

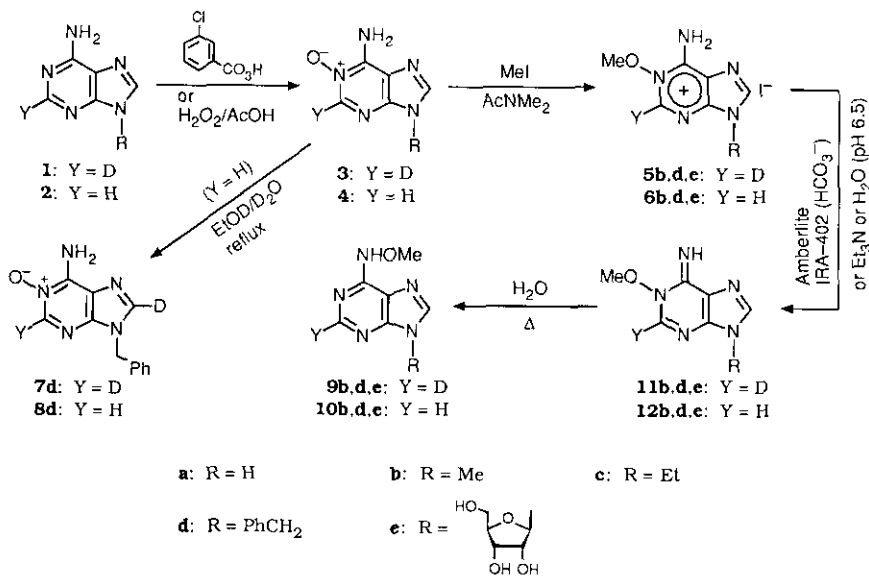
SYNTHESES OF THE 1-*N*-OXIDES AND 1-METHOXY AND *N*<sup>6</sup>-METHOXY  
DERIVATIVES OF 2-DEUTERIOADENINES SUBSTITUTED OR UNSUBSTITUTED  
AT THE 9-POSITION

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*Abstract*—Peracid oxidations of adenine-2-*d* (**1a**) and its 9-substituted derivatives (**1b—e**) produced the corresponding 1-*N*-oxides (**3a—e**) in fair yields. Methylations of 9-methyl- (**3b**) and 9-benzyladenine-2-*d* 1-oxide (**3d**) and adenosine-2-*d* 1-oxide (**3e**) with MeI in AcNMe<sub>2</sub> afforded the corresponding 1-methoxy derivatives **5b,d** and **11e** in good yields. Dimroth rearrangement of **5b**, **5d**, and **11e** gave the *N*<sup>6</sup>-isomers **9b**, **9d**, and **9e**, but their isotopic purities were unsatisfactory. Unambiguous assignments of the purine-ring proton signals in the nmr spectra of the unlabeled adenines (**4a—e**, **6b,d**, and **12e**) have been made by comparison with those of the labeled species (**3a—e**, **5b,d**, and **11e**).

In a previous communication<sup>1</sup> from this laboratory, we described the syntheses of some 2-deuterioadenines (type **1**), substituted or unsubstituted at the 9-position, starting from 9-substituted adenines (type **2**) and utilizing the "fission and reclosure" technology<sup>2,3</sup> developed for modification of the adenine ring. Because of their stability to isotopic exchange,<sup>1</sup> these C(2)-H labeled compounds should be useful as starting materials for syntheses of a variety of adenine and related structures, which may often be required for biochemical and spectroscopic studies. Now we wish to report the transformations of the 2-deuterioadenines (type **1**) into the corresponding 1-*N*-oxides (type **3**) and 1-methoxy and *N*<sup>6</sup>-methoxy derivatives (types **5**, **11**, and **9**). Although the unlabeled species (types **4**, **6**, **12**, and **10**) of these *N*-oxygenated derivatives assume an important role in the above "fission and reclosure" technology,<sup>2,3</sup> the <sup>1</sup>H nmr spectra of most of them have been awaiting unambiguous assignments of purine-ring proton signals.

The conversion of **1** into **9** via **3**, **5**, and **11** investigated in the present study was essentially the same as that reported previously for the unlabeled series (**2**→**4**<sup>1,4</sup>→**6**<sup>4c,5</sup>→**12**<sup>4b,5</sup>→**10**<sup>6</sup>), as shown in Scheme 1. Thus, oxidation of adenine-2-*d* (**1a**)<sup>1</sup> in AcOH with 30% aqueous H<sub>2</sub>O<sub>2</sub> at room temperature for 7 days produced the 1-*N*-oxide **3a**, which was isolated in 61% yield in the form of the monohydrate (**3a**·H<sub>2</sub>O), mp >300°C. Oxidations of 9-methyladenine-2-*d* (**1b**)<sup>1</sup>, 9-ethyladenine-2-*d* (**1c**)<sup>1</sup>, 9-benzyladenine-2-*d* (**1d**)<sup>1</sup> and adenosine-2-*d* (**1e**)<sup>1</sup> with *m*-chloroperbenzoic acid in MeOH at room temperature or 30°C for 4—4.5 h afforded the corresponding 1-*N*-oxides **3b**·H<sub>2</sub>O (mp >300°C; 65% yield), **3c** [mp 281—284.5°C (dec.); 72%], **3d** [mp 271—272°C (dec.); 71%], and **3e**·H<sub>2</sub>O [mp 231°C (dec.) (sintered at 220°C); 59%]. In an attempt to



Scheme 1

obtain **3a** from **3e** by glycosidic hydrolysis, **3e**-H<sub>2</sub>O was heated with 0.5 N aqueous HCl under reflux for 10 min or at 80°C for 10–210 min. However, we were unable to isolate **3a**-H<sub>2</sub>O. This lack of success was attributable to the instability of the adenine ring caused by the *N*-oxide function.<sup>7</sup>

Methylation of **3b**-H<sub>2</sub>O with MeI in AcNMe<sub>2</sub> at room temperature for 36 h gave 1-methoxy-9-methyladenine-2-*d* hydriodide (**5b**), mp 214°C (dec.), in 93% yield. A similar methylation of **3d** for 48 h furnished 9-benzyl-1-methoxyadenine-2-*d* hydriodide (**5d**), mp 194–196°C (dec.), in 98% yield. Adenosine-2-*d* 1-oxide monohydrate (**3e**-H<sub>2</sub>O) was likewise methylated for 24 h, and the product presumed to be **5e** was treated with Et<sub>3</sub>N in EtOH, giving the free nucleoside **11e**, mp 190–195°C (dec.), in 66% yield. Although all 1-*N*-oxides **3a**–**e** and the 1-methoxy derivatives **5b**,**d** had deuterium contents at the specified position equal in order of magnitude to those of the starting 2-deuterioadenines (**1a**–**e**), the deuterium content in **11e** was 60%, as determined by <sup>1</sup>H nmr spectroscopic analysis. The partial delabeling was probably owing to isotopic exchange through an ionic process similar to that<sup>8</sup> proposed for isotopic exchange of C(8)-H of purines, and it might have been facilitated by the electron-withdrawing 1-methoxy group on treatment of crude **5e** with Et<sub>3</sub>N in MeOH. Finally, the hydriodide salt **5b** was converted into the free base **11b** by use of Amberlite IRA-402 (HCO<sub>3</sub><sup>-</sup>) in H<sub>2</sub>O, and treatment of **11b** with boiling H<sub>2</sub>O for 3 h provided *N*<sup>6</sup>-methoxy-9-methyladenine-2-*d* (**9b**),<sup>6c</sup> mp 244–245°C (dec.), in 51% yield. Treatment of **5d** with boiling 0.5 M phosphate buffer (pH 6.5) for 4 h gave the *N*<sup>6</sup>-methoxy isomer **9d**,<sup>6c</sup> mp 223.5–224.5°C (dec.), in 81% yield, and **11e** underwent similar Dimroth rearrangement (H<sub>2</sub>O, 80–85°C, 5 h) to furnish **9e**, mp 192–194°C (dec.), in 41% yield. The deuterium contents in **9b**, **9d**, and **9e** as determined by <sup>1</sup>H nmr or mass spectroscopic analysis were 82%, 77%, and ca. 60%, respectively.

With the completion of the above syntheses and characterization of the *N*-oxygenated derivatives of 9-substituted 2-deuterioadenines, it was possible to compare their <sup>1</sup>H nmr spectra with those of the unlabeled species. Table I lists the

Table I. Chemical Shifts for Purine Ring Protons of N(1)-Oxygenated Adenines in Me<sub>2</sub>SO-*d*<sub>6</sub>

No.	Compound		Chemical shift ( $\delta$ ) <sup>a)</sup>		
	N(9)-R <sup>b)</sup>	Label at C(2)	C(2)-H	C(8)-H	$\Delta\delta$ <sup>c)</sup>
3a	H	D	—	8.28	—
4a	H	None	8.59	8.29	+0.30
3b	Me	D	—	8.27	—
4b	Me	None	8.65	8.29	+0.36
3c	Et	D	—	8.33	—
4c	Et	None	8.62	8.33	+0.29
3d	PhCH <sub>2</sub>	D	—	8.43	—
4d	PhCH <sub>2</sub>	None	8.65	8.46	+0.19
3e	Rib	D	—	8.54	—
4e	Rib	None	8.61	8.55	+0.06
5b	Me	D	—	8.52	—
6b	Me	None	9.17	8.52	+0.65
5d	PhCH <sub>2</sub>	D	—	8.71	—
6d	PhCH <sub>2</sub>	None	9.15	8.71	+0.44
11e <sup>d)</sup>	Rib	D	(8.48) <sup>d)</sup>	8.27	(+0.21)
12e	Rib	None	8.42	8.23	+0.19

a) Measured in Me<sub>2</sub>SO-*d*<sub>6</sub> at 7—41 mM concentration and expressed in ppm downfield from internal Me<sub>4</sub>Si.

b) Rib =  $\beta$ -D-ribofuranosyl

c)  $\Delta\delta = \delta_{C(2)-H} - \delta_{C(8)-H}$

d) Found to contain the delabeled species (12e) to the extent of 40%. See the text for details.

chemical shifts for the purine ring protons of 3a—e, 4a—e, 5b,d, 6b,d, 11e, and 12e.<sup>9</sup> It may be seen that the C(2)-proton in all 1-*N*-oxides (4a—e) resonates at lower field than the C(8)-proton by 0.06—0.36 ppm, reflecting the dipolar structure of the *N*-oxide function in the pyrimidine moiety. This tendency is even more pronounced in the cases of the 1-methoxy derivatives 6b and 6d, where the positive charge and the electron-withdrawing methoxy group in the pyrimidine moiety lower the electron density at C(2). A similar effect of the 1-methoxy group is still operative in the free nucleoside 12e, in which the C(2)-proton is less shielded than the C(8)-proton by 0.19 ppm. It appears that the C(8)-protons of the 9-benzyl and 9-ribosyl analogues are somewhat less shielded than those of the other 9-alkyl analogues, paralleling our experience in similar structures.<sup>1,3f,6c</sup>

It is well known that adenine and 9-substituted adenines (type 2) undergo hydrogen exchange at C(8) much faster than at C(2).<sup>8b,c,f,i</sup> In order to investigate the effect of the 1-*N*-oxide function on such selectivity, 9-benzyladenine 1-oxide (4d) was heated in a 10% (w/w) solution of EtOD in D<sub>2</sub>O under reflux. Deuteration at C(8) (to form 8d) was 65% at 6 h; ca. 100% at C(8) at 24 h with 10% deuteration at C(2) (to form 7d). Further labeling in boiling CD<sub>3</sub>CO<sub>2</sub>D for 9 h did not complete hydrogen exchange at C(2). These results revealed that the effect of the 1-*N*-oxide function on isotopic exchange of C(2)-H is not significant.

In conclusion, the above results have established a general synthetic route to N(1)-oxygenated 2-deuterioadenines (types 3 and 5) of high isotopic purity. Conversion of 5 into the *N*<sup>6</sup>-methoxy isomer (9) was possible by Dimroth rearrangement, but the deuterium content of 9 was unsatisfactory. As a result of the syntheses of these 2-deuterated species, unambiguous assignments of the C(2)- and C(8)-proton signals in the nmr spectra of isotopically unmodified species have become possible.

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9. See ref. 6c for the interpretation of the <sup>1</sup>H nmr spectra of 10b, 10d, and 10e.

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