

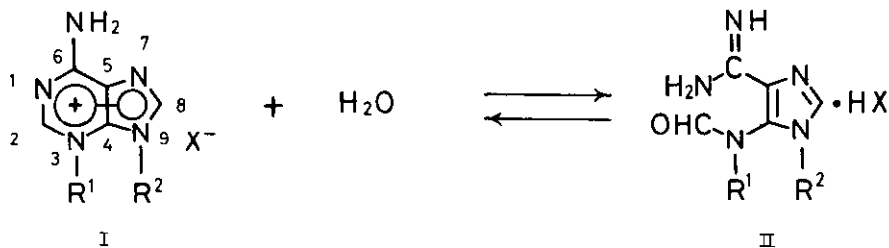
SYNTHESIS AND SODIUM BOROHYDRIDE REDUCTION OF 3,9-DIMETHYLADENINE
PERCHLORATE DEUTERATED AT THE 2-POSITION

Tozo Fujii,* Tohru Saito, Tsuyoshi Nakasaka, and Kyoko Kizu
*Faculty of Pharmaceutical Sciences, Kanazawa University,
Takara-machi, Kanazawa 920, Japan*

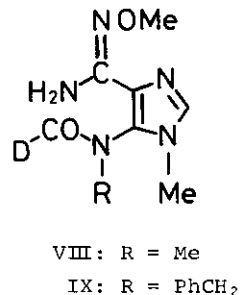
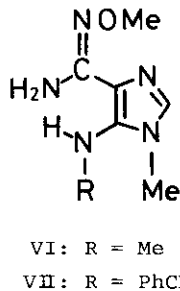
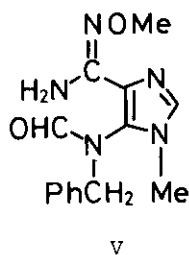
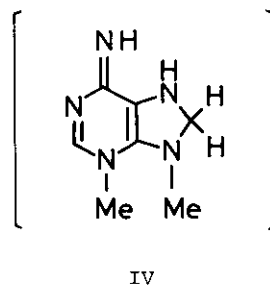
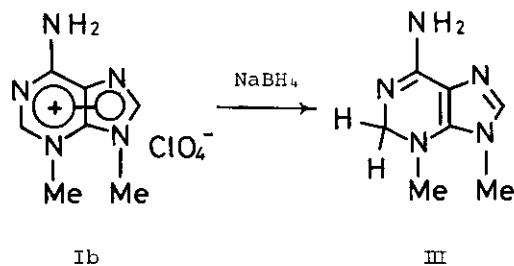
Abstract — The NaBH_4 reduction of 3,9-dimethyladenine perchlorate (Ib) in MeOH was found to give the 1,2-dihydro derivative III. The structure of III was confirmed by a similar reduction of the 2-deuterated isomer XIV, which was synthesized from the methylaminoimidazole VI through the deuterioformamido derivatives VIII and XI. 3-Benzyl-9-methyladenine-2-*d* perchlorate (XV) was similarly prepared from the *N*-benzylformamidoimidazole V through the deformed derivative VII and the deuterioformamido derivatives IX and XII. Comparison of the nmr spectra of Ib and 3-benzyl-9-methyladenine perchlorate (Ie) with those of XIV and XV permitted a distinction between C(2)- and C(8)-proton signals observed for 3,9-dialkyladenine salts (Ia-1); the C(2)-proton resonates at lower field than does the C(8)-proton.

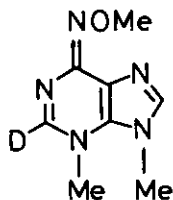
The most notable feature of the chemical behavior of 3,9-disubstituted adenine salts (type I)¹⁻⁴ is that they readily undergo reversible ring opening to equilibrate with the formamidoimidazoles (type II) in aqueous solution.²⁻⁴ This suggests that the center of low electron density in I is at C-2 rather than C-8. With the expectation of obtaining further evidence in support of this view, we investigated the NaBH_4 reduction of 3,9-dimethyladenine perchlorate (Ib) to see whether the hydride ion attack occurs at C-2 and not at C-8.

Treatment of Ib with NaBH_4 in MeOH at room temperature for 30 min afforded the 1,2-dihydro derivative III [77% yield; mp 168–170°C (dec.);⁵ mass spectrum m/e : 165 (M^+); $\lambda_{\text{max}}^{95\% \text{ EtOH}}$ 291 nm (ϵ 5040); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 291 (5180); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 289 (5420); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 265 (shoulder) (4230); nmr ($\text{Me}_2\text{SO}-d_6$) δ : 2.66 (3H, s, N(3)-Me), 3.54 (3H, s, N-

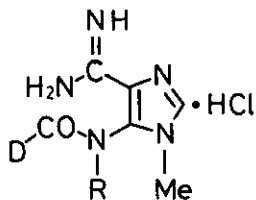


- a: R¹ = Me; R² = Me; X = Cl
- b: R¹ = Me; R² = Me; X = ClO₄
- c: R¹ = Et; R² = Me; X = ClO₄
- d: R¹ = Me₂CH; R² = Me; X = ClO₄
- e: R¹ = PhCH₂; R² = Me; X = ClO₄
- f: R¹ = *p*-(MeO)C₆H₄CH₂; R² = Me; X = ClO₄
- g: R¹ = Me; R² = Et; X = ClO₄
- h: R¹ = Et; R² = Et; X = ClO₄
- i: R¹ = PhCH₂; R² = Et; X = ClO₄
- j: R¹ = Me; R² = PhCH₂; X = ClO₄
- k: R¹ = Et; R² = PhCH₂; X = ClO₄
- l: R¹ = PhCH₂; R² = PhCH₂; X = ClO₄

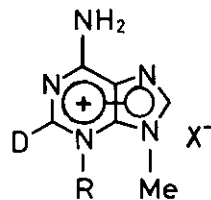




X

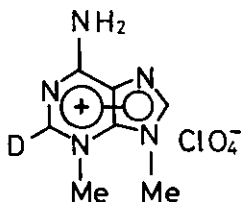


XI: R = Me

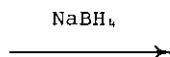
 XII: R = PhCH₂


XIII: R = Me; X = Cl

 XIV: R = Me; X = ClO₄

 XV: R = PhCH₂; X = ClO₄


XIV



XVI

(9)-Me), 4.38 (2H, s, CH₂), 7.38 (1H, s, C(8)-H), 2.0–7.0 (NH₂)]. In order to prove the structure of III and rule out the alternative 7,8-dihydro structure IV, we next tried to synthesize the 2-deuterated isomer XIV of Ib, which should be reduced with NaBH₄ in a similar manner. Thus, the methylaminoimidazole VI,^{1,2} prepared from 1-methoxy-9-methyladenine hydriodide^{6–8} according to our previous procedure,^{1,2,9} was treated with an excess of DCO₂D (of more than 99% isotopic purity) in MeCN at 30°C for 24 h to produce the deuterioformamido derivative VIII (76% yield; mp 160–161°C) together with the cyclized derivative X [4% yield; mp 280–280.5°C (dec.)]. Hydrogenolysis of VIII was effected with Raney Ni and H₂ (1 atm, H₂O + 1 molar equiv. of HCl, 21°C, 3.5–4 h) to furnish crude XI, which cyclized to 3,9-dimethyladenine-2-d hydrochloride (XIII)¹⁰ [48% yield; mp 285.5–287.5°C (dec.); nmr (Me₂SO-d₆) δ: 4.11 (3H, s, N(9)-Me),¹¹ 4.21 (3H, s, N(3)-Me),¹¹ 8.34 (1H, s, C(8)-H), 9.10 and 9.17 (=NH₂⁺ or 2 × NH)] on treatment with Et₃N in boiling EtOH for 30 min. Alternatively, cyclization of the crude XI in MeOH (reflux, 7 h) in the presence of 70% aq. HClO₄ gave the perchlorate XIV [mp >300°C; nmr (Me₂SO-d₆) δ: 4.10 (3H, s, N(9)-Me),¹¹ 4.19 (3H, s, N(3)-Me),¹¹ 8.32 (1H, s, C(8)-H), 9.10 and 9.17 (=NH₂⁺ or 2 × NH)] in 71% yield.

The general utility of the above route for the synthesis of 2-deuterated 3,9-dialkyladenine salts was then checked by a parallel synthesis of the 3-benzyl analogue XV. The N-benzylformamidoimidazole V² was hydrolyzed (1 N aq. NaOH, reflux, 1 h) to give

TABLE 1. Chemical Shifts for C(2)- and C(8)-Protons of 3,9-Dialkyladenine Salts

No.	Compound			Chemical shift (δ) ^{a)}		
	R ¹	R ²	X	C(2)-H	C(8)-H	$\Delta\delta$ ^{b)}
Ia	Me	Me	Cl	8.61	8.34	-0.27
Ib	Me	Me	ClO ₄	8.58	8.32	-0.26
Ic	Et	Me	ClO ₄	8.67	8.34	-0.33
Id	Me ₂ CH	Me	ClO ₄	8.83	8.34	-0.49
Ie	PhCH ₂	Me	ClO ₄	8.78	8.26	-0.52
If	<i>p</i> -(MeO)C ₆ H ₄ CH ₂	Me	ClO ₄	8.73	8.26	-0.47
Ig	Me	Et	ClO ₄	8.59	8.43	-0.16
Ih	Et	Et	ClO ₄	8.68	8.46	-0.22
Ii	PhCH ₂	Et	ClO ₄	8.79	8.40	-0.39
Ij	Me	PhCH ₂	ClO ₄	8.53	8.49	-0.04
Ik	Et	PhCH ₂	ClO ₄	8.64	8.49	-0.15
Il	PhCH ₂	PhCH ₂	ClO ₄	8.72	8.37	-0.35
XIII ¹⁰	Me	Me	Cl	—	8.34 ^{c)}	—
XIV	Me	Me	ClO ₄	—	8.32	—
XV	PhCH ₂	Me	ClO ₄	—	8.25	—

a) Measured in Me₂SO-*d*₆ at 0.02–0.07 M concentration and expressed in ppm downfield from internal Me₄Si.

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

c) Determined on 10⁻³ M solution.

the benzylamino derivative VII (81% yield; mp 97–98°C). Treatment of VII with DCO₂D (*vide supra*) in MeCN (30°C, 118 h) provided the deuterioformamido derivative IX (80% yield) as a thick oil. Hydrogenolysis (Raney Ni/H₂, H₂O + 1 molar equiv. of HCl, 21°C, 8 h) of IX and cyclization of the resulting XII (MeOH + 70% aq. HClO₄, reflux, 8 h) gave XV [mp 265.5°C (dec.); nmr (Me₂SO-*d*₆) δ: 3.74 (3H, s, N(9)-Me), 5.88 (2H, s, PhCH₂), 7.1–7.5 (5H, m, Ph), 8.25 (1H, s, C(8)-H), 9.33 and 9.40 (=NH₂⁺ or 2 × NH)] in 45% yield.

The NaBH₄ reduction of XIV was carried out in a manner similar to that described above for Ib, and the desired compound XVI [mp 169–170.5°C; mass spectrum *m/e*: 166 (M⁺); nmr (Me₂SO-*d*₆) δ: 2.65 (3H, s, N(3)-Me), 3.54 (3H, s, N(9)-Me), 4.36 (1H, s, C(2)-H), 7.36 (1H, s, C(8)-H), 3.5–6.5 (NH₂)] was obtained in 73% yield. The nmr spectra of XVI and III were virtually identical except that the former displayed a one-proton singlet at δ 4.36 [C(2)-H], whereas the latter exhibited a two-proton singlet at δ 4.38 (CH₂). This established the 1,2-dihydro structure of III and excluded the 7,8-dihydro structure IV. The 6-amino structure of III and XVI was suggested by their ir spectra in dilute solutions (3.58 × 10⁻³ M and 3.37 × 10⁻³ M) in CHCl₃, which showed two sharp NH₂ absorption bands at 3540 (ν_{antisym}) and 3425 cm⁻¹ (ν_{sym}).

Now that the deuterated analogues XIII–XV have been available, interpretation of the nmr spectra of 3,9-dialkyladenine salts (type I) becomes easier. Table 1 lists the chemical shifts for the purine ring protons of Ia–l.^{1,2,4} It may be seen that one of the purine proton signals falls within the range 8.26–8.49 δ and the other, in the 8.53–8.83 δ region. Since the C(8)-protons of the deuterated analogues XIII–XV resonate in the former range, it is reasonable to assign the higher field signal of Ia–l to the C(8)-proton; and the lower field signal, to the C(2)-proton. It follows that the contribution of resonance structures with the positive charge in the pyrimidine part may be fairly important for 3,9-dialkyladenine salts (type I).

In conclusion, the results described above confirm that hydride ion attacks Ib at C-2 rather than C-8. The synthesis of the 3,9-dialkyladenines deuterated at the 2-position has made it possible to distinguish between the C(2)- and C(8)-protons of the salts Ia–l nmr spectroscopically. It should be emphasized that this synthesis also presents a good example of the utilization of the facile ring opening⁹ of 1-alkoxy-9-alkyladenines for chemical modification of the adenine ring.

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10. $C_7H_8DN_5 \cdot HCl \cdot 1/2 H_2O$.
11. The assignment of the N(3)- and N(9)-Me signals was based on comparison of these with the N-Me signals of Ic and Ig.

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