the first example of the radical chain mechanism designated $S_{RN}1$ by Bunnett[3] to explain the C-alkylation of nitronate anion by *p*-nitrobenzyl chloride. The extensions of that reaction at sp^3 carbons attached to heterocyclic systems have been studied extensively[4,5] because $S_{RN}1$ methodology produced excellent yields of pure products under mild conditions. As the isoquinoline nucleus is found in alkaloids in the group of opium bases such as papaverine, narcotine, and apomorphine, many isoquinolines have been synthesized and possess interesting pharmacological actions as quinisocaïne (local anesthesic), praziquantel (antiparasitic).. Recently, the inhibitory potency of isoquinoline thiosemicarbazone derivatives[6] for the enzyme ribonucleotide reductase has been reported. The interest of the isoquinoline ring for medicinal chemistry led us to consider that $S_{RN}1$ chemistry might provide easy and versatile access to various 1-substituted 5-nitroisoquinolines.

For the preparation of 1-chloromethyl-5-nitroisoquinoline (**5**), an analogous heterocyclic derivative of *p*-nitrobenzyl chloride (scheme 1), the starting material was the 1-methyl-3,4-dihydroisoquinoline (**1**) which was dehydrogenated with diphenyl disulfide[7] to the corresponding isoquinoline (**2**).

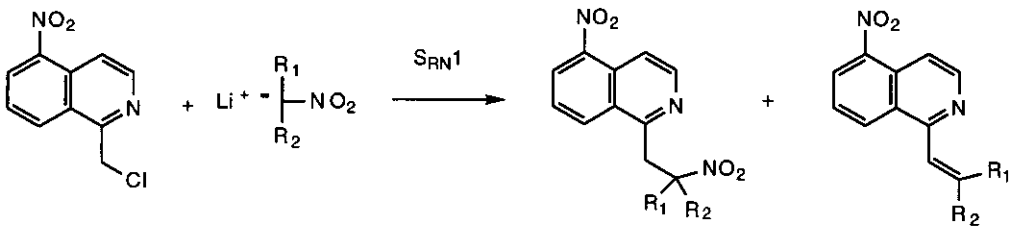
Scheme 1



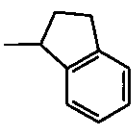
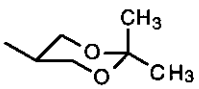
1 **2** 81 % **3** 79 % **4** 88 % **5** 75 %

As previously reported,[8] nitration of 1-methylisoquinoline with a mixture of concentrated sulfuric and nitric acids resulted in only one isomer, 1-methyl-5-nitroisoquinoline (**3**) while nitration of 3-methyl-isoquinoline[9] occurred predominantly at the 5-position with smaller amounts of the 8-substituted derivative being also formed. The free radical chlorination[10] using *N*-chlorosuccinimide (NCS) led to a mixture of the required chloride, the dichloromethyl derivative and unreacted starting material. Because product separation and isolation led to lower mass balances, an alternative approach was selected. Thus, 1-methyl-5-nitroisoquinoline-*N*-oxide (**4**) was prepared by the action of *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform[5] on 1-methyl-5-nitroisoquinoline (**3**) in 88% yield. When the derivative (**4**) was treated with phosphorus oxychloride,[11] only one product 1-chloromethyl-5-nitroisoquinoline (**5**) was obtained in good yield (75%). This chloride (**5**) was treated under conditions conducive to $S_{RN}1$ reactions (inert atmosphere, photostimulation) with various aliphatic, cyclic or heterocyclic nitronate anions. The 5-nitro-1,3-dioxane salt (**6i**) was prepared from the previously described 2,2-dimethyl-5-hydroxymethyl-5-nitro-1,3-dioxane[12] after treatment with lithium methoxide which induced a formaldehyde splitt-off. By using 3 equivalents of nitronate anion in DMF during 24 h under Kornblum conditions,[1] the C-alkylation product (**7**) and/or the ethylenic derivative (**8**) formed from the C-alkylation product by base-promoted nitrous acid elimination were isolated as shown in Scheme 2.

Scheme 2



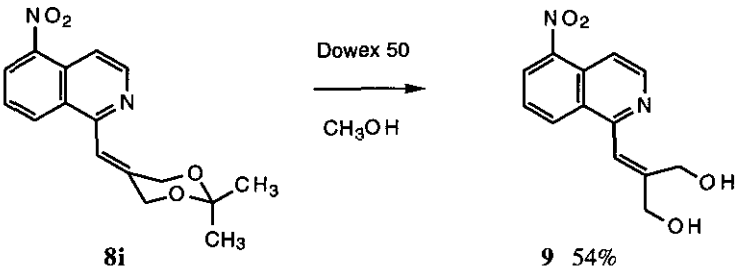
5 **6** **7** **8**

	R_1	R_2	7 Yield (%)	8 Yield (%)
a	CH_3	CH_3	29	58
b	$-(CH_2)_4-$		28	30
c	$-(CH_2)_5-$		35	52
d	$-(CH_2)_6-$		49	-
e	CH_3	$(CH_2)_2CH_3$	-	50
f	CH_3	$(CH_2)_2CH(CH_3)_2$	-	45
g			15	52
h			-	40
i			-	68

The $S_{RN}1$ mechanism was confirmed in the reaction of **5** with 2-nitropropane anion[13] by depression of reaction rate by addition of classical inhibitors. Unsaturated compounds (**8**) were unique or major products except for the reaction with nitrocycloheptane anion. This difference in the elimination of nitrous acid has been already observed in 5-nitroimidazole series[14] and should be related to basicity of cyclic nitronate anions.[15] When ethylenic derivative was unsymmetrical, the *E* isomer was the predominant product with a ratio *E*/*Z* of 3/1 (proportions calculated from ^1H NMR, the stereochemical assignment of each isomer being

established as previously reported[16]). This selectivity may be explained by favored conformations: for example, in the compound **8h** where only *E* isomer was isolated, the conformation in which the indane ring is placed between two hydrogen atoms is more stable than conformation in which a steric hindrance is observed between the indane ring and isoquinoline system.

Derivative **8i** was readily subject to ring opening[17] by heating in methanol with ion-exchange resin (Dowex 50X 8-50) to give the corresponding 2-hydroxymethyl-3-(5-nitroisoquinolyl)-2-propen-1-ol (**9**).



8i **9** 54%

In conclusion, the reaction of 1-chloromethyl-5-nitroisoquinolines with various aliphatic, cyclic or heterocyclic nitronate anions offers an interesting alternative for the synthesis of new 1-substituted 5-nitroisoquinolines which are difficult to obtain by classical chemical means and extends the scope of the $S_{RN}1$ reactions.

ACKNOWLEDGEMENTS

The support of this work by the Centre National de la Recherche Scientifique is gratefully acknowledged. We express our thanks to M. Noailly for collection of spectroscopic data.

EXPERIMENTAL

Melting points were taken on a Büchi apparatus using glass capillary tubes and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker 200 MHz instrument and chemical shifts are reported in δ units (ppm) relative to internal TMS. Microanalyses were performed by the Microanalytical Section of St-Jérôme Faculty, Aix-Marseille 3 University, France.

1-Methyl-5-nitroisoquinoline (3)

To a solution of 1-methylisoquinoline (16.40 g, 0.114 mol) in 96% sulfuric acid (40 mL), 65% nitric acid (16 mL) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 0.5 h and heated at 60 °C for 2 h. The mixture was poured into cold ice, neutralized with an aqueous 10 % NH_4OH solution. The resulting precipitate was filtered and dissolved in chloroform. The solvent was dried over anhydrous

magnesium sulfate and evaporated under vacuum. The solid was purified by recrystallization from absolute ethanol to afford 17.02 g (79%) of 1-methyl-5-nitroisoquinoline (**4**) mp 150 °C , lit.,[8] mp 150-151 °C.

1-Methyl-5-nitroisoquinoline-*N*-oxide (4)

In a round-bottomed flask equipped with a reflux condenser surmounted by a calcium chloride drying tube, a solution of 1-methyl-5-nitroisoquinoline (4 g, 21.3 mmol) in chloroform (100 mL) was added dropwise to a solution of *m*-chloroperbenzoic acid (12 g, 52.8 mmol, 76% pure) in chloroform (100 mL). After stirring at rt for 12 h, the reaction mixture was washed with an aqueous 1N NaOH solution (2 x 150 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated under vacuum. After purification by recrystallization from isopropanol, **4** was obtained as a yellow solid (3.82 g, 88%), mp 182 °C, ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 3H, CH_3); 8.78 (dd, J = 8.5 and 7.8 Hz, 1H, H_7); 8.29 (d, J = 8.5 Hz, 1H, H_8); 8.35 (d, J = 7.8 Hz, 1H, H_6); 8.35-8.41 (m, 2H, H_3 and H_4). Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.82; H, 3.94; N, 13.70.

1-Chloromethyl-5-nitroisoquinoline (5)

1-Methyl-5-nitroisoquinoline-*N*-oxide (2 g, 9.8 mmol) was dissolved in chloroform (50 mL) and cooled at 0 °C. Phosphorus oxychloride (9.1 mL, 9.8 mmol) was added dropwise with stirring. The reaction mixture was heated at reflux for 8 h. After cooling, the precipitate formed was decomposed in water (100 mL) and made alkaline with saturated Na_2CO_3 solution. The mixture was extracted with chloroform. The solvent was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude solid was purified by recrystallization from isopropanol to give 1.63 g (75%) of the product as beige needles,[13] mp 120 °C, ^{1}H NMR ($CDCl_3$) δ 5.19 (s, 2H, CH_2); 7.80 (dd, J = 8.3 and 8.0 Hz, 1H, H_7); 8.45 (d, J = 6.2 Hz, 1H, H_4); 8.53 (d, J = 8.0 Hz, 1H, H_6); 8.63 (d, J = 8.3 Hz, 1H, H_8); 8.70 (d, J = 6.2 Hz, 1H, H_3), ^{13}C NMR ($CDCl_3$) δ 44.95 (CH_2); 116.58 (CH); 126.19 (CH); 126.81 (C_{8a}); 128.04 (CH); 129.05 (C_{8b}); 131.84 (CH); 144.99 (CH); 145.59 (C_5); 156.49 (C_1). Anal. Calcd for $C_{10}H_7N_2O_2Cl$: C, 53.93; H, 3.17; N, 12.58; Cl, 15.92. Found: C, 54.01; H, 3.19; N, 12.50; Cl, 16.00.

The nitroalkanes were commercially available or prepared from secondary amines by oxidation with *m*-CPBA[18,19] in refluxing 1,2-dichloroethane for 3 h (**6d-h**) and 2,2-dimethyl-5-nitro-1,3-dioxane (**6i**) was obtained as previously described.[19]

Preparation of the lithium salt of nitroalkanes

A lithium methoxide was prepared by careful addition of lithium (175 mg, 0.025 at.g) to 15 mL of methanol. After the solution had become clear, 0.025 mol of nitroalkane was added, the solution was stirred at rt for 2 h and concentrated under vacuum. When the solution became viscous, about 300 mL of

ether was added to cause precipitation. The lithium salt was filtered, washed by ether and kept under oil-pump vacuum for 24 h.

Procedure for $S_{RN}1$ reactions in Kornblum conditions

To a solution of 0.50 g (2.25 mmol) of 1-chloromethyl-5-nitroisoquinoline (**5**) in 20 mL of dry DMF, the lithium salt of nitroalkane or 2,2-dimethyl-5-nitro-1,3-dioxane was added under nitrogen and anhydrous conditions. The reaction mixture was then irradiated with two 60 W fluorescent lamps from a distance of 10 cm. After stirring at rt for 24 h, the reaction mixture was poured into water (200 mL). The aqueous solution was extracted with benzene (3 x 40 mL) and ether (1 x 40 mL). The organic extracts were washed with water (3 x 100 mL), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Purification by chromatography on a silica gel column eluting with chloroform gave the required compounds.

1-(2-Methyl-2-nitropropyl)-5-nitroisoquinoline (**7a**), 29% yield, pincky white solid,[13] mp 108 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 6H, $2CH_3$); 4.01 (s, 2H, CH_2); 7.73 (dd, J = 8.5 and 8.3 Hz, 1H, H_7); 8.31 (d, J = 6.2 Hz, 1H, H_4); 8.44 (d, J = 8.3 Hz, 1H, H_6); 8.48 (d, J = 8.5 Hz, 1H, H_8); 8.65 (d, J = 6.2 Hz, 1H, H_3). Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.74; H, 4.77; N, 15.29.

1-(2-Methyl-1-propenyl)-5-nitroisoquinoline (**8a**), 58% yield, yellow solid, mp 78-80 °C (hexane), lit.,[13,20] mp 79 °C, ^{1}H NMR ($CDCl_3$) δ 1.88 (d, J = 1.2 Hz, 3H, CH_3); 2.09 (d, J = 1.2 Hz, 3H, CH_3); 6.82 (s, 1H, ethylenic H); 7.66 (dd, J = 8.1 and 8.0 Hz, 1H, H_7); 8.29 (d, J = 6.2 Hz, 1H, H_4); 8.47 (d, J = 8.0 Hz, 1H, H_6); 8.52 (d, J = 8.1 Hz, 1H, H_8); 8.73 (d, J = 6.2 Hz, 1H, H_3). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.30; H, 5.31; N, 12.18.

1-(1-Nitrocyclopentylmethyl)-5-nitroisoquinoline (**7b**), 28% yield, dark yellow solid, mp 102-103 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.74-1.99 [m, 4H, $(CH_2)_2$]; 2.00-2.14 (m, 2H, CH_2); 2.71-2.84 (m, 2H, CH_2); 4.12 (s, 2H, allylic CH_2); 7.71 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.25 (d, J = 6.2 Hz, 1H, H_4); 8.44 (d, J = 7.6 Hz, 1H, H_6); 8.45 (d, J = 8.6 Hz, 1H, H_8); 8.58 (d, J = 6.2 Hz, 1H, H_3). Anal. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.81; H, 5.08; N, 13.85.

1-Cyclopentylidenemethyl-5-nitroisoquinoline (**8b**), 30% yield, dark red solid, mp 98 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.72-1.81 [m, 4H, $(CH_2)_2$]; 2.66-2.72 (m, 4H, allylic CH_2); 7.11 (s, 1H, ethylenic H); 7.64 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.20 (d, J = 6.1 Hz, 1H, H_4); 8.44 (d, J = 7.6 Hz, 1H, H_6); 8.58 (d, J = 8.6 Hz, 1H, H_8); 8.70 (d, J = 6.1 Hz, 1H, H_3). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.78; H, 5.60; N, 10.94.

1-(1-Nitrocyclohexylmethyl)-5-nitroisoquinoline (**7c**), 35% yield, brown solid, mp 120 °C

(isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.32-1.78 [m, 6H, $(CH_2)_3$]; 1.84-1.93 (m, 2H, CH_2); 2.45-2.52 (m, 2H, CH_2); 3.87 (s, 2H, allylic CH_2); 7.68 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.29 (d, J = 6.2 Hz, 1H, H_4); 8.36 (d, J = 8.6 Hz, 1H, H_8); 8.43 (d, J = 7.6 Hz, 1H, H_6); 8.65 (d, J = 6.2 Hz, 1H, H_3). Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.44; N, 13.33. Found: C, 60.96; H, 5.42; N, 13.30.

1-Cyclohexylidenemethyl-5-nitroisoquinoline (**8c**), 52% yield, brown solid, mp 108 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.51-1.83 [m, 6H, $(CH_2)_3$]; 2.31 (t, J = 6.1 Hz, 2H, allylic CH_2); 2.46 (t, J = 6.1 Hz, 2H, allylic CH_2); 6.72 (s, 1H, ethylenic H); 7.65 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.27 (d, J = 6.2 Hz, 1H, H_4); 8.46 (d, J = 7.6 Hz, 1H, H_6); 8.52 (d, J = 8.6 Hz, 1H, H_8); 8.71 (d, J = 6.2 Hz, 1H, H_3). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.60; H, 6.03; N, 10.43.

1-(1-Nitrocycloheptylmethyl)-5-nitroisoquinoline (**7d**), 49% yield, off-white solid, mp 125 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.62-1.65 [m, 8H, $(CH_2)_4$]; 2.20 (dd, J = 15 and 8 Hz, 2H, $C^{3'}H\beta$ and $C^{8'}H\beta$); 2.60 (dd, J = 15 and 8 Hz, 2H, $C^{3'}H\alpha$ and $C^{8'}H\alpha$); 4.02 (s, 2H, CH_2); 7.75 (dd, J = 8.6 and 7.7 Hz, 1H, H_7); 8.33 (d, J = 6.2 Hz, 1H, H_4); 8.46 (d, J = 8.6 Hz, 1H, H_8); 8.50 (d, J = 7.7 Hz, 1H, H_7); 8.67 (d, J = 6.2 Hz, 1H, H_3). Anal. Calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.06; H, 5.74; N, 12.81.

1-(2-Methyl-1-pentenyl)-5-nitroisoquinoline (**8e**), 50% yield, brown solid, mp 58 °C (hexane), *E*/*Z* = 3/1, *E* isomer: ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$); 1.50 (sextuplet, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$); 2.10 (d, J = 1.0 Hz, 3H, CCH_3); 2.27 (t, J = 7.5 Hz, 2H, allylic CH_2); 6.85 (s, 1H, ethylenic H); 7.70 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.33 (d, J = 6.2 Hz, 1H, H_4); 8.52 (d, J = 7.6 Hz, 1H, H_6); 8.57 (d, J = 8.6 Hz, 1H, H_8); 8.76 (d, J = 6.2 Hz, 1H, H_3). *Z* isomer: ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$); 1.72 (sextuplet, J = 7.5 Hz, 2H, $C\underline{H}_2CH_3$); 1.89 (d, J = 1.0 Hz, 3H, CCH_3); 2.38 (t, J = 7.5 Hz, 2H, allylic CH_2); 6.85 (s, 1H, ethylenic H); 7.70 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.33 (d, J = 6.2 Hz, 1H, H_4); 8.52 (d, J = 7.6 Hz, 1H, H_6); 8.55 (d, J = 8.6 Hz, 1H, H_8); 8.78 (d, J = 6.2 Hz, 1H, H_3). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.33; H, 6.33; N, 10.98.

1-(2,5-Dimethyl-1-hexenyl)-5-nitroisoquinoline (**8f**), 45% yield, brown solid, mp 49-50 °C (hexane), *E*/*Z* = 3/1, *E* isomer: ^{1}H NMR ($CDCl_3$) δ 0.75 [d, J = 6.5 Hz, 6H, $(CH_3)_2$]; 1.25-1.74 (m, 3H, $C\underline{H}_2C\underline{H}(CH_3)_2$); 2.07 (d, J = 1.4 Hz, 3H, CCH_3); 2.22 (t, J = 7.2 Hz, 2H, allylic CH_2); 6.78 (br s, 1H, ethylenic H); 7.65 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.30 (d, J = 6.1 Hz, 1H, H_4); 8.47 (d, J = 7.6 Hz, 1H, H_6); 8.53 (d, J = 8.6 Hz, 1H, H_8); 8.71 (d, J = 6.1 Hz, 1H, H_3). *Z* isomer: ^{1}H NMR ($CDCl_3$) δ

0.94 [d, J = 6.8 Hz, 6H, $(CH_3)_2$]; 1.25-1.74 [m, 3H, $C\underline{H}_2C\underline{H}(CH_3)_2$]; 1.85 (d, J = 1.4 Hz, 3H, CCH_3); 2.34 (t, J = 7.2 Hz, 2H, allylic CH_2); 6.81 (s, 1H, ethylenic H); 7.67 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.30 (d, J = 6.1 Hz, 1H, H_4); 8.47 (d, J = 7.6 Hz, 1H, H_6); 8.52 (d, J = 8.6 Hz, 1H, H_8); 8.75 (d, J = 6.1 Hz, 1H, H_3). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.45; H, 7.41; N, 9.38.

1-(2-Nitro-2-norbornylmethyl)-5-nitroisoquinoline (7g), 15% yield, pink solid, mp 152 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.31-1.80 (m, 6H, norbornyl CH_2); 1.90 (m, 1H, $C^{3'}H$*exo*); 2.41 (br s, 1H, $C^{4'}H$); 2.71 (m, 1H, $C^{3'}H$*endo*); 2.77 (br s, 1H, $C^{7'}H$); 3.80 (d, J = 16.8 Hz, 1H, $C^{1'}H$); 4.53 (d, J = 16.8 Hz, 1H, $C^{1'}H$); 7.71 (dd, J = 8.6 and 7.7 Hz, 1H, H_7); 8.27 (d, J = 6.2 Hz, 1H, H_4); 8.41 (d, J = 8.6 Hz, 1H, H_8); 8.46 (d, J = 7.7 Hz, 1H, H_6); 8.59 (d, J = 6.2 Hz, 1H, H_3). Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.24; N, 12.84. Found: C, 62.36; H, 5.35; N, 12.83.

1-(2-Norbornylidenemethyl)-5-nitroisoquinoline (8g), 52% yield, yellow solid, mp 69 °C (isopropanol), *E*/*Z* = 3/1, *E* isomer: ^{1}H NMR ($CDCl_3$) δ 1.19-1.57 (m, 4H, norbornyl CH_2); 1.60-1.90 (m, 2H, norbornyl CH_2); 2.48-2.60 (m, 3H, CH and allylic CH_2); 3.03 (br s, 1H, allylic H); 7.13 (s, 1H, ethylenic H); 7.63 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.16 (d, J = 6.1 Hz, 1H, H_4); 8.42 (d, J = 7.6 Hz, 1H, H_6); 8.56 (d, J = 8.6 Hz, 1H, H_8); 8.68 (d, J = 6.1 Hz, 1H, H_3), *Z* isomer: ^{1}H NMR ($CDCl_3$) δ 1.19-1.57 (m, 4H, norbornyl CH_2); 1.60-1.90 (m, 2H, norbornyl CH_2); 2.48-2.60 (m, 3H, CH and allylic CH_2); 3.58 (br s, 1H, allylic H); 6.81 (s, 1H, ethylenic H); 7.63 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.22 (d, J = 6.1 Hz, 1H, H_4); 8.46 (d, J = 7.6 Hz, 1H, H_6); 8.64 (d, J = 8.6 Hz, 1H, H_8); 8.71 (d, J = 6.1 Hz, 1H, H_3). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.81; H, 5.70; N, 9.94.

1-(Indan-2-ylidenemethyl)-5-nitroisoquinoline (8h), 40% yield, dark orange solid, mp 132 °C (isopropanol), *E* isomer: ^{1}H NMR ($CDCl_3$) δ 3.11 (t, J = 7.5 Hz, 2H, benzylic CH_2); 3.42 (td, J = 6.5 and 2.5 Hz, 2H, allylic CH_2); 7.34-7.37 (m, 3H, 2 benzenic H + ethylenic H); 7.67-7.81 (m, 3H, 2 benzenic H + H_7); 8.21 (d, J = 6.1 Hz, 1H, H_4); 8.45 (d, J = 7.6 Hz, 1H, H_6); 8.71 (d, J = 8.6 Hz, 1H, H_8); 8.78 (d, J = 6.1 Hz, 1H, H_3). Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.26. Found: C, 75.33; H, 4.66; N, 9.25.

1-(2,2-Dimethyl-1,3-dioxan-5-ylidenemethyl)-5-nitroisoquinoline (8i), 68% yield, brown solid, mp 111 °C (isopropanol), ^{1}H NMR ($CDCl_3$) δ 1.43 [s, 6H, $(CH_3)_2$]; 4.50 (s, 2H, CH_2O); 4.82 (s, 2H, CH_2O); 6.96 (s, 1H, ethylenic H); 7.62 (dd, J = 8.6 and 7.6 Hz, 1H, H_7); 8.19 (d, J = 6.2 Hz, 1H, H_4); 8.40 (d, J = 7.6 Hz, 1H, H_6); 8.49 (d, J = 8.6 Hz, 1H, H_8); 8.64 (d, J = 6.2 Hz, 1H, H_3). Anal.

Calcd for $C_{16}H_{16}N_2O_4$: C, 64.19; H, 5.37; N, 9.33. Found: C, 64.24; H, 5.36; N, 9.36.

2-Hydroxymethyl-3-(5-nitroisoquinolyl)-2-propen-1-ol (9)

A stirred mixture of 1-(2,2-dimethyl-1,3-dioxan-5-ylidenemethyl)-5-nitroisoquinoline (**8i**) (200 mg, 0.72 mmol) and 100 mg of ion-exchange resin (Dowex 50X 8-50 Aldrich) in 10 mL of methanol was refluxed for 24 h. After filtration of resin and evaporation under reduced pressure, the residue was purified by recrystallization from ethyl acetate to give 104 mg (54%) of 2-hydroxymethyl-3-(5-nitroisoquinolyl)-2-propen-1-ol (**9**) as yellow solid. mp 151 °C, ^{1}H NMR ($CDCl_3$) δ 4.29 (s, 2H, CH_2); 4.37 (s, 2H, CH_2); 5.03 (br s, 1H, OH); 5.25 (br s, 1H, OH); 7.32 (s, 1H, ethylenic H); 7.89 (dd, J = 8.1 and 7.7 Hz, 1H, H_7); 8.14 (d, J = 6.1 Hz, 1H, H_4); 8.63 (d, J = 7.7 Hz, 1H, H_6); 8.70 (d, J = 8.1 Hz, 1H, H_8); 8.74 (d, J = 6.1 Hz, 1H, H_3). Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.02; H, 4.71; N, 10.77.

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Received, 22nd April, 1997