

A NEW SYNTHETIC ROUTE TO 2-DEUTERIOADENINES SUBSTITUTED OR
UNSUBSTITUTED AT THE 9-POSITION[†]

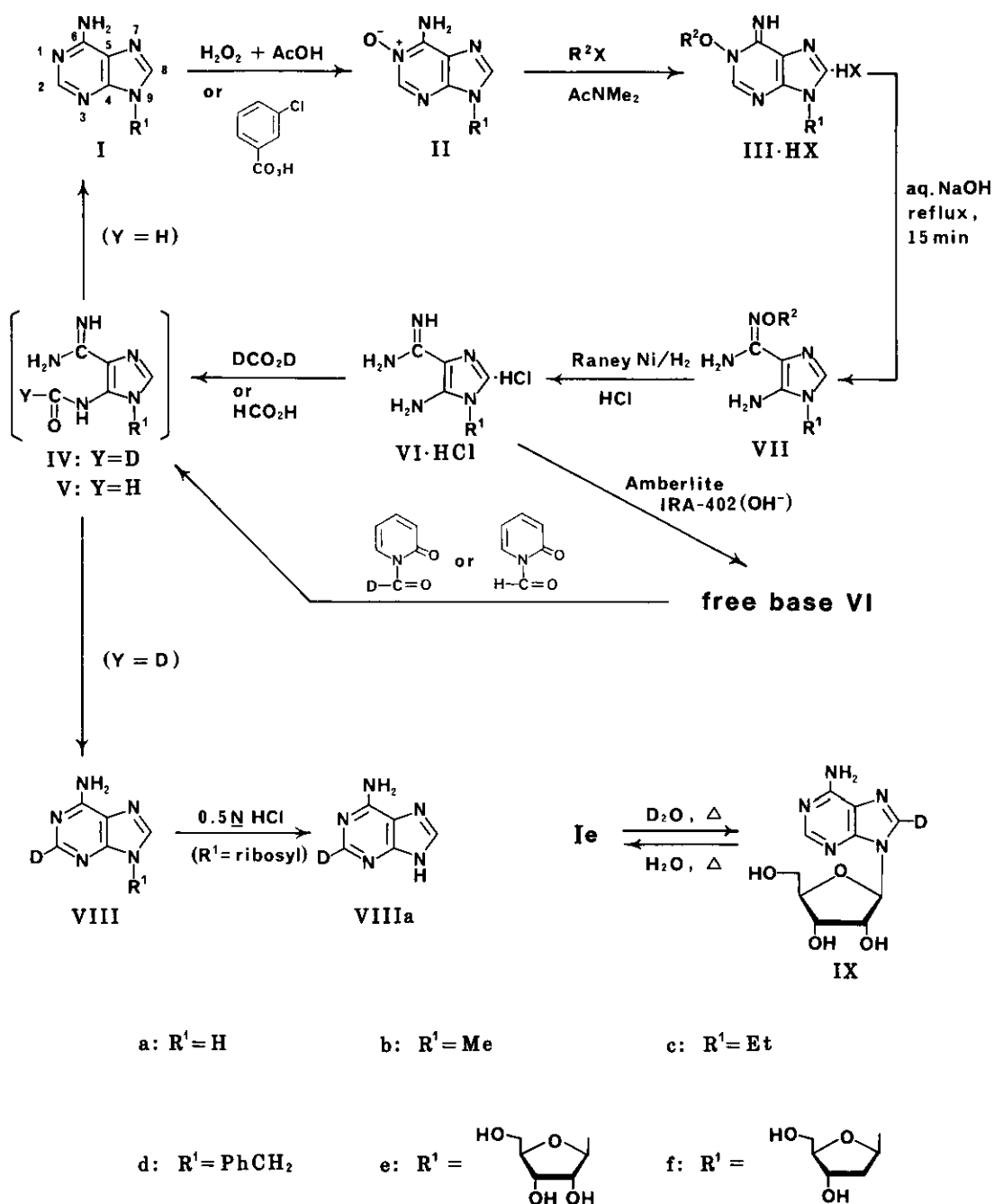
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Abstract— 9-Alkyl-2-deuterioadenines (VIIIb-d), adenosine-2-*d* (VIIIe), and 2'-deoxyadenosine-2-*d* (VIIIf) were synthesized from the 9-substituted adenines Ib-f through cyclization of the monocyclic intermediates VIb-f with formic acid-*d*₂ or 1-(formyl-*d*)-2(1*H*)-pyridone. Hydrolysis of VIIIe, prepared through this synthetic route, with 0.5 *N* aqueous HCl (reflux, 2 h) gave adenine-2-*d* (VIIIa) in 77% yield. Unambiguous assignments of the purine ring protons in the nmr spectra of the unlabeled adenines Ia-f have been made by comparison with those of the labeled adenines VIIIa-f.

Isotopically labeled adenine and its derivatives are of importance for biochemical, mechanistic, and spectroscopic studies. The hydrogen at C-8 of purines can undergo isotopic exchange through the ionic process, offering, for example, a ready access to labeled adenine.¹ However, the exchange is reversible in H₂O,^{1c,f,2} rendering sometimes the use of C(8)-H labeled purines rather limited. The more stable C(2)-H labeled purines^{1c} may be obtained by catalytic hydrogen exchange at both C-2 and C-8 and subsequent selective delabeling from C-8 in H₂O² or by isotopic hydrogenolysis of 2-halopurines.³ Depending on the target purine structures, these methods may frequently be inconvenient to carry out and may not always guarantee¹ⁱ the correctness of the position and/or the magnitude of labeling. Now we wish to report a new and unambiguous pathway from the 9-substituted adenines Ib-f to the title 2-deuterioadenines VIIIa-f, which has utilized our knowledge⁴ concerning fission and reclosure of the adenine ring.

[†]Dedicated to Prof. Nelson J. Leonard, University of Illinois, on the occasion of his 70th birthday with gratitude for the inspiration, both human and scientific, that he has always provided.



SCHEME 1

Prior to the present work, the route from the starting 9-substituted adenines (type I) to the key intermediates (type VI) had already been extended through the 1-oxides (type II), 1-alkoxy derivatives (type III), and monocyclic *N'*-alkoxycarboxamides (type VII).⁵ Thus, VIb·e·HCl were prepared according to the previously reported procedure,⁵ and VIId,e·HCl were alternatively obtained in 75% and 54% overall yields from the 1-methoxy analogues IIIId·HI ($R^2 = \text{Me}$)⁶ and IIIe ($R^2 = \text{Me}$)⁷ through VIIId ($R^2 = \text{Me}$) [mp 118.5–119.5°C; 82% yield from IIIId·HI ($R^2 = \text{Me}$)]⁸ and VIIe ($R^2 = \text{Me}$) [mp 148.5–149.5°C; 57% yield from IIIe ($R^2 = \text{Me}$)]. Adenosine 1-oxide (IIe), the intermediate for the synthesis of IIIe from adenosine (Ie), had previously been prepared in 65% yield in the form of the monohydrate by oxidation of Ie with 30% aqueous H_2O_2 in AcOH at 30°C for 5 days.⁹ We found that the reaction proceeded much faster with a higher yield (81%) of IIe·H₂O when Ie (52.5 mmol) was oxidized with *m*-chloroperbenzoic acid (105 mmol) in MeOH (1.5 l) at 30°C for 7 h.

The synthesis of the 2-deoxyribofuranosyl analogue VIIf·HCl followed a similar reaction sequence. Thus, IIIf¹⁰ was allowed to react with MeI in AcNMe₂ at 13–14°C for 6.5 h. The methylated product [IIIIf·HI ($R^2 = \text{Me}$)] was treated successively with Amberlite IRA-402 (HCO_3^-) and boiling aqueous NaOH (15 min), and the resulting *N'*-methoxycarboxamide VIIIf ($R^2 = \text{Me}$) (mp 138–139°C; 64% overall yield from IIIf) was hydrogenolyzed in the usual manner to yield VIIf·HCl.

Cyclization of VIb·d·HCl to the 9-alkyl-2-deuterioadenines VIIIb–d through IVb–d by incorporation of a deuterated C₁ unit was effected in formic acid-*d*₂ (of over 99% isotopic purity) at 70–75°C for 16 h, producing VIIIb (mp > 300°C; 84% yield), VIIIc (mp 194–196°C; 54% yield), and VIId (mp 231.5–232.5°C; 52% overall yield from VIId). For an alternative deuterioformylation, 1-(formyl-*d*)-2(1*H*)-pyridone (hygroscopic solid) was prepared from 2(1*H*)-pyridone by treating it with formic acid-*d*₂ (of over 99% isotopic purity) and dicyclohexylcarbodiimide in CH_2Cl_2 at 0°C for 2 h, the procedure being patterned after that reported¹¹ for the synthesis of 1-formyl-2(1*H*)-pyridone. Treatment of the free base VIb, obtained from VIb·HCl by passing its aqueous solution through a column packed with Amberlite IRA-402 (OH^-), with 1-(formyl-*d*)-2(1*H*)-pyridone (5 molar eq.) in boiling MeCN for 1.5 h furnished VIIIb in 57% yield. The latter cyclization method was then applied to the nucleoside VIe with a slight modification. The hydrochloride VIe·HCl was converted [by the use of Amberlite IRA-402 (OH^-)] into VIe, which was allowed to react with 1-(formyl-*d*)-2(1*H*)-pyridone (6 molar eq.) in AcNMe₂ at room temperature for 4.5 h, affording adenosine-2-*d* (VIIIe) (mp 233–234°C) in 42% overall yield (from VIIe). 2'-Deoxyadenosine-2-*d*

TABLE 1. Chemical Shifts for Purine Ring Protons of Adenine and Its 9-Substituted Derivatives in Me₂SO-d₆

No.	Compound		Chemical shift (δ) ^{a)}		
	N(9)-R ¹	Label at C(2)	C(2)-H	C(8)-H	Δδ ^{b)}
VIIIa	H	D	—	8.07	—
Ia	H	None	8.10	8.07	+0.03
VIIIb	Me	D	—	8.08	—
Ib	Me	None	8.15	8.08	+0.07
VIIIc	Et	D	—	8.15	—
Ic	Et	None	8.15	8.15	±0.00
VIIId	PhCH ₂	D	—	8.24	—
Id	PhCH ₂	None	8.14	8.24	-0.10
VIIIe	Rib ^{c)}	D	—	8.34	—
Ie	Rib ^{c)}	None	8.13	8.34	-0.21
VIIIf	dRib ^{d)}	D	—	8.32	—
If	dRib ^{d)}	None	8.13	8.32	-0.19

a) Measured in Me₂SO-d₆ at 20-80 mM concentration and expressed in ppm downfield from internal Me₄Si.

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

c) Rib = β-D-ribofuranosyl

d) dRib = 2-deoxy-β-D-ribofuranosyl

(VIIIf) (mp 189.5-191°C) was likewise prepared from VIf·HCl in 37% overall yield (from VIIf). Hydrolysis of VIIIe in boiling 0.5 N aqueous HCl for 2 h provided adenine-2-d (VIIIa) (mp > 300°C) in 77% yield. The correctness of the above synthetic outcome was supported by parallel cyclizations of VIlb·HCl with formic acid and of VIf with 1-formyl-2(1H)-pyridone, which gave 9-methyladenine (Ib)¹² and adenosine (Ie) in 70% (from VIIb) and 43% (from VIIe) yields, respectively. All the 2-deuterioadenines VIIIa-f thus prepared were of deuterium content equal in order of magnitude to that of the formic acid-d₂ used.

Now that a series of the 2-deuterioadenines substituted or unsubstituted at N-9 was in our hands, it became possible to compare their ¹H nmr spectra with those of the unlabeled counterparts. Table 1 lists the chemical shifts for the purine ring pro-

tons of VIIIa-f and Ia-f in $\text{Me}_2\text{SO}-d_6$. It may be seen that the C(2)-proton in adenine (Ia) resonates at lower field than the C(8)-proton, whereas the reverse are the cases of 9-benzyladenine (Id), adenosine (Ie), and 2'-deoxyadenosine (If). This is in agreement with what has been reported.¹³ However, the generalization^{13b} that the C(2)-proton of 9-substituted adenines resonates at higher field than the C(8)-proton does not hold true for 9-methyladenine (Ib) and 9-ethyladenine (Ic). It is interesting that in this series the regions where the C(2)- and C(8)-protons resonate have a crossing at the N(9)-Et level, suggestive of the importance of careful assignments of the ring protons in nmr spectra of 9-substituted adenines. It is well known that adenine (Ia) and 9-substituted adenines including adenosine (Ie) undergo hydrogen exchange at C-8 much faster than at C-2.^{1b,c,f,i} In our hands, adenosine-8- d (IX), prepared from Ie according to the reported deuterium labeling procedure,¹⁴ underwent delabeling in H_2O at 85°C at a rate of 0.41 h^{-1} (half life 1.7 h). On the other hand, the label of adenosine-2- d (VIIIe) was quite stable under similar conditions for at least 6 h.

In conclusion, a general and unambiguous synthetic route to 9-substituted 2-deuterioadenines (type VIII) of high isotopic purity has been exemplified in the present work. Because of their stability to isotopic exchange, these labeled compounds should be useful as starting materials for syntheses of a variety of adenine structures which may often be required for biochemical and spectroscopic investigations.

ACKNOWLEDGMENT This work was supported by a Grant-in-Aid for Scientific Research (No. 57771456, to T. S.) from the Ministry of Education, Science and Culture, Japan, and by a grant from the Japan Research Foundation for Optically Active Compounds.

REFERENCES

1. See, for example, (a) W. J. Wechter, Collect. Czech. Chem. Commun., 1970, 35, 2003; (b) M. Maeda, M. Saneyoshi, and Y. Kawazoe, Chem. Pharm. Bull., 1971, 19, 1641; (c) J. A. Elvidge, J. R. Jones, and C. O'Brien, J. Chem. Soc., Chem. Commun., 1971, 394; (d) M. Tomasz, J. Olson, and C. M. Mercado, Biochemistry, 1972, 11, 1235; (e) D. Lichtenberg and F. Bergmann, J. Chem. Soc., Perkin Trans. 1, 1973, 789; (f) J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, J. Chem. Soc., Perkin Trans. 2, 1973, 2138; (g) Idem, ibid., 1974, 174; (h) S. Mansy and R. S. Tobias, J. Chem. Soc., Chem. Commun., 1974, 957;

- (i) J. L. Wong and J. H. Keck, Jr., ibid., 1975, 125.
2. M. Maeda and Y. Kawazoe, Tetrahedron Lett., 1975, 1643.
3. See, for example, (a) W. C. Coburn, Jr., M. C. Thorpe, J. A. Montgomery, and K. Hewson, J. Org. Chem., 1965, 30, 1110; (b) Idem, ibid., 1965, 30, 1114; (c) T. Sugiyama, H. Iwasawa, and T. Hashizume, Agric. Biol. Chem., 1980, 44, 1057.
4. For a recent review, see T. Fujii, T. Itaya, and T. Saito, Yuki Gosei Kagaku Kyokai Shi, 1983, 41, 1193.
5. T. Fujii, T. Itaya, T. Saito, and M. Kawanishi, Chem. Pharm. Bull., 1978, 26, 1929, and references cited therein.
6. T. Fujii, C. C. Wu, and T. Itaya, Chem. Pharm. Bull., 1971, 19, 1368.
7. T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, and K. Yamamoto, Chem. Pharm. Bull., 1983, 31, 3149.
8. Satisfactory spectral data and/or elemental analyses were obtained for all the new compounds described.
9. (a) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, J. Am. Chem. Soc., 1958, 80, 2755; (b) T. Fujii, T. Saito, T. Itaya, and K. Yokoyama, Chem. Pharm. Bull., 1973, 21, 209.
10. (a) H. Klenow and S. Frederikson, Biochim. Biophys. Acta, 1961, 52, 384; (b) T. Ueda, K. Miura, and T. Kasai, Chem. Pharm. Bull., 1978, 26, 2122; (c) M. Saneyoshi, S. Nishimura, M. Okabe, and F. Fukuoka, J. Pharmacobio-Dyn., 1980, 3, 105.
11. F. Effenberger, M. Keil, and E. Bessey, Chem. Ber., 1980, 113, 2110.
12. T. Fujii, S. Sakurai, and T. Uematsu, Chem. Pharm. Bull., 1972, 20, 1334.
13. (a) J. H. Keck, Jr., R. A. Simpson, and J. L. Wong, J. Org. Chem., 1978, 43, 2587, and references cited therein; (b) M. Ishino, T. Sakaguchi, I. Morimoto, and T. Okitsu, Chem. Pharm. Bull., 1981, 29, 2403, and references cited.
14. M. P. Schweizer, S. I. Chan, G. K. Helmkamp, and P. O. P. Ts'o, J. Am. Chem. Soc., 1964, 86, 696.

Received, 23rd June, 1986