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

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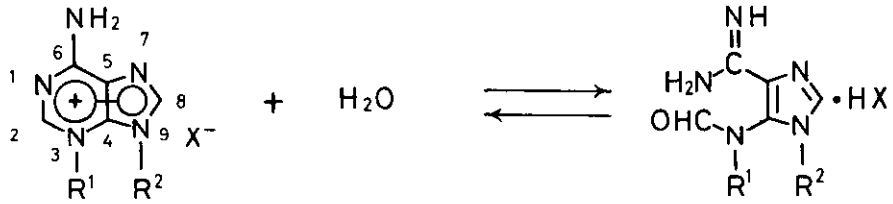
Abstract —— The $NaBH_4$ reduction of 3,9-dimethyladenine perchlorate (Ib) in MeOH was found to give the 1,2-dihydro derivative III. The structure of III was confirmed by a similar reduction of the 2-deuterated isomer XIV, which was synthesized from the methylaminoimidazole VI through the deuteroformamido derivatives VIII and XI. 3-Benzyl-9-methyladenine-2-*d* perchlorate (XV) was similarly prepared from the N-benzylformamidoimidazole V through the deformylated derivative VII and the deuteroformamido 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–l); the C(2)-proton resonates at lower field than does the C(8)-proton.

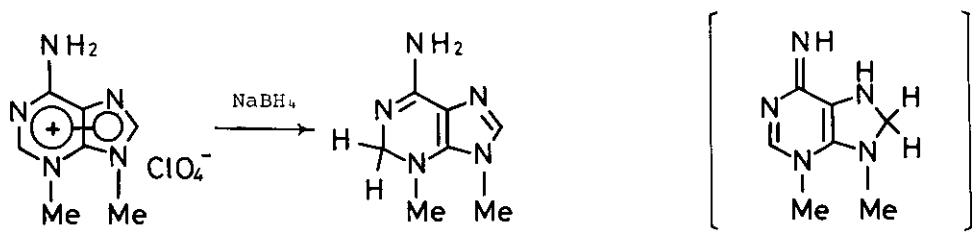
The most notable feature of the chemical behavior of 3,9-disubstituted adenine salts (type I)[1–4] is that they readily undergo reversible ring opening to equilibrate with the formamidoimidazoles (type II) in aqueous solution.[2–4] This suggests that the center of low electron density in I is at C-2 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^+); $\lambda_{max}^{95\%\ EtOH}$ 291 nm (ε 5040); $\lambda_{max}^{H_2O}$ (pH 1) 291 (5180); $\lambda_{max}^{H_2O}$ (pH 7) 289 (5420); $\lambda_{max}^{H_2O}$ (pH 13) 265 (shoulder) (4230); nmr (Me_2SO-d_6) δ: 2.66 (3H, s, N(3)-Me), 3.54 (3H, s, N-

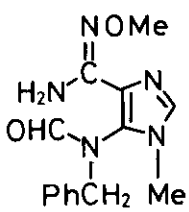


I　　II

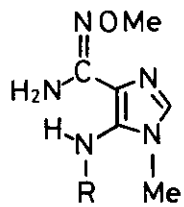
a: R^1 = Me; R^2 = Me; X = Cl
b: R^1 = Me; R^2 = Me; X = ClO_4
c: R^1 = Et; R^2 = Me; X = ClO_4
d: R^1 = Me_2CH; R^2 = Me; X = ClO_4
e: R^1 = $PhCH_2$; R^2 = Me; X = ClO_4
f: R^1 = *p*-(MeO)$C_6H_4CH_2$; R^2 = Me; X = ClO_4
g: R^1 = Me; R^2 = Et; X = ClO_4
h: R^1 = Et; R^2 = Et; X = ClO_4
i: R^1 = $PhCH_2$; R^2 = Et; X = ClO_4
j: R^1 = Me; R^2 = $PhCH_2$; X = ClO_4
k: R^1 = Et; R^2 = $PhCH_2$; X = ClO_4
l: R^1 = $PhCH_2$; R^2 = $PhCH_2$; X = ClO_4



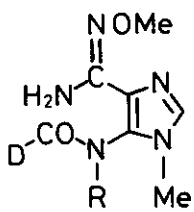
Ib　　III　　IV



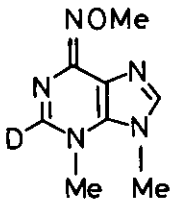
V



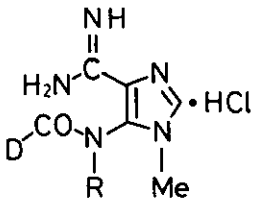
VI: R = Me
VII: R = $PhCH_2$



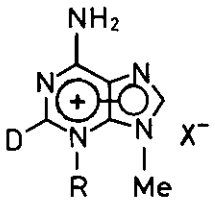
VIII: R = Me
IX: R = $PhCH_2$



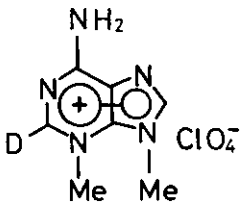
X



XI: R = Me
XII: R = $PhCH_2$



XIII: R = Me; X = Cl
XIV: R = Me; X = ClO_4
XV: R = $PhCH_2$; X = ClO_4



XIV

$NaBH_4$

XVI

(9)-Me), 4.38 (2H, s, CH_2), 7.38 (1H, s, C(8)-H), 2.0–7.0 (NH_2)]. 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 $NaBH_4$ 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 DCO_2D (of more than 99% isotopic purity) in MeCN at 30°C for 24 h to produce the deuteroformamido 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 H_2 (1 atm, H_2O + 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 (Me_2SO-d_6) 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 ($=NH_2^+$ or 2 × NH)] on treatment with Et_3N in boiling EtOH for 30 min. Alternatively, cyclization of the crude XI in MeOH (reflux, 7 h) in the presence of 70% aq. $HClO_4$ gave the perchlorate XIV [mp >300°C; nmr (Me_2SO-d_6) 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 ($=NH_2^+$ 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 V[2] 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

Compound				Chemical shift (δ)[a]		
No.	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_2CH	Me	ClO_4	8.83	8.34	−0.49
Ie	$PhCH_2$	Me	ClO_4	8.78	8.26	−0.52
If	*p*-(MeO)$C_6H_4CH_2$	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 Me_2SO-d_6 at 0.02–0.07 *M* concentration and expressed in ppm downfield from internal Me_4Si.

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 DCO_2D (*vide supra*) in MeCN (30°C, 118 h) provided the deuteroformamido derivative IX (80% yield) as a thick oil. Hydrogenolysis (Raney Ni/H_2, H_2O + 1 molar equiv. of HCl, 21°C, 8 h) of IX and cyclization of the resulting XII (*MeOH + 70% aq. $HClO_4$, reflux*, 8 h) gave XV [mp 265.5°C (dec.); nmr (Me_2SO-d_6) δ: 3.74 (3H, s, N(9)-Me), 5.88 (2H, s, $PhC\underline{H}_2$), 7.1–7.5 (5H, m, Ph), 8.25 (1H, s, C(8)-H), 9.33 and 9.40 ($=NH_2^+$ or 2 × NH)] in 45% yield.

The $NaBH_4$ 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 (Me_2SO-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 (NH_2)] 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 (CH_2). 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 $CHCl_3$, which showed two sharp NH_2 absorption bands at 3540 ($\nu_{antisym}$) 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 opening[9] 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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