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

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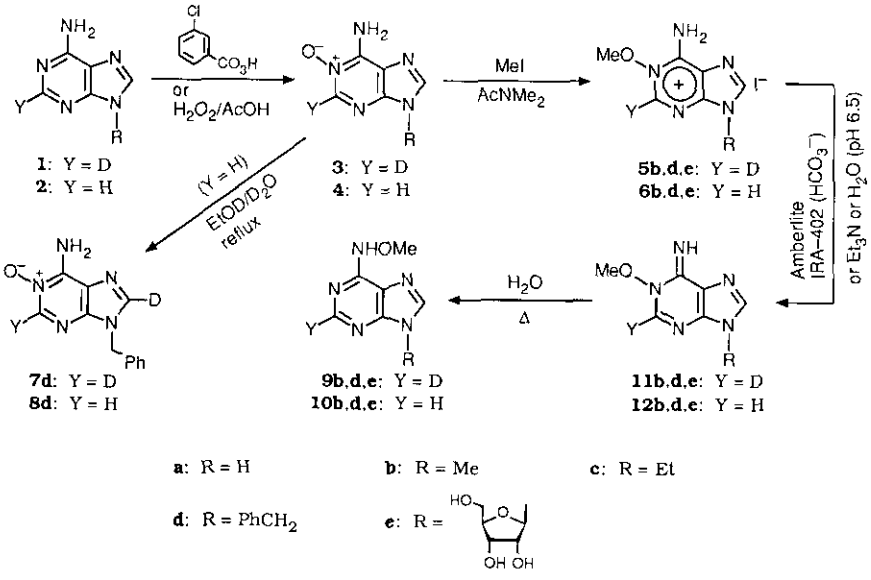
Abstract—Peracid oxidations of adenine-*2-d* (**1a**) and its 9-substituted derivatives (**1b—e**) produced the corresponding 1-*N*-oxides (**3a—e**) in fair yields. Methylations of 9-methyl- (**3b**) and 9-benzyladenine-*2-d* 1-oxide (**3d**) and adenosine-*2-d* 1-oxide (**3e**) with MeI in $AcNMe_2$ afforded the corresponding 1-methoxy derivatives **5b,d** and **11e** in good yields. Dimroth rearrangement of **5b**, **5d**, and **11e** gave the N^6-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[1] 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[2,3] developed for modification of the adenine ring. Because of their stability to isotopic exchange,[1] 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^6-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,[2,3] the ^1H 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**[1,4]→**6**[4c,5]→**12**[4b,5]→**10**[6]), as shown in Scheme 1. Thus, oxidation of adenine-*2-d* (**1a**)[1] in AcOH with 30% aqueous H_2O_2 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_2O), mp >300°C. Oxidations of 9-methyladenine-*2-d* (**1b**),[1] 9-ethyladenine-*2-d* (**1c**),[1] 9-benzyladenine-*2-d* (**1d**),[1] and adenosine-*2-d* (**1e**)[1] 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_2O (mp >300°C; 65% yield), **3c** [mp 281—284.5°C (dec.); 72%], **3d** [mp 271—272°C (dec.); 71%], and **3e**·H_2O [mp 231°C (dec.) (sintered at 220°C); 59%]. In an attempt to



Scheme 1

obtain **3a** from **3e** by glycosidic hydrolysis, **3e**·H_2O 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_2O. This lack of success was attributable to the instability of the adenine ring caused by the *N*-oxide function.[7]

Methylation of **3b**·H_2O with MeI in $AcNMe_2$ 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_2O) was likewise methylated for 24 h, and the product presumed to be **5e** was treated with Et_3N 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 ^1H nmr spectroscopic analysis. The partial delabeling was probably owing to isotopic exchange through an ionic process similar to that[8] 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_3N in MeOH. Finally, the hydriodide salt **5b** was converted into the free base **11b** by use of Amberlite IRA-402 (HCO_3^-) in H_2O, and treatment of **11b** with boiling H_2O for 3 h provided N^6-methoxy-9-methyladenine-2-*d* (**9b**),[6c] 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^6-methoxy isomer **9d**,[6c] mp 223.5—224.5°C (dec.), in 81% yield, and **11e** underwent similar Dimroth rearrangement (H_2O, 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 ^1H 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 ^1H 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_2SO-d_6

Compound			Chemical shift (δ)[a]		
No.	N(9)-R[b]	Label at C(2)	C(2)-H	C(8)-H	$\Delta\delta$[c]
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	$PhCH_2$	D	——	8.43	——
4d	$PhCH_2$	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	$PhCH_2$	D	——	8.71	——
6d	$PhCH_2$	None	9.15	8.71	+0.44
11e[d]	Rib	D	(8.48)[d]	8.27	(+0.21)
12e	Rib	None	8.42	8.23	+0.19

a) Measured in Me_2SO-d_6 at 7—41 mM concentration and expressed in ppm downfield from internal Me_4Si.

b) Rib = β-D-ribofuranosyl

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

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**.[9] 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.[1,3f,6c]

It is well known that adenine and 9-substituted adenines (type **2**) undergo hydrogen exchange at C(8) much faster than at C(2).[8b,c,f,i] 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_2O 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_3CO_2D 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^6-methoxy isomer (**9**) was possible by Dimroth rearangement, 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 ^{1}H nmr spectra of **10b**, **10d**, and **10e**.

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