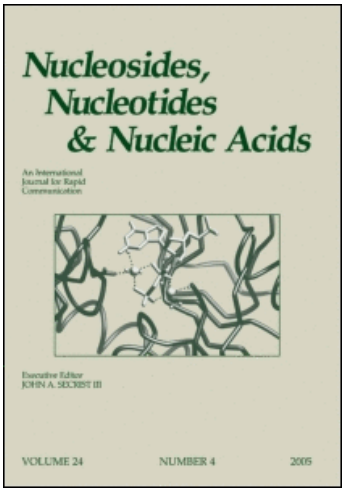


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# Selective N1-Alkylation of Pyrimidine Bases *via* Radical ($S_{RN}1$) Mechanism.

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***Abstract** : Under photostimulated $S_{RN}1$ conditions the cytosine nitranion behaves as a nucleophile toward the carbon radical generated from gem halonitro, or gem dinitroalcane derivatives to give regiospecifically the N-1 alkyled cytosine compound which is representative of a new series of cytosine acyclonucleosides. Uracile and its 5-fluoro or 5-nitro analogs fail to react and thymine gives an unexpected disubstituted $S_{RN}1$ product whose formation is discussed.*



Studies aimed at bonding a carbon radical intermediate to an azole anion by reactions proceeding via the $S_{RN}1$ mechanism were initiated in our laboratory where it was observed that the anion of imidazole, and that of other azoles were good nucleophiles in reactions with an extended range of variously functionalized gem halo-nitro derivatives[1]. In the course of our ensuing studies on azoles we have investigated the reactivity of 6-chloropurine and 2-amino-6-chloropurine as nucleophiles[2]. In this present paper we report our results with pyrimidine bases of biological relevance, cytosine, uracile and some of its analogs .

I. CYTOSINE (Scheme 1)

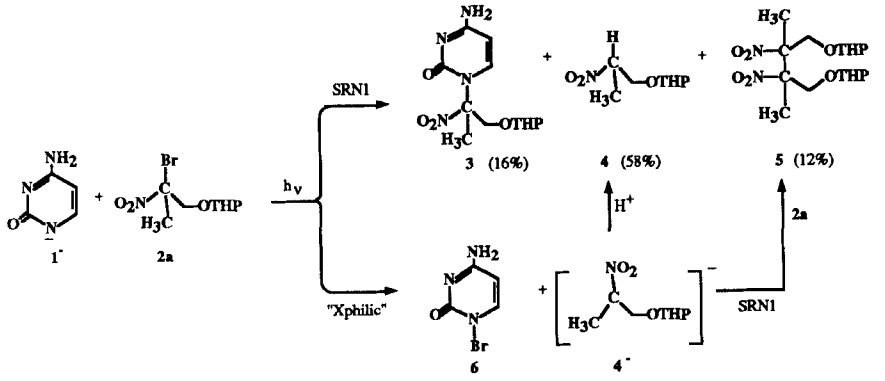
Under photostimulated $S_{RN}1$ conditions the cytosine anion **1** (Table) generated by $K_2CO_3$ in DMSO reacts with the tetrahydropyrannyl (THP) protected gem bromonitroalcool **2a** to give a mixture of products (entry 1). The N-1 alkylated cytosine derivative **3** (10%) is the minor product, others being the nitroalcohol **4** and the dimeric compound **5**. When the cytosine anion $\mathbf{1}^-$ is generated by NaH in dimethylformamide (entry 2), an increased yield of **3** and a lower quantity of **5** are obtained. The major product is still the nitroalcohol **4**, but interestingly the N-bromo-cytosine **6** can be isolated and identified.

The N-1 alkylation of cytosine does not occur in experiments carried out either in the dark (entry 3) or under illumination but in the presence of a less than stoechiometric amount of electron scavenging *meta*-dinitrobenzene (*meta*-D.N.B.) (entry 4) and the major product formed in both experiments is the nitroalcohol **4**.

The products of exp. 1-4 are those typically resulting from two superimposed reactions:

- A four-step $S_{RN}1$ reaction[3] which produces the N-1 alkylated cytosine **3** as a result of attack of the regiospecifically generated N-1 cytosine anion $\mathbf{1}^-$ by the carbon radical $[CH_3\dot{C}(NO_2)CH_2OTHP]$.

†. Deceased 02 August 1991.



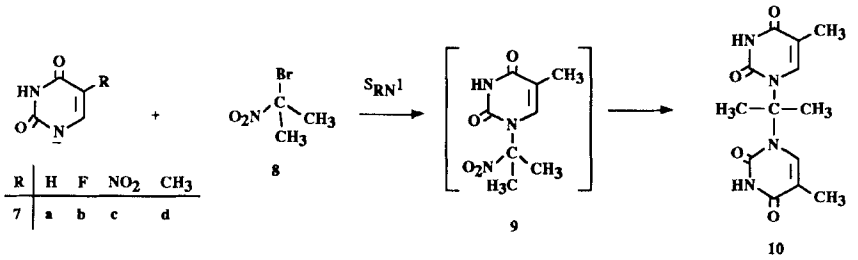

Scheme 1

Table

| Entry | Substrate | | Conditions | | | | Products % | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | X | Solvent | Base | Addition | Time (min) | 3 | 4 | 5 | 6 |
| 1 | 2a | Br | DMSO | $K_2CO_3$ | D | 210 | 10 | 52 | 27 | |
| 2 | | | DMF | NaH | D a) | 150 | 16 | 58 | 12 | <5 |
| 3 | | | | | | 75 b) | 0 | 51 | <10 | |
| 4 | | | | | | 75 c) | 0 | 31 | 8 | |
| 5 | | | DMF | NaH | R d) | 75 | 43 | 36 | 10 | |
| 6 | 2b | Cl | DMSO | NaH | R | 240 | 35 | 41 | | |
| 7 | 2c | $NO_2$ | | | R | 240 | 25 | 0 | | |
| 8 | | | | | D | 420 | 52 | 0 | | |
| 9 | | | | | R | 780 | 68 | 0 | | |

*a) Direct addition (D): see general procedure for $S_{RN}1$ reaction (in experimental section); b) in the darkness; c) para-Dinitrobenzene (10% molar) added before illumination; d) Reverse addition (R): (id)*

- An ionic "halogenophilic" reaction[4], affected neither by darkness nor by *meta*-D.N.B., which produces two compounds: the N-1 bromocytosine **6** by transfer of the labile $Br^+$ of **2a** to the sufficiently reducing anion **1**⁻ *and* the nitronate **4**⁻. This latter species reacts in part with the radical $[CH_3\dot{C}(NO_2)CH_2OTHP]$ in a side $S_{RN}1$ reaction to give the dimeric compound **5** and the excess of **4**⁻ is found as nitroalcohol **4** after acidic work up. Thus the observed low yield of N-1 alkylated cytosine derivative **3** is rationnalized by -*i*) Substrate **2a** consumption by the halogenophilic reaction -*ii*) Competitive $S_{RN}1$ reaction leading to vic dinitroalcane **5**.




Scheme 2

The "halogenophilic" reaction is thus detrimental to N-1 alkylation of cytosine affording **5** in good yield, and we tried to control it by:

- *Reverse addition of reagents*. Portionwise addition of $\mathbf{1}^-$ into the solution of **2a** under permanent illumination leads to diminished concentration of $\mathbf{1}^-$ in the reaction medium, and expectedly to significant increase in yield of **3**, but nevertheless to appreciable quantities of **4** and **5** (entry 5).

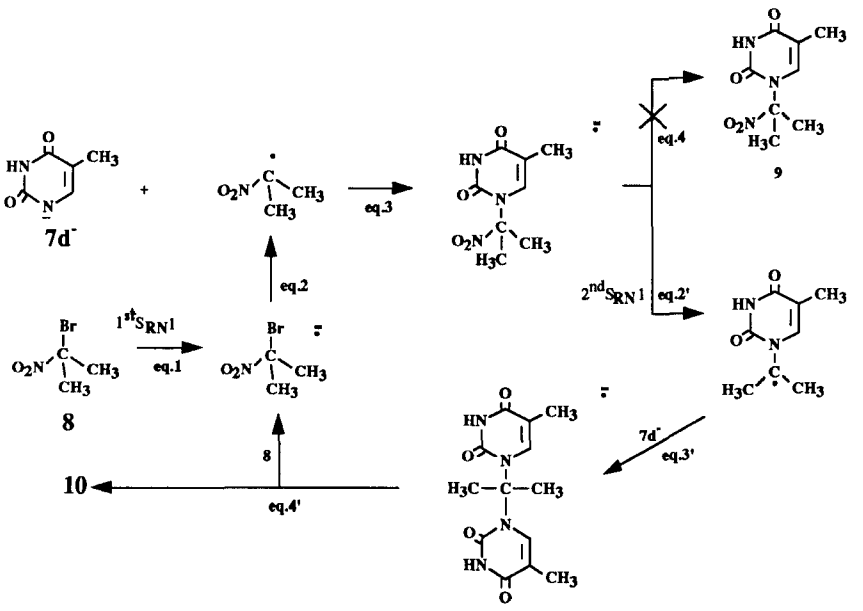
- *Replacement of the leaving group of 2a*. The ease of halogen transfer decreases[4] from $Br^+$ to $Cl^+$ but the transfer takes also place from the chloronitro derivative **2b**, even by reverse addition (entry 6). The nitro group of the gem dinitro derivative **2c** cannot undergo transfer to the anion, and so the undesired reaction is suppressed. The target compound **3** is thus obtained as the unique product either by reverse (entry 7) or direct addition of reagents (entry 8) but the reaction is slow so that a longer reaction time is necessary to afford to **3** in satisfactory yield (entry 9).

## II. OTHER PYRIMIDINE BASES

Under reverse addition conditions identical to those used for cytosine, uracile **7a**, its 5-fluoro and 5-nitro analogs **7b-c** and thymine **7d** display various behavior as nucleophiles. In reactions with 2-bromo-2-nitro propane **8** which is one of the most commonly used substrates in aliphatic $S_{RN}1$ chemistry, **7a-c** were inert and were recovered unchanged after reaction times as long as 24 hours. In contrast, thymine in excess (2.1 eq. over **8** reacted well and fast (60 min.) to give **10**, in 64% yield (scheme 2). Obviously, this molecule encompasses within its carbon framework the substrate ($CH_3$-C-$CCH_3$) and two molecules of thymine. We postulated that a stoechiometric amount (1.2 eq.) of **7d** and a shorter reaction time (30 min.) could give rise to some amount of the expected N-1 alkylated product **9** but we obtained only a smaller yield (47%) of **10**.

These experiments tend to indicate that **10** is not formed *via* **9** and that reactions of **8** with **7a-d** could be understood on considering that *i*) uracile **7a** and its analogs **7b,c** bearing electron withdrawing substituents in position 5 are weak nucleophiles and poor electron donors which cannot transfer electron to the substrate to initiate (eq. 1) the chain $S_{RN}1$ mechanism[3] *ii*) Thymine, on which reverse electronic effect is exerted by the electron releasing 5-methyl group is a much better reactant towards **8**, furthermore thymine undergoes no side "X philic" reaction at difference with cytosine.

When the thymine derived N-1 anion reacts with the radical $\dot{A}NO_2$ (eq. 3), the resulting radical anion $ANO_2Nu^{\bullet-}$ is labile because of enhanced electron density and extrudes $NO_2$ to give $\dot{A}Nu$ (eq. 2') instead of



Scheme 3

being deactivated (eq. 4) to give $ANuNO_2$ **9**. Then, $\dot{A}Nu$, in a sequential $S_{RN}1$ reaction reacts with a second molecule of $Nu^-$ (thymine anion) to give ANuNu *via* eq. 3', 4' which sustain the chain process (scheme 3).

Such fragmentation of radical anion is known in $S_{RN}1$ reaction of aromatic compounds bearing two leaving groups of different nucleofugicity[6], but to the best of our knowledge, this example is the first one to be observed in aliphatic $S_{RN}1$ chemistry.

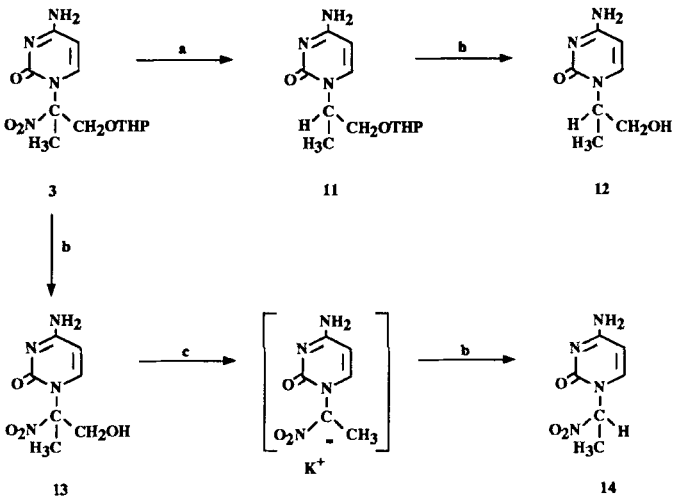
## III. FUNCTIONAL GROUP TRANSFORMATIONS

Chemical transformations were carried out on the N-1 alkylated pyrimidine derivative **3** produced in good yield from $S_{RN}1$ reaction of cytosine with the substrate **2c**.

Replacement of the nitro group by hydrogen (H), carried out with $HBu_3Sn$[7] is a reaction fully compatible with the cytosine ring leading to **11**. Subsequent treatment of the latter compound under acidic conditions affords **12** whose structure is that of an acyclonucleoside. Similar acidic treatment effected on **3** (before removal of the nitro group) leads to a gem-nitrocytosyl alcohol **13**, prone to undergo a retro Michael reaction, under alkaline conditions[8], with loss of a molecule of formaldehyde to give **14** (scheme 4).

## CONCLUSION

Although uracile and some of its analogs, and to a lesser extent thymine failed to undergo N-1 alkylation in reactions with gem-halonitro substrates, the unprotected and not activated cytosine reacted chemio-[9] and regiospecifically[10] with gem-dinitro derivatives to give N-1 alkylated compounds in good yield. This useful reaction comes in addition to the well established methodology for synthesis of nucleosides and acyclonucleosides[11].



a) $HBu_3Sn$/AIBN/benzene/reflux; b) $H^+$/MeOH; c) KOH/MeOH

scheme 4



**Experimental Section:**

**Reagents.** All chemical reagents and solvents were purchased from Aldrich (France) and were used without further purification.

**General Methods.** The IR spectra were recorded on a Nicolet (205, FT-IR). The UV spectra were obtained on a Perkin-Elmer lambda 5 UV/VIS spectrophotometer. The mass spectra were recorded on a KRATOS MS 80 (MS-AB) and on a EI.MS-9 (MS-CI). The proton and carbon NMR were recorded on a Bruker spectrometre 4.7 T (200 Mz). Chemical schifts are reported in δ units, parts per million (ppm) downfield from internal TMS for $^1H$ NMR (δ = 0) and from DMSO d6 for $^{13}C$ NMR (δ = 39.45). Column chromatography utilized silica gel 60 (230-400 mesh) from E. Merck laboratories as the solid phase.

General procedure for SRN1 reactions:

*Direct addition* (D): The pyrimidine base **1, 7a-d** (0.110 g, 1mmol), potassium carbonate or sodium hydride (washed twice by pentane) 1.2 eq, and freshly distilled DMSO or DMF (10 ml) are introduced in a Pyrex flask caped with a rubber septum. The mixture is stirred 30 min. under argon. Then a solution of the substrate **2 a,b,c** or **8** (1mmol) in the corresponding solvent (2.5 ml) is added to the mixture by a syringe and the reaction medium is illuminated by a 400W HANAU mercury lamp untill complete consumption of the substrate (T.L.C.)

*Reverse addition* (R): The substrate **2 a,b,c,**[8] (1mmol) is dissolved in DMF or DMSO (5 ml) in a Pyrex flask caped with a rubber septum. The anion is prepared in a separate flask caped with a rubber septum from the pyrimidine base **1, 7a-d** (1 mmol), sodium hydride (1.2 mmol) in the corresponding solvent (7.5 ml). Before illumination, only a portion of the anion slurry (1.5 ml) is transferred via a canula under

argon pressure into the flask containing the solution of substrate**2 a,b,c**,[8] and after consumption (TLC) another portion is transferred, etc until complete consumption of the reagents.

The work up is similar in either procedures: water addition (50 ml) and neutralization by a 1% aqueous citric acid solution are followed by $CH_2Cl_2$ extraction (3x30 ml). The organic phase is washed with water, dried over $Na_2SO_4$ and evaporated. Purification is achieved by silica gel colum chromatography or preparative thin layer chromatography ($CH_2Cl_2$/MeOH: 95/5).

[2-Nitro-1-(2-oxytetrahydropyrannyl)-propane-2-yl] cytosine **3**:

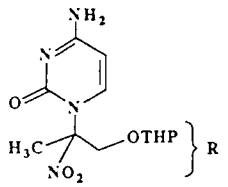
Oil.

**IR** ($CH_2Cl_2$) ν ($cm^{-1}$): 3400-3200 ($NH_2$), 1675 and 1642 (strong, C=O), 1568 and 1376 ($NO_2$).

**UV** (EtOH): λmax = 274.0 nm (lit[12]: 273-275).

**MS** (FAB), m/z: 321 $(MNa)^+$, 299 $(MH)^+$, 252 $(MH^+-HNO_2)$, 215 $(MH^+-THP+H)^+$, 112 $(cytosine+H)^+$, 85 $(THP)^+$.

**H[1] RMN** ($CDCl_3$) (mixture of 2 diastereoisomers): δ 1.26-1.87 (m, 6H, $(CH_2)_3$/THP), 2.10 (s, 3H, $CH_3$), 3.33-3.66 and 3.70-3.93 (2m, 2H, $CH_2O$/THP), 4.10-4.43 (2d, 1H, J= 10Hz, $CH_2OTHP$, 1st diastereoisomer), 4.33 and 4.50 (2d, 1H, J= 10Hz, $CH_2OTHP$, 2nd diastereoisomer), 4.52 and 4.70 (2s, 1H, OCHO), 6.02 (d, 1H, J= 7Hz, $H_5$), 7.37 and 8.01 (2s, 2H, $NH_2$), 7.50 (d, 1H, J= 7Hz, $H_6$). In DMSO d6, $H_5$ and $H_6$ signals are observed respectively at δ 5.87 and δ 7.35 ppm.




| RMN $^{13}C$ DMSO d6 | C4 | C2 | C6 | C5 |
|---|---|---|---|---|
| **3** | 165.59 | 155.33 | 142.03 | 94.61 |
| lit.[13] | 166.25 | 155.76 | 141.32 | 94.30 |

R: 100.11, 98.42, 92.85, 67.49, 67.16, 61.59, 60.92, 29.97, 29.41, 24.64, 24.31, 22.09, 21.76, 18.62, 18.34.

N-1-bromocytosine **6**:

Oil

**M.S.** (C.I, $NH_3$) m/z 210, 208 $(M+NH_4)^+$, 193, 191 $(MH)^+$, 112 $(cytosine+H)^+$.

**NMR $^1H$** ($CD_3OD$) δ ppm 5.97 (d, 1H, J=7Hz, $H_5$), 7.37 (d, 1H, J=7Hz, $H_6$).

2,2-(thymin-1-yl)-propane **10**:

**m.p.**: 242-243.

**IR** (KBr), ν ($cm^{-1}$): 3350 (NH), 1681 (C=O)

**NMR $^1H$** (DMSO d6): δ ppm 1.85 (s, 3H, $CH_3$), 2.23 (s, 3H, $CH_3$), 7.6 (s, 2H, $H_6$), 11.2 (broad s, 2H, NH).

**Anal. Calc.** for $C_{13}H_{16}N_4O_4$: C: 53.42, H: 5.51. Found: C: 53.12, H: 5.49.

1-[1-(2-oxy-tetrahydropyrannyl)-propan-2-yl]-cytosine **11**:

A mixture of compound **3** (1mmole), $Bu_3SnH$ (2 mmoles), and AIBN (0,2 mmole) in benzene (6mL) was refluxed under an inert atmosphere. Reaction progress was followed by TLC. After the reaction was complete, the solvent was removed in vacuo and the oil was chromatographed on silica gel (eluent: $CH_2Cl_2$/MeOH: 95/5). The cytosine derivative 11 was obtained in 71% yield.

Oil.

**IR** ($CH_2Cl_2$) ν ($cm^{-1}$): 3500-3200 ($NH_2$), 1649 (strong, C=O).

**MS** (I.C.), m/z: 254 $(MH)^+$, 170 $(MH^+$-THP+H$)^+$, 112 (cytosine+H)$^+$, 85 $(THP)^+$.

**$H^1$ RMN** ($CDCl_3$) (mixture of 2 diastereoisomers): δ 1.17-1.96 (m, 6H, $(CH_2)_3$/THP), 3.33-3.66; 3.68-4.02 and 4.03-4.51 (3m, 4H, $CH_2$-O), 4.53 and 4.61 (2s, 1H, OCHO), 5.03 (m, 1H, CH-cyt.), 5.87 (d, 1H, J= 7Hz, $H_5$), 6.53 and 7.77 (2s, 2H, $NH_2$), 7.47 (d, 1H, J= 7Hz, $H_6$).

2-(N-1 cytosine)-propanol **12**:

The cytosine derivative**11** was stirred in methanol (5mL/mmol) with a catalytic amount of TsOH (10%) at room temperature and progress of the reaction was followed by TLC on silica gel untill the reaction was completeTLC. The solution neutralized to pH 6-7 by solid sodium bicarbonate was partly evaporated under reduced pressure, diluted with methylene chloride and the resulting precipitate was filtered off. The filtrate was evapored under reduced pressure and the residual oil purified by chromatography on silica gel ($CH_2Cl_2$/MeOH: 95/5) gave pure alcohol **12** in 97% yield.

**m.p.**: 231-233.

**IR** (KBr), ν ($cm^{-1}$): 3150-3500 ($NH_2$ and OH), 1662 (C=O).

**NMR $^1$H** (DMSO d6): δ ppm 1.27 (d, 3H, J= 7Hz, $CH_3$), 3.31 (s, 1H, OH), 3.67 (d, 2H, J'= 4Hz, $CH_2$-O), 4.33 (broad s, 2H, $NH_2$), 4.80 (m, 1H, J= 7Hz, J'= 4Hz, CH-cyt.), 6.01 (d, 1H, J"= 7Hz, $H_5$), 7.88 (d, 1H, J"= 7Hz, $H_6$).

2-(N-1 cytosine)-2-nitropropanol **13**:

The compound **7** treated with TsOH in methanol at room temperature for 45 min. gave After chromatography on silica gel (eluent: $CH_2Cl_2$/MeOH: 95/5) pure alcohol **13** in 95% yield

Oil.

**MS** (FAB), m/z: 237 $(MNa)^+$, 221 $(MNa^+$-OH), 215 $(MH)^+$, 190 (MNa-$HNO_2$), 134 (cytosine+Na), 112 (cytosine+H).

**NMR $^1$H** ($CDCl_3$+DMSO d6): δ ppm 2.03 (s, 3H, $CH_3$), 4.18 and 4.50 (2dd, 2H, J= 12Hz, J'= 4Hz, $CH_2$-O), 6 (t, 1H, J'= 4Hz, OH), 6.05 (d, 1H, J"= 8Hz, $H_5$), 7.52 and 7.68 (broad 2s, 2H, $NH_2$), 7.92 (d, 1H, J"= 8Hz, $H_6$).

**$H^1$ RMN** ($CDCl_3$): δ 159.59 (C4), 147.03 (C2), 145.76 (C6), 100.34, 94.73 (C5), 62.79, 21.15.

1-(N-1 cytosine)-1-nitroethane **14**:

The alcohol **13** (1.1 mmol) dissolved in methanol (10mL) and powdered potassium hydroxide (1.2 mmole) were maintained at room temperature untill disappearance of the substrate (TLC). The reaction mixture was then poured into water (15mL), neutralized with 5% HCl and extracted with methylene chloride (2x10mL). The organic phase dried over $Na_2SO_4$, concentrated and purified by silica gel column chromatography ($CH_2Cl_2$/MeOH: 95/5), gave the nitroalcane **14** in 73% yield.

Oil.

**MS** (FAB), m/z: 207 $(MNa)^+$, 185 $(MH)^+$, 112 (cytosine+H)$^+$.

**NMR $^1$H** (DMSO d6): δ ppm 1.90 (d, 3H, J= 7Hz, $CH_3$), 5.87 (d, 1H, J'= 8Hz, $H_5$), 6.47 (q, 1H, J=7Hz, CH-$NO_2$), 7.50 and 7.53 (broad 2s, 2H, $NH_2$), 7.67 (d, 1H, J'= 8Hz, $H_6$).

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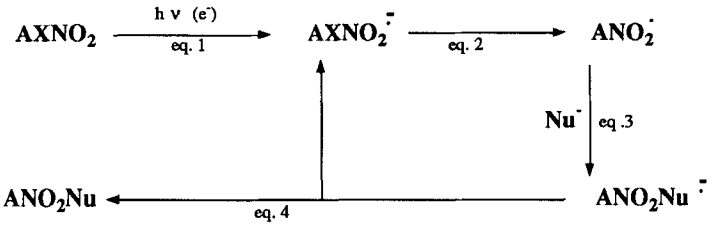


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