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## Nucleosides, Nucleotides and Nucleic Acids

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## A Highly Selective and Efficient Access to N-9 Alkylated Purine Derivatives *via* Radical $S_{RN}1$ Chemistry.

Tawfik Gharbaoui, Rachid Benhida, André Lechevallier<sup>†</sup>, Phillipe Maillos  
and René Beugelmans\*.

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**Abstract:** 6-Chloropurine and 2-amino-6-chloropurine were discovered to be efficient nucleophiles in  $S_{RN}1$  reactions with various gem halonitroalkane derivatives as substrates to give high yield of N-9 alkylated purine derivatives in a N-9/N-7 ratio greater than 95/5.



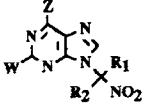
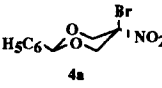
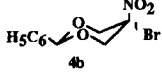
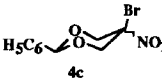
N-9 substituted 6-chloropurines are intermediates in the classical methodology for the synthesis of various 6-9 disubstituted purines from the commercially available 6-chloropurine and 2-amino-6-chloropurine<sup>1</sup>. Substitution at N-9 is often, but not always selective, so that mixtures of N-9 and of unwanted N-7 substituted derivatives are formed. Therefore the interest for selective methods is constant<sup>2</sup> and has increased when purine derivatives became needed as potentially useful antiviral drugs<sup>3</sup>. This prompted us to explore new developments based upon radical  $S_{RN}1$  chemistry which presents original features.

$S_{RN}1$  reactions in which a substrate  $R_1R_2C(NO_2)X$  undergoes replacement of the halide  $X$  (Cl, Br) by a nucleophile  $Nu^-$  are very efficient and generally not (or little) subject to steric hindrance, but in contrast to the great number of carbon-carbon bond forming reactions where carbanions are the nucleophilic reagents<sup>4</sup>, carbon-nitrogen bond formation is much less documented. Besides the preliminary report by N. Kornblum on amines<sup>5</sup>, the only relevant contributions are those of R. Bowman's group on nitroimidazoles<sup>6</sup> and our's on imidazoles<sup>7</sup>. We report herein our first results on 6-chloropurine **1a** and 2-amino-6-chloropurine **1b** as nucleophiles in reactions with variously functionalized substrates (TABLE).

The photostimulated reactions between 6-chloropurine **1a** dissolved in a mixture of DMSO/ $CH_3CN$  (1:2) (heterogeneous system)<sup>7,8</sup> and the simple 2-bromo-2-nitropropane **2** or the monofunctionalized substrate<sup>9</sup> **3** gave a single product **5** or **6** (N.M.R; thin layer chromatography). Such was not the case with **4a** or **4b** since either of them yielded a mixture of two compounds **7a** and **7b** which were separated by

<sup>†</sup>. Deceased 02 August 1991.

TABLE

Nucleophiles <sup>a</sup>	Substrates	time (min)	Products (yield%) <sup>b</sup>
			
1a Z=Cl W=H	2 R <sub>1</sub> =R <sub>2</sub> =CH <sub>3</sub>	180	5 (96)
	3 R <sub>1</sub> =CH <sub>3</sub> , R <sub>2</sub> =CH <sub>2</sub> OTHP	120	6 (91) (diastereoisomers)
	 4a	120	7a+7b (a/b:90/10) <sup>c</sup> (60)
	 4b	90	7a+7b (a/b:90/10) <sup>c</sup> (50)
	 4c	90	7a+7b (a/b:90/10) <sup>c</sup> (81)
1b Z=Cl W=NH <sub>2</sub>	2 R <sub>1</sub> =R <sub>2</sub> =CH <sub>3</sub>	210	8 (88)
	3 R <sub>1</sub> =CH <sub>3</sub> , R <sub>2</sub> =CH <sub>2</sub> OTHP	105	9 (95) (diastereoisomers)

a) 1.5 eq. Nu; 1.5 eq. K<sub>2</sub>CO<sub>3</sub>; DMSO/CH<sub>3</sub>CN (1/2); illumination by HANAU 100W UV lamp. b) isolated pure products. c) ratio determined from isolated pure products.

column chromatography. A third experiment using **4c** (mixture of cis/trans isomers) gave also a mixture of **7a** and **7b** in a ratio similar to that determined in reactions from pure **4a** or **4b**.

The quantitative conversion of **7a** to the hypoxanthine derivative **10** (whose structure was unambiguously determined by X Ray crystallography, FIG.) (scheme 1) indicates that the substitution reaction was highly selective on N-9 and the comparison of the NMR spectra of **6**, **7a**, **7b** and **10** unambiguously shows that **6** is a diastereoisomeric mixture and that **7a** and **7b** are conformationally stable isomers.

Comparative examination of NMR data of **7a** and **7b** indicated that the 6-chloropurine substituent of the minor product **7b** has *cis* equatorial configuration. In the chair conformation of the dioxane ring, the NO<sub>2</sub> group of the planar radical intermediate **4** is quasi equatorial and from the product distribution, one can assume that the attack from  $\beta$  face is favored over that from the  $\alpha$  face in a ratio (9:1) which reflects the greater steric hindrance to the approach of **1a**<sup>-</sup> caused by two axial hydrogen atoms on carbon C-4 and C-6 (scheme 2).

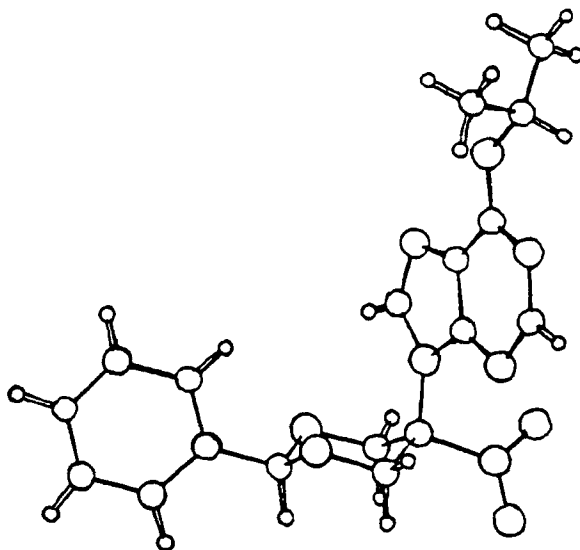
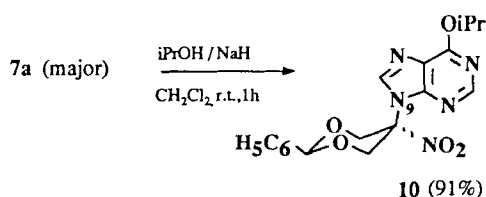


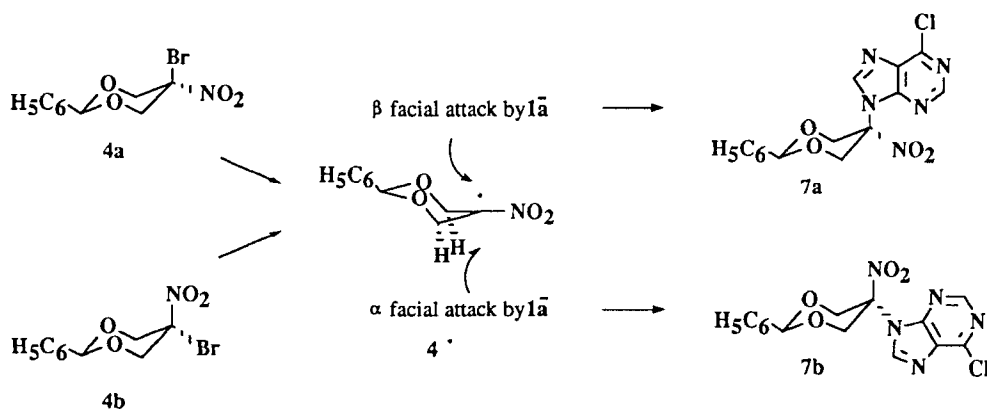
FIG.



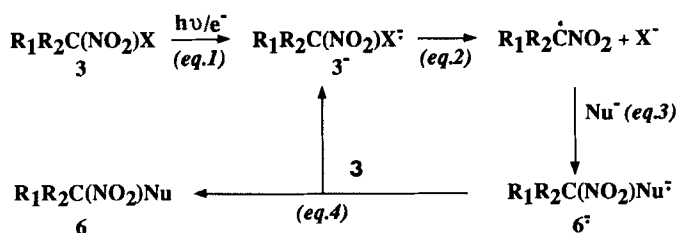
scheme 1

We then turned our attention to the 2-amino-6-chloropurine **1b** as a nucleophile in these reactions, since it is molecule of major importance for the syntheses of guanine derivatives. The  $S_{\text{RN}}1$  reaction carried out between the derived anion **1b**<sup>−</sup> and the substrates **2** and **3** gave the corresponding N-9 alkylated products **8** and **9** in high yield. Thus, the electron releasing 2-amino group does not affect the nucleophilic behaviour of **1b** as compared with **1a**.

Since neither of these purine derived anions were used before as nucleophiles in  $S_{\text{RN}}1$  reactions, we have performed classical experiments supporting the four step mechanism (scheme 3) on a model reaction between **1** and **3**.



scheme 2



scheme 3

For the same reaction time (120 min) it was observed that -i) In the dark, no substitution product was obtained, since illumination which initiates the chain by providing the activation energy for the monoelectronic transfer to  $R_1R_2C(NO_2)X$  and formation of the radical anion  $R_1R_2C(NO_2)X^{\cdot-}$  was suppressed. -ii) Under illumination, but in presence of a catalytic amount of *para* dinitrobenzene (5%) acting as an electron trap towards the two radical anions  $R_1R_2C(NO_2)X^{\cdot-}$  and  $R_1R_2C(NO_2)Nu^{\cdot-}$  the yield of  $R_1R_2C(NO_2)Nu$  was significantly diminished (16% instead of 91%). -iii) Under illumination, but in the presence of galvinoxyle which acts as a radical scavenger towards  $R_1R_2C(NO_2)Nu^{\cdot-}$ , no substitution product was formed.

**Conclusion.** For the first time, 6-chloro **1a** or 2-amino-6-chloropurine **1b** are demonstrated to be efficient nucleophiles for  $S_{RN}1$  reaction with gem bromo-nitro derivatives leading to N-9 alkylated purines. Thus, radical  $S_{RN}1$  reactions which are highly regioselective and furthermore compatible with chlorine borne on C-6 of purines are promising for the synthesis of various adenine and guanine derivatives. The scope and limitations of this methodology are currently under active investigation.

**Experimental Section:**

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

**General Methods.** Melting point was obtained on a Reichert apparatus. The IR spectra were recorded on a Nicolet (205, FT-IR) spectrometer. The UV spectra were obtained on a Perkin-Elmer lambda 5 UV/VIS spectrophotometer. The mass spectra were recorded on a AEI.MS-50 (MS-EI) or EI.MS-9 (MS-CI) spectrometer. The proton and carbon NMR spectra were recorded on either a Bruker spectrometer 4.7 T (200 Mz) or 9.4 T (400 Mz). Chemical shifts are reported in  $\delta$  units, parts per million (ppm) downfield from TMS for  $^1\text{H}$  NMR ( $\delta = 0$ ) and from  $\text{CDCl}_3$  for  $^{13}\text{C}$  NMR ( $\delta = 77.14$ ). Column chromatography utilized silica gel 60 (230-400 mesh) from E. Merck laboratories as the solid phase.

General procedure for the preparation of gem nitro-N-9-(6-chloro or 2-amino-6-chloropurine)alkanes:

A solution of **1a** or **1b** (1.5 eq) in a mixture of dry DMSO/ $\text{CH}_3\text{CN}$  (ratio 1:2 and 10 ml/mmol) was stirred with  $\text{K}_2\text{CO}_3$  (1.5 eq) about 30 min under argon. The gem bromonitroalkane (1 eq), dissolved in 2 ml of DMSO/ $\text{CH}_3\text{CN}$ , was then added by syringe to the heterogeneous mixture. After exposure to 100W fluorescent light (HANAU), under argon (reaction monitored by TLC silica gel), the mixture was poured onto ice-water and extracted twice by  $\text{CH}_2\text{Cl}_2$ . The organic layer was dried and the solvent was removed. The crude product was purified by silica gel column chromatography (Ether/pentane/methanol: 70/25/5).

6-chloro-9-(2-nitro-propane-2-yl)-purine **5**

Oil.

**SM (CI):**  $m/z$  242, 244 ( $\text{MH}^+$ ), 195, 197 ( $\text{MH}^+ - \text{HNO}_2$ ), 155, 157 (6-chloro-purine+H) $^+$ .

**$^1\text{H}$  NMR** ( $\text{CDCl}_3$ ):  $\delta$  (ppm) 2.54 (s, 6H), 8.31 (s, 1H,  $\text{H}_8$  purine), 8.67 (s, 1H,  $\text{H}_2$  purine).

**$^{13}\text{C}$  NMR**(DMSO- $\text{D}_6$ ):  $\delta$  (ppm) 151.8 (C2), 145.7 (C8), 97.1, 24.9.

**Anal.** Calc. for  $\text{C}_8\text{H}_8\text{N}_5\text{ClO}_2$ : C: 39.75; H: 3.31. Found: C: 39.91; H: 3.51.

6-chloro-[2-nitro-1-(2-oxy-tetrahydropyranyl)-propane-2-yl]-purine **6**.

1st diastereoisomer:

Oil

**IR** ( $\text{CDCl}_3$ ):  $\nu$  ( $\text{cm}^{-1}$ ) 1030, 1130, 1200, 1220, 1290, 1340, 1560 ( $\text{NO}_2$ ), 1580, 2940.

**SM (CI):**  $m/z$  342-344 ( $\text{MH}^+$ ), 295-297 ( $\text{MH}^+ - \text{HNO}_2$ ), 155-157 (6-chloro purine), 85 (THP) $^+$ , 57.

**UV** ( $\text{CH}_3\text{OH}$ ):  $\lambda$  max (nm) 263.

**$^1\text{H}$  NMR** ( $\text{CDCl}_3$ ):  $\delta$  (ppm) 1.33-1.90 (large, 6H), 2.55 (s, 3H), 3.55 (m, 1H), 3.83 (m, 1H), 4.60 (d, 1H,  $J=10\text{Hz}$ ), 4.63 (broad s, 1H), 4.72 (d, 1H,  $J=10\text{Hz}$ ), 8.66 (s, 1H,  $\text{H}_8$  purine), 8.80 (s, 1H,  $\text{H}_2$  purine).

**$^{13}\text{C}$  NMR** ( $\text{CDCl}_3$ ):  $\delta$  (ppm) 152.25 (C6), 151.95 (C2), 151.6 (C4), 144.4, (C8), 131.95 (C5), 100.2, 97.65, 69.8, 63.45, 30, 24.9, 21.5, 19.4.

2nd diastereoisomer:

Oil

**IR** ( $\text{CDCl}_3$ ):  $\nu$  ( $\text{cm}^{-1}$ ) 1030, 1130, 1200, 1220, 1290, 1340, 1560 ( $\text{NO}_2$ ), 1580, 2940.

**SM (IC):**  $m/z$  342-344 ( $MH^+$ ), 295-297 ( $MH^+ - HNO_2$ ), 155-157 (6-chloro purine), 85 (THP) $^+$ , 57.

**UV** ( $CH_3OH$ ):  $\lambda$  max (nm) 263.

**$^1H$  NMR** ( $CDCl_3$ ):  $\delta$  (ppm) 1.48-1.68 (large, 6H), 2.56 (s, 3H), 3.45-3.55 (m, 2H), 4.3 (d, 1H,  $J=10Hz$ ), 4.78 (m, 1H), 4.88 (d, 1H,  $J=10Hz$ ), 8.52 (s, 1H,  $H_8$  purine), 8.75 (s, 1H,  $H_2$  purine).

**$^{13}C$  NMR** ( $CDCl_3$ ):  $\delta$  (ppm) 151.95 (C2), 151.83 (C6), 145.87 (C4), 144.15 (C8), 151.8 (C6), 98.95, 97.42, 69.07, 62.5, 29.9, 24.7, 21.4, 18.7.

#### 6-Chloro-9-(5-nitro-2-phenyl-1,3-dioxanne-5-yl)purine:

Trans isomer **7a**:

Oil.

**IR** ( $CDCl_3$ ),  $\nu$  ( $cm^{-1}$ ): 1123, 1220, 1311, 1410, 1484, 1565 ( $NO_2$ ), 1590, 2887, 3134.

**M.S.(IE):**  $m/z$ : 316-314 ( $M^+ - HNO_2$ ), 270, 209, 157-155 (6-chloropurine), 105, 77.

**$^1H$  NMR** ( $CDCl_3$ ):  $\delta$  (ppm) 4.93 (d, 2H,  $J=13Hz$ , H ax.), 5.43 (d, 2H,  $J=13Hz$ , H eq.), 5.83 (s, 1H, O-CH-O), 7.26 (br s, 5H, H ar), 8.63 (s, 1H,  $H_8$  purine), 8.76 (s, 1H,  $H_2$  purine).

**$^{13}C$  NMR** ( $CDCl_3$ ):  $\delta$  (ppm) 152.47, 152.15, 151.6, 143.9, 135.1, 132.15, 130, 128.5, 126.05, 103.15, 69.45.

**Anal.** Calcd. for  $C_{15}H_{12}ClN_5O_4$ : C (49.81), H (3.34). Found: C (49.48), H (3.42).

Cis isomer **7b**:

Oil.

**IR** ( $CDCl_3$ ),  $\nu$  ( $cm^{-1}$ ): 1134, 1233, 1296, 1388, 1441, 1569 ( $NO_2$ ), 1595, 2874, 3107.

**M.S.(EI):**  $m/z$ : 316-314 ( $M^+ - HNO_2$ ), 270, 209, 157-155 (6-chloropurine), 105, 77.

**$^1H$  NMR** ( $CDCl_3$ ):  $\delta$  (ppm) 4.75 (d, 2H,  $J=13Hz$ , H ax.), 5.8 (d, 2H,  $J=13Hz$ , H eq.), 5.8 (s, 1H, O-CH-O), 7.45 (br s, 5H, H ar), 8.33 (s, 1H,  $H_8$  purine), 8.8 (s, 1H,  $H_2$  purine).

**$^{13}C$  NMR** ( $CDCl_3$ ):  $\delta$  (ppm) 153, 151.7, 141.3, 135.3, 131.65, 130, 128.8, 126.35, 101.7, 89.85, 68.2.

#### 2-Amino-6-chloro-9-(2-nitro-propane-2-yl)purine **8**

**m.p.:** 163°C.

**IR** ( $CDCl_3$ ),  $\nu$  ( $cm^{-1}$ ): 1275, 1567, 1620, 2975, 3425.

**M.S. (IC):**  $m/z$  259-257 ( $MH^+$ ), 212-210 ( $MH^+ - HNO_2$ ), 172-170 (2-amino-6-chloropurine+H) $^+$ .

**$^1H$  NMR** ( $DMSO d_6$ ):  $\delta$  (ppm) 2.36 (s, 6H), 7.05 (large s, 2H,  $NH_2$ ), 8.5 (s, 1H,  $H_8$  purine).

**$^{13}C$  NMR** ( $DMSO d_6$ ):  $\delta$  (ppm) 159.5, 153.7, 150.15, 140.6, 123.75, 96.5, 24.85.

**Anal.** Calcd. for  $C_8H_9N_6O_2$ : C: 36.99; H: 3.47. Found: C: 37.06; H: 3.56.

#### 2-Amino-6-chloro-9-[2-nitro-1-(2-oxy-tétrahydropyranyl)-propane-2-yl]purine **9**

Oil.

1st diastereoisomer:

**IR** ( $CDCl_3$ ):  $\nu$  ( $cm^{-1}$ ) 1020, 1060, 1110, 1120, 1160, 1280, 1320, 1490, 1560, 1600, 2925, 3000-3500, 3400, 3500.

**SM (IC):**  $m/z$  359-357 ( $MH^+$ ), 314-312 ( $MH^+ - HNO_2$ ), 172-170 (2-amino 6-chloropurine), 85 (THP) $^+$

57.

**UV** ( $CH_3OH$ ):  $\lambda$  max (nm) 254.

**$^1H$  NMR** ( $CDCl_3$ ):  $\delta$  (ppm) 1.33-1.76 (large, 6H), 2.43 (s, 3H), 3.6 (m, 1H), 3.83 (m, 1H),

4.48 (d, 1H, J=10Hz), 4.6 (d, 1H, J=10Hz and s, 1H), 5.26 (broad s, 2H, NH<sub>2</sub>), 8.21 (s, 1H, H<sub>8</sub> purine).  
<sup>13</sup> C NMR (CDCl<sub>3</sub>): δ (ppm) 158.95 (C2), 144.35 (C4), 140.95 (C8), 124.9 (C5), 100.2, 97.4, 69.85, 63.3, 30.15, 25.05, 21.45, 19.30.

**Anal.** Calcd. for C<sub>13</sub>H<sub>17</sub>ClN<sub>6</sub>O<sub>4</sub>: C: 43.51; H: 4.74. Found: C: 43.38; H: 4.65.

2nd diastereoisomer:

**SM (IC):** m/z 359-357 (MH<sup>+</sup>), 314-312 (MH<sup>+</sup>- HNO<sub>2</sub>), 172-170 (2-amino 6-chloropurine), 85 (THP)<sup>+</sup>,

57.

**UV** (CH<sub>3</sub>OH): λ max (nm) 251.

<sup>1</sup> H NMR (CDCl<sub>3</sub>): δ (ppm) 1.33-1.75 (large, 6H), 2.43 (s, 3H), 3.5 (m, 2H), 4.23 (d, 1H, J=10Hz), 4.8 (d, 1H, J=10Hz and s, 1H), 5.26 (broad s, 1H, NH<sub>2</sub>), 8.1 (s, 1H, H<sub>8</sub> purine).

<sup>13</sup> C NMR (CDCl<sub>3</sub>): δ (ppm) 159.1 (C2), 154.1 (C6), 151.95 (C4), 140.50 (C8), 125.25 (C5), 98.9, 97.2, 69.1, 62.35, 30, 24.9, 21.35, 18.7.

#### Synthesis of 6-isopropoxy-9-(5-nitro-2-phenyl-1,3-dioxanne-5-yl)purine 10:

Sodium hydride (50 mg, 2 mmol washed twice by pentane), and CH<sub>2</sub>Cl<sub>2</sub> (10 ml) introduced in a pyrex flask capped with a rubber septum are cooled in an ice bath and stirred for 10 min. under argon. Isopropyl alcohol (154 μl, 2 mmol) is slowly added by syringe and the mixture is kept at room temperature for 15 min. The purine derivative **7a** (723 mg, 2 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) is then introduced by syringe and stirring is maintained at room temperature for 1 hour. After classical work-up, the crude product is purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH : 95/5) to give **8**, white solid (700 mg, 91%) slowly recrystallized for several days in pure MeOH to yield the monocrystal required for X-ray crystallography.

**m.p.:** 180°C.

**IR** (CDCl<sub>3</sub>), ν (cm<sup>-1</sup>): 1113, 1155, 1250, 1315, 1470, 1566 (NO<sub>2</sub>), 1600, 1610, 2915, 3050, 3075.

**M.S.(EI):** m/z : 385 (M<sup>+</sup>), 339 (M<sup>+</sup>-NO<sub>2</sub>), 297, 234, 191.

<sup>1</sup> H NMR (CDCl<sub>3</sub>): δ (ppm) 1.5 (d, 6H, J= 6Hz, (CH<sub>3</sub>)<sub>2</sub>CHO), 4.9 (d, 2H, J= 13Hz, H ax.), 5.46 (d, 2H, J= 13Hz, H eq.), 5.68 (m, 1H, J= 6Hz, pur-O-CH), 5.82 (s, 1H, O-CH-O), 7.36 (br s, 5H, H ar), 8.42 (s, 1H, H<sub>8</sub> purine), 8.5 (s, 1H, H<sub>2</sub> purine).

**Anal.** Calcd. for C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>O<sub>5</sub>: C (56.10), H (4.94). Found: C (56.08), H (4.73).

**Crystal data:** C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>O<sub>5</sub>, M= monoclinic, space group C2/c, a= 21.411(9), b= 12.577(6), c= 15.032(7) Å, β= 112.88(7)°, U= 3729 Å<sup>3</sup>. Dc= 0.8\*0.4\*0.4 mm<sup>3</sup>. A Philips automatic diffractometer, graphite monochromator, λ= 0.7107 Å, ω= 0.025°. s<sup>-1</sup>, larg. 1.4°, 3 reflexions /3hours. 3764 reflexions were recorded, of which 2856 unique reflexions were observed with I>3.0 σ (I).

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We acknowledge Dr J. Guilhem and Dr C. Pascard (ICSN,CNRS), for the X-ray crystal determination and the Wellcome Foundation (UK) and Laboratoire Wellcome (France) for the generous financial support.



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