# Meisenheimer Spiro Picryl Complex of Adenosine. An Example of a Stereoselective Dioxolane Ring Opening in an Acidic Medium[1]

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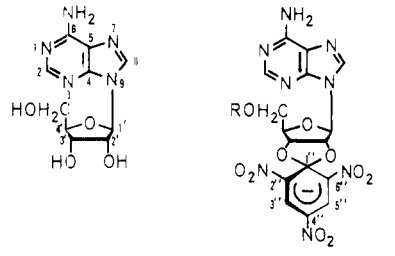
$^1H$ and $^{13}C$ NMR studies show that the acidic decomposition of the spiro Meisenheimer picryl complex of adenosine (**2a**) in aqueous and in dimethyl sulfoxide solutions gives 3′-*O*-(2,4,6-trinitrophenyl)adenosine (**3a**), the opening of the dioxolane ring of **2a** occurring exclusively at the $O_{2'}$ oxygen. In agreement with the chirality of the ribose ring, the two sides of the cyclohexadienyl ring of the spiro complex **2a** are inequivalent. However, the large anisochrony observed in $^1H$ and $^{13}C$ spectra also reflects the steric inhibition of resonance of the endo 6″-nitro group. Vicinal proton–proton coupling constants indicate the ribose ring to be essentially flattened in the complex **2a** but to exist chiefly as the type S conformer in the ether **3a**. In dimethyl sulfoxide–trifluoroacetic acid mixtures, the adenine moiety of **3a** is monoprotonated only at the $N_1$ nitrogen up to acid concentrations of 50% by volume.

Azegami and Iwai have reported that the ribose moiety of adenosine (1) is easily trinitrophenylated by 2,4,6-trinitrobenzenesulfonate at pH 9.5 in aqueous solution to form the Meisenheimer spiro complex **2a**.[3] Hiratsuka and



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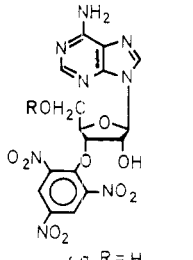

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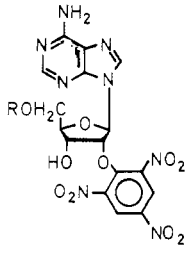

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Uchida have synthesized under similar conditions the spiro complex **2b** derived from adenosine 5′-triphosphate (ATP) and used it as a reporter-labeled substrate of heavy meromyosin ATPase.[4] Acidification of **2a** and **2b** under mild conditions resulted in the opening of the dioxolane ring.[3,4] However, due to the unsymmetrical nature of the dioxolane ring of **2a** and **2b**, the opening may occur unequivocally at one of the two oxygens $O_{2'}$ or $O_{3'}$ to yield either 3′-*O*- or 2′-*O*-(2,4,6-trinitrophenyl)adenosine derivatives **3** or **4** or concurrently at both of these oxygens to give a mixture of these products. This problem has not been investigated though of general interest in the context of the acidic decomposition of such spiro complexes, all examples previously studied having a symmetrical dioxolane ring.[5,6]

We have carried out a thorough investigation of the formation and decomposition of the complex **2a** by NMR. Our results give evidence that the acidic decomposition of **2a** is stereoselective in water and in dimethyl sulfoxide, the opening of the dioxolane ring occurring at the 2′-oxygen to yield 3′-*O*-(2,4,6-trinitrophenyl)adenosine (**3a**) as the only product. Moreover, the NMR parameters obtained for **2a** and **3a** reveal some interesting features regarding the conformation of these molecules.

## Results

The structure of the red adduct **2a** was deduced from a comparison of its $^1H$ and $^{13}C$ NMR data with those for adenosine (1) in the same solvent ($Me_2SO$). Similarly, the NMR parameters of the ether **3a** were compared to those of adenosine dissolved in the same $Me_2SO$-$d_6$/$CF_3CO_2D$ mixtures. Under these experimental conditions, the adenine moiety of **1** and **3a** was protonated at N-1, in agreement with a recent determination, by $^{15}N$ NMR, of the site of protonation of adenosine (1).[7] These species will be noted 1-$H^+$ and 3-$H^+$, respectively, although the use of deuterated trifluoroacetic acid gives mainly 1-$D^+$ and 3-$D^+$ in the solutions.

The pale yellow ether **3a** was quantitatively precipitated by acidification of an aqueous solution of **2a** (see Experimental Section). Dissolution of this **3a** in pure $Me_2SO$-$d_6$ yields again **2a** by rapid ring closure. This result, which emphasizes the high stability of the adduct **2a** in $Me_2SO$, is not unexpected since this solvent is known to strongly stabilize large polarizable anions such as Meisenheimer complexes.[8-10] Moreover, it also shows that we are in fact

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dealing with an equilibrium between **2a** and **3a** in $Me_2SO$, which requires the presence of acid if only **3a** is to be present.

The conversion of **2a** into **3a** was also studied "in situ" by adding increasing amounts of trifluoroacetic acid to a $Me_2SO$ solution of **2a** in an NMR tube. As expected, the $^1H$ NMR spectra showed the gradual disappearance of the signals belonging to **2a** and the concomitant formation of the single ether **3a**. However, side reactions occur with time under these experimental conditions.

**$^1H$ NMR Spectra.** The signals of the various protons belonging to the ribose moiety of adenosine (1), protonated adenosine (1-$H^+$), and adduct **2a** did not overlap in $Me_2SO$-$d_6$ containing a small amount of $D_2O$ to deuterate hydroxylic protons. They were unambiguously assigned by proton–proton decoupling experiments. In order to distinguish between the $H_2$ and $H_8$ signals in these species, we prepared 8-deuterated adenosine according to the method previously described,[11] and this was used to synthesize the corresponding 8-deuterated adduct. In the three derivatives, $H_8$ was found to be less shielded than $H_2$ (Table I).

In the adduct **2a**, the cyclohexadienate protons $H_{3''}$ and $H_{5''}$ were seen to be anisochronous and gave an AB system at low field ($\delta_A$ 8.70 $\delta_B$ 8.51) with a coupling constant $J_{AB}$ = 2.9$_5$ Hz, which is consistent with those reported for other trinitrobenzene adducts.[12-15] The proton spectrum of **2a** was also recorded in $D_2O$, but $H_{2'}$ and $H_{3'}$ have nearly the same chemical shifts in this solvent, preventing an accurate determination of the coupling constants.

The ether **3a** was dissolved in various $Me_2SO$-$d_6$/$CF_3CO_2D$ mixtures, and the results for 90:10 (v/v) and 50:50 (v/v) mixtures are given in Table I. The presence of a low-field singlet at about $\delta$ 9.05 points out the formation of an aromatic ring with equivalent $H_{3''}$ and $H_{5''}$ protons. The chemical shifts of the ribose protons of **3a**-$H^+$ were observed to be dependent on the acid content of the $Me_2SO$-$d_6$/$CF_3CO_2D$ solvent mixture. A similar dependence was also observed for protonated adenosine 1-$H^+$. In both cases, increasing the acid content resulted in a low-field shift of the various ribose protons. When the ether **3a** was dissolved in a 90:10 (v/v) $Me_2SO$-$d_6$/$CF_3CO_2D$ mixture, the chemical shifts of $H_{2'}$ and $H_{3'}$ were nearly the same so that $H_{1'}$, which is the X part of an ABX system, appeared to be virtually coupled to $H_{3'}$.[16,17] This virtual coupling disappeared by increasing the acid content as $H_{2'}$ progressively moved downfield. A 50:50 (v/v) $Me_2SO$-$d_6$/$CF_3CO_2D$ mixture allowed a complete assignment of the ribose protons by double-resonance experiments. The parameters obtained were confirmed by a 250-MHz $^1H$ NMR spectrum. The increased chemical shift difference between $H_{2'}$ and $H_{3'}$ observed at this high frequency allowed us to obtain a more precise value of $J_{1'2'}$ from the $H_{1'}$ signal.

**$^{13}C$ NMR Spectra.** $^{13}C$ chemical shifts were obtained from proton noise decoupled $^{13}C$ spectra (Table II).

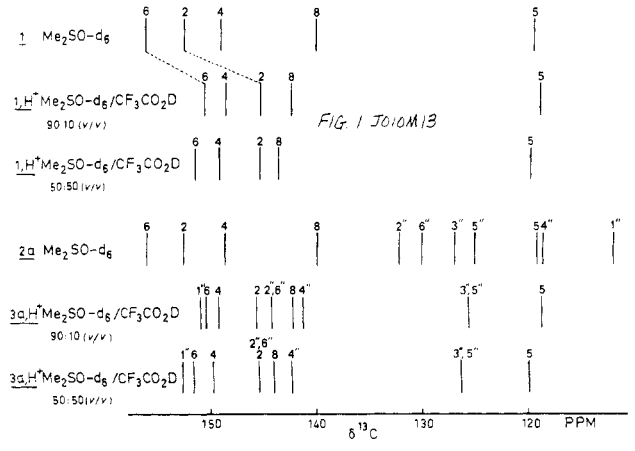


**Figure 1.** Correlation diagram for the $^{13}C$ chemical shifts (with respect to $Me_4Si$) of the aglycon and picryl (or cyclohexadienyl) carbons of adenosine (1), protonated adenosine (1-$H^+$), the protonated ether **3a**-$H^+$, and the adduct **2a**.

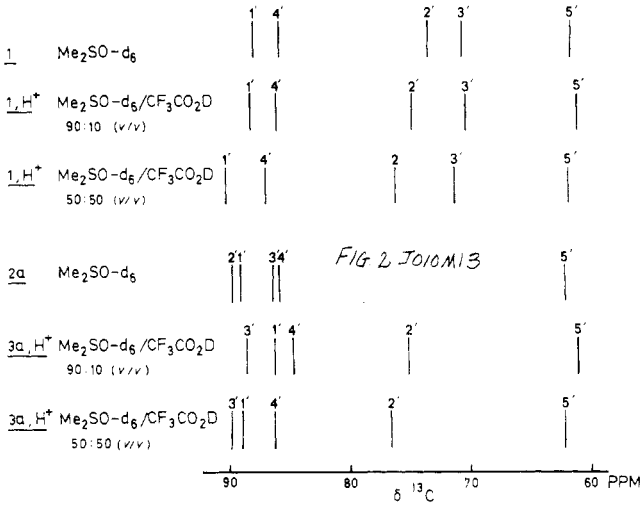


**Figure 2.** Correlation diagram for the $^{13}C$ chemical shifts (with respect to $Me_4Si$) of the ribose carbons of adenosine (1), protonated adenosine (1-$H^+$), the protonated ether, **3a**-$H^+$, and the adduct **2a**.

Hydrogen-bearing carbons were assigned by selective proton-decoupling experiments and from residual coupling observed in off-resonance decoupled spectra. Fully substituted carbons were identified from the long-range $^nJ_{^{13}CH}$ values observed in the proton-coupled $^{13}C$ spectra.

The results obtained for adenosine (1) in $Me_2SO$-$d_6$ are in agreement with previous reports.[18,19] The carbons of the ribose part of **2a** and **3a** were more shielded than the aglycon carbons, as in 1 (Figures 1 and 2).

In agreement with the absence of symmetry in the adduct **2a**, its proton noise decoupled $^{13}C$ spectrum exhibits 16 signals corresponding to the 16 carbons of this adduct, seven of them being fully substituted. Selective proton irradiation allowed the identification of the five ribose carbons and of the aglycon $C_2$ and $C_8$ carbons. Moreover, selective irradiation of the low-field A part ($H_{3''}$) of the AB system showed that this proton was bonded to the less shielded $C_{3''}$ carbon. Similarly, the $H_{5''}$ proton (B part) was found to be bonded to the more shielded $C_{5''}$ carbon. Thus, the nonequivalence is of the same sign in the $^1H$ and $^{13}C$ spectra.

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Table I. Proton NMR Parameters[a] of Adenosine (1), Protonated Adenosine (1-H$^+$), the Spiro Complex 2a and the Protonated Ether 3a-H$^+$

| compd | solvent | $\delta_{H_3''}$ | $\delta_{H_5''}$ | $\delta_{H_8}$ | $\delta_{H_2}$ | $\delta_{NH_2}$ | $\delta_{H_1'}$ | $\delta_{H_2'}$ | $\delta_{H_3'}$ | $\delta_{H_4'}$ | $\delta_{H_5'}$ | $^4J_{3''5''}$ | $^3J_{1'2'}$ | $^3J_{2'3'}$ | $^3J_{3'4'}$ | $^3J_{4'5'}$ | $^2J_{5'5'}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $Me_2SO$-$d_6$ + $D_2O$ | | | 8.37 | $8.18_6$ | 7.29 | $5.92_3$ | 4.64 | 4.21 | 4.05 | $3.71_6$, $3.61_5$ | | $6.1_5$ | 5.0 | 3.0 | $3.2_3$, $3.6_2$ | −12.3 |
| 1-H$^+$ | $Me_2SO$-$d_6$/$CF_3CO_2D$ (90:10 v/v) | | | $8.76_5$ | $8.56_3$ | | 6.03 | $4.55_8$ | $4.24_8$ | $4.05_8$ | $3.74_6$, $3.65_3$ | | 5.2 | 5.0 | 3.8 | 3.4, 3.9 | −12.1 |
| 1-H$^+$ | $Me_2SO$-$d_6$/$CF_3CO_2D$ (50:50 v/v) | | | 8.87 | 8.57 | 9.01 | $6.22_7$ | $4.81_6$ | 4.59 | 4.37 | ~$4.03_6$ | | 4.6 | | | | |
| 2a | $Me_2SO$-$d_6$ | $8.71_7$ | $8.52_7$ | 8.43 | $8.17_7$ | $7.27_7$ | $6.41_3$ | 5.43 | $5.28_6$ | 4.42 | ~$3.67_5$ | 2.9$_5$ | $2.8_5$ | 8.1 | $3.3_5$ | ~4.7 | |
| 3a-H$^+$ | $Me_2SO$-$d_6$/$CF_3CO_2D$ (90:10 v/v) | $9.07_4$ | | $8.76_6$ | 8.64 | | 6.06 | 4.90 | | 4.57 | ~3.72 | | | | | | |
| 3a-H$^+$ | $Me_2SO$-$d_6$/$CF_3CO_2D$ (50:50 v/v) | 9.04 | | $8.76_8$ | $8.57_2$ | | $6.22_3$ | $5.02_6$ | $4.97_2$ | 4.84 | ~$4.03_4$ | | ~6.5 | 5.0 | nr[c] | | |
| | *b* | $9.08_6$ | | 8.84 | $8.62_6$ | | $6.25_5$ | $5.04_4$ | 4.98 | 4.88 | ~4.06 | | 7.5 | 4.8 | nr[c] | | |

[a] δ, chemical shifts in parts per million from internal $Me_4Si$; *J*, coupling constants in hertz. [b] Recorded at 250 MHz. [c] nr = unresolved.

Table II. $^{13}C$ NMR Parameters[a] of Adenosine (1), Protonated Adenosine (1-H$^+$), the Spiro Complex 2a, and the Protonated Ether 3a-H$^+$

| compd | solvent | $\delta_{C_2}$ ($^1J_{CH}$) | $\delta_{C_4}$ | $\delta_{C_5}$ | $\delta_{C_6}$ | $\delta_{C_8}$ ($^1J_{CH}$) | $\delta_{C_1'}$ | $\delta_{C_2'}$ | $\delta_{C_3'}$ | $\delta_{C_4'}$ | $\delta_{C_5'}$ | $\delta_{C_1''}$ | $\delta_{C_2''}$ | $\delta_{C_6''}$ | $\delta_{C_3''}$ ($^1J_{CH}$) | $\delta_{C_5''}$ ($^1J_{CH}$) | $\delta_{C_4''}$ | $^3J_{C_5H_8}$ | $^3J_{C_6H_2}$ | $^3J_{C_8H_1'}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $Me_2SO$-$d_6$ | $152.2_7$ (199.6) | $148.9_4$ | $119.2_6$ | $156.0_5$ | $139.8_6$ (213.2) | $87.9_0$ | $73.4_2$ | $70.5_9$ | $85.8_3$ | $61.6_0$ | | | | | | | 11.3 | 11.3 | 3.8[b] |
| 1-H$^+$ | $Me_2SO$-$d_6$/ $CF_3CO_2D$ (90:10 v/v) | $145.1_9$ (214.2) | $148.4_9$ | $118.8_3$ | $150.5_2$ | $142.3_4$ (217.9) | $88.1_5$ | $74.7_7$ | $70.2_6$ | $86.0_3$ | $61.0_8$ | | | | | | | 11.8 | 7.7 | 3.9[c] |
| 1-H$^+$ | $Me_2SO$-$d_6$/ $CF_3CO_2D$ (50:50 v/v) | $145.2_9$ (214.5) | $149.1_4$ | $119.6_6$ | $151.4_1$ | $143.5_4$ (218.9) | $90.1_8$ | $76.1_8$ | $71.2_7$ | $86.9_3$ | $61.9_1$ | | | | | | | 11.4 | 7.9 | |
| 2a | $Me_2SO$-$d_6$ | $152.5_5$ (199.7) | $148.6_3$ | $119.1_4$ | $156.0_3$ | $139.8_6$ (215.4) | $89.0_4$ | $89.6_9$ | $86.2_9$ | $85.8_2$ | $62.1_6$ | $111.9_4$ | $132.1_5$ | $130.0_6$ | $126.9_2$ (167.1) | $125.0_1$ (165.9) | $118.5_9$ | 8.9 | 11.7 | 3[d] |
| 3a-H$^+$ | $Me_2SO$-$d_6$/ $CF_3CO_2D$ (90:10 v/v) | $145.6_1$ (216.3) | $149.1_9$ | $118.7_2$ | $150.3_7$ | $142.1_7$ (217.5) | $86.1_7$ | $75.1_0$ | $88.4_9$ | $84.7_4$ | $61.1_2$ | $150.9_3$ | $144.1_8$ | | $125.6_4$ | (176.0) | $141.2_3$ | | 7.7 | 5.5[e] |
| 3a-H$^+$ | $Me_2SO$-$d_6$/ $CF_3CO_2D$ (50:50 v/v) | ~$145.4_1$ | $149.7_2$ | $119.8_7$ | $151.5_7$ | $144.0_4$ | $88.9_3$ | $76.5_9$ | $89.7_7$ | $86.1_6$ | $62.2_1$ | $152.6_2$ | $145.4_1$ | | $126.2_9$ | | $142.2_8$ | | | |

[a] δ, chemical shifts in parts per million from internal $Me_4Si$; $J_{CH}$, coupling constants in hertz. [b] $^3J_{C_4H_2}$ = 12.2 Hz, $^3J_{C_4H_8}$ = 4.9 Hz, $^3J_{C_4H_1'}$ = 3.3 Hz. [c] $^3J_{C_4H_2}$ = 12.8 Hz, $^3J_{C_4H_8}$ = 5.1 Hz, $^3J_{C_4H_1'}$ = 2.3 Hz. [d] $^3J_{C_4H_2}$ = 12.3 Hz, $^3J_{C_4H_8}$ + $^3J_{C_4H_1'}$ = 7.3 Hz, $^2J_{C_2''H_3''}$ = 5.5 Hz, $^2J_{C_6''H_5''}$ = 4.8 Hz, $^3J_{C_3''H_5''}$ = 5.1 Hz, $^3J_{C_5''H_3''}$ = 4.7 Hz, $^2J_{C_4''H_3''}$ = $^2J_{C_4''H_5''}$ = 4.3 Hz. [e] $^3J_{C_1''H_3''}$ = $^3J_{C_1''H_5''}$ = 6.7 Hz, $^2J_{C_2''H_3''}$ + $^4J_{C_2''H_5''}$ = 6.0 Hz, $^3J_{C_3''H_5''}$ = 5.6 Hz, $^2J_{C_4''H_3''}$ = $^2J_{C_4''H_5''}$ = 5.2 Hz.

Assignments of the seven fully substituted carbons were deduced from the multiplets observed in the proton-coupled $^{13}C$ spectra: double doublets were observed for $C_4$ ($^3J_{C_4H_3}$, $^3J_{C_4H_2}$), $C_{3''}$ ($^1J_{C_3''H_3''}$, $^3J_{C_3''H_5''}$), and $C_{5''}$ ($^1J_{C_5''H_5''}$, $^3J_{C_5''H_3''}$); doublets were observed for $C_5$ ($^3J_{C_5H_3}$), $C_{2''}$ ($^2J_{C_2''H_3''}$), and $C_{6''}$ ($^2J_{C_6''H_5''}$); a triplet was observed for $C_{4''}$ ($^2J_{C_4''H_3''} = {}^2J_{C_4''H_5''}$). $C_{1''}$ appeared as a poorly resolved multiplet, suggesting long-range couplings with $H_{2'}$, $H_{3'}$, $H_{3''}$, and $H_{5''}$. The values of the various $J_{^{13}CH}$ coupling constants in the cyclohexadienate moiety of **2a** are very similar to those we have previously reported for a number of Meisenheimer adducts.[20,21]

The proton noise decoupled $^{13}C$ spectra of the ether **3a**-$H^+$ showed 14 signals in 90:10 (v/v) $Me_2SO$-$d_6$/$CF_3CO_2D$, pointing out the equivalence of both sides of the aromatic ring. As observed in the $^1H$ spectra, an increase in the acid content of the solvent mixture induces a low-field shift of the ribose carbons of **3a**-$H^+$. This phenomenon, which was also observed with protonated adenosine (1-$H^+$), is probably due to the protonation of the oxygen atom of $Me_2SO$[22,23] (Figure 2).

Hydrogen-bearing carbons were assigned by selective proton-decoupling experiments; however, the assignment of $C_{2'}$ and $C_{3'}$ could be made only in 50:50 (v/v) $Me_2SO$-$d_6$/$CF_3CO_2D$, since the corresponding $H_{2'}$ and $H_{3'}$ protons accidentally have the same chemical shift in 90:10 (v/v) $Me_2SO$-$d_6$/$CF_3CO_2D$. Nevertheless, the difference between the chemical shifts of these carbons ($\delta_{C_{3'}} - \delta_{C_{2'}} \simeq 13$ ppm) is an order of magnitude greater than the variations induced by changing the acid concentrations ($\Delta\delta \simeq 1.5$ ppm). There is, therefore, no doubt that $C_{2'}$ is more shielded than $C_{3'}$ in both solvent mixtures (Figure 2).

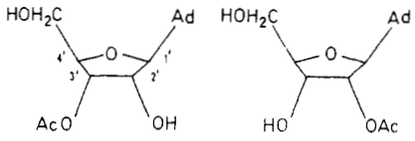
It should also be noted that $C_2$ and $C_{2''6''}$ fortuitously have the same chemical shift in 50:50 (v/v) $Me_2SO$-$d_6$/$CF_3CO_2D$; as a result, only 13 signals were observed in this medium.

The slow decomposition of **3a** in the 50:50 (v/v) mixture prevented a long-term acquisition and did not allow us to obtain the proton-coupled $^{13}C$ spectra, but the latter could be accumulated in a 90:10 (v/v) mixture, and the observed multiplets allowed us to assign the fully substituted carbons. Only the $C_{1''}$ and $C_{4''}$ aromatic carbons gave triplets by spin coupling with the equivalent $H_{3''}$ and $H_{5''}$ protons ($^3J_{C_1''H}$ and $^2J_{C_4''H}$, respectively). The downfield triplet could be assigned to $C_{1''}$ since our previous results for substituted 4-X-2,6-dinitroanisoles and related 1,1-dimethoxyl $\sigma$ adducts have shown that $C_{1''}$ is always less shielded than $C_{4''}$.[20]

## Discussion

**Opening of the Dioxolane Ring.** Although the acidic decomposition of the adduct **2a** could conceivably follow two courses, NMR results indicate that, in water or in dimethyl sulfoxide, the opening of the dioxolane ring unequivocally occurs at only one of the two oxygens $O_{2'}$ or $O_{3'}$ to yield either 3′-*O*-(2,4,6-trinitrophenyl)adenosine (**3a**) or its 2′-*O* isomer **4a**. This stereoselectivity is somewhat unexpected since various ortho ester derivatives of ribonucleosides have been shown to decompose in acidic medium into a mixture of isomeric 2′ and 3′ esters.

Griffin and co-workers[25] have shown that these isomers may be safely distinguished by $^1H$ NMR on the basis of $\delta_{H_{1'}}$ and $J_{H_{1'}H_{2'}}$ values. Their data for adenosine (**1**) and its 3′-*O*- and 2′-*O*-acetyl derivatives **5** and **6** indicate that




5 6

$H_{1'}$ chemical shifts are similar in **1** and the 3′-*O* derivatives **5** while this proton is deshielded in the 2′-*O* isomer **6**. Moreover, $J_{H_{1'}H_{2'}}$ decreases on going from adenosine to the 2′-*O* isomer **6** while it increases for the 3′-*O* derivative **5**.

In our case, a comparison of $^1H$ NMR parameters for the ether and for protonated adenosine (1-$H^+$) in the same solvent mixture (Table I) indicates similar chemical shifts for $H_{1'}$ in both compounds and an increased $J_{H_{1'}H_{2'}}$ coupling constant in the ether. Thus, we can conclude that we are dealing with 3′-*O*-(2,4,6 trinitrophenyl)adenosine (**3a**). This conclusion is further supported by the downfield shifts observed for $H_{2'}$, $H_{3'}$, and $H_{4'}$ in this ether and by a comparison of the $^{13}C$ data: $C_{3'}$ is the only carbon to be strongly shifted to lower field when going from protonated adenosine 1-$H^+$ to protonated ether **3a**-$H^+$ (Figure 2).

**Dissymmetry of the Adduct 2a.** In agreement with the chirality of the four ribose ring carbons, the two sides of the cyclohexadienyl ring of **2a** are nonequivalent. However, the magnitude of the anisochrony observed in the proton spectrum ($\delta_{H_{3''}} - \delta_{H_{5''}} = 0.19$ ppm) and in the $^{13}C$ spectrum ($\delta_{C_{2''}} - \delta_{C_{6''}} = 2.1$ ppm; $\delta_{C_{3''}} - \delta_{C_{5''}} = 1.9$ ppm) suggests that a conformational feature, such as the twisting of a nitro group, enhances the dissymmetry of **2a**. Examination of a space-filling molecular model of **2a** reveals the existence of a strong steric interaction between the $H_{1'}$ and $H_{4'}$ ribose protons and the oxygen atoms of the 6″-nitro group. This steric hindrance results in the steric inhibition of resonance of the 6″-nitro group, while the 2″- and 4″-nitro groups lie closer to the plane of the cyclohexadienyl ring. The twisting of the "endo" 6″-nitro group in **2a** is an important feature since it not only explains the important anisochrony observed in the $^1H$ and $^{13}C$ NMR spectra but it also allows us to distinguish between the "endo" and "exo" sides of the cyclohexadienyl ring.

In aromatic derivatives, the substituent effect of a nitro group is known to deshield the protons in ortho, meta, and para positions, in ageement with its electron-withdrawing character (–M, –I).[26] Similarly, downfield shifts are observed in the $^{13}C$ NMR for the ipso, meta, and para carbons; only the ortho carbon is slightly shielded, suggesting that the electronic effect is more than cancelled by a $\gamma$ effect.[27] The steric inhibition of resonance of the 6″-nitro group, decreasing its electron-withdrawing effect, would be expected to result in an upfield shift of the neighboring atoms. Moreover, the anisotropy of the nitro group[28] provides an additional shielding to $H_{5''}$, so that it may be concluded that the endo $H_{5''}$ proton is more shielded than $H_{3''}$ and constitutes the B part of the AB system. Similarly, the endo $C_{6''}$ carbon is expected to be shielded relative to the exo $C_{2''}$ carbon.[20] The situation is not so clear for $C_{5''}$

(20) M. P. Simonnin, M. J. Pouet, and F. Terrier, *J. Org. Chem.*, **43**, 855 (1978).
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(24) (a) B. E. Griffin, M. Jarman, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2301 (1967); (b) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *ibid.*, **23**, 2315 (1967).
(25) H. P. M. Fromageot, B. E. Griffin, C. B. Reese, J. E. Sulston, and D. R. Trentham, *Tetrahedron*, **22**, 705 (1966).
(26) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, 1969, pp 80–81.
(27) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, pp 196–199.
(28) (a) A. C. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962); (b) ref 26, p 79.

since the disappearance of the $\gamma$ effect can more or less cancel the expected upfield shift; however, since selective proton-decoupling experiments have shown that the nonequivalence is of the same sign in the $^1H$ and $^{13}C$ spectra, the endo $C_{5''}$ carbon is also more shielded than $C_{3''}$.

**Protonation of Adenosine (1) and Ether 3a in $Me_2SO/CF_3CO_2D$.** The usefulness of $^{13}C$ NMR parameters to detect protonation sites of nitrogen heterocycles is well documented.[29] The main changes induced by N-protonation are as follows: a characteristic upfield shift of the $\alpha$ carbons, an increase in $^1J_{^{13}CH}$ in the protonated ring, an increase in the geminal $^2J_{C_\alpha H_\beta}$ coupling constant but a decrease in $^2J_{C_\beta H_\alpha}$, a decrease in the vicinal $^3J_{C_\alpha NC_\alpha H_\alpha}$ coupling constant which involves the protonated nitrogen.

A comparison of the $^{13}C$ data obtained for adenosine (Table II) dissolved in $Me_2SO$ and in a 90:10 (v/v) $Me_2SO/CF_3CO_2D$ mixture shows an upfield shift of $C_2$ ($\Delta\delta_{C_2} = -7.08$ ppm) and of $C_6$ ($\Delta\delta_{C_6} = -5.53$ ppm), an increase in $^1J_{C_2H_2}$ ($\Delta^1J_{C_2H_2} = 14.6$ Hz), and a decrease in $^3J_{C_6N_1C_2H_2}$ ($\Delta^3J_{C_6H_2} = -3.6$ Hz). All these results indicate that protonation occurs at the $N_1$ nitrogen of adenosine.

Similar changes are observed on going from the adduct **2a** dissolved in $Me_2SO$ to the ether **3a** dissolved in a 90:10 (v/v) $Me_2SO/CF_3CO_2D$ mixture: i.e., an upfield shift of $C_2$ ($\Delta\delta_{C_2} = -6.94$ ppm) and of $C_6$ ($\Delta\delta_{C_6} = -5.65$ ppm), an increase in $^1J_{C_2H_2}$ ($\Delta^1J_{C_2H_2} = 16.6$ Hz), and a decrease in $^3J_{C_6H_2}$ ($\Delta^3J_{C_6H_2} = -4.0$ Hz). Therefore, the $N_1$ nitrogen of **3a** is also protonated in 90:10 (v/v) $Me_2SO/CF_3CO_2D$.

For adenosine as for the ether **3a**, a further increase in the acid concentration results in a slight downfield shift of all the aglycon carbons, so that it may be concluded that a second protonation of the adenine moiety of 1-$H^+$ or **3a**-$H^+$ does not occur in 50:50 (v/v) $Me_2SO/CF_3CO_2D$ mixture (Figure 1).

Regarding the protonation of the adenine moiety in our derivatives, our conclusions are in agreement with previous results. Adenosine monophosphate has been shown, by $^{13}C$ NMR, to be protonated at $N_1$,[29] and $^{15}N$ NMR indicates that the protonation of adenosine, dissolved in $Me_2SO$, also takes place mainly at $N_1$.[7] Furthermore, it has been shown by $^1H$ NMR that monoprotonation of adenine occurs at $N_1$ in trifluoroacetic acid, while dication and trication formation are observed only in the superacid media $FSO_3H$ and $FSO_3H$–$SbF_5$–$SO_2$, respectively.[30]

The great similarity of the $^{13}C$ aglycon parameters in 1-$H^+$ and **3a**-$H^+$ indicates that the presence of the trinitrophenyl group at the $O_{3'}$ oxygen has a very small influence, although a change in the conformation of the ribose ring is evidenced by the proton–proton coupling constants, as shown below.

**Conformation of the Ribose Ring.** It has been shown that the ribose moiety of $\beta$-nucleosides may exist in two conformations, which have been classified as type N ($C_{2'}$ exo, $C_{3'}$ endo) and type S ($C_{2'}$ endo, $C_{3'}$ exo).[31]

Altona and Sundaralingam have defined a Karplus-type equation relating $^3J_{HH}$ coupling constants to the dihedral torsion angles, $\phi_{HH}$, of the sugar ring.[31] These authors have shown that important information can be deduced from these vicinal coupling constants. While the values of $J_{2'3'}$ and of the sum $J_{1'2'} + J_{3'4'}$ are practically independent of the position of the N $\rightleftharpoons$ S conformational equilibrium, a bias of this equilibrium toward the type S conformer will increase $J_{1'2'}$ but decrease $J_{3'4'}$. Moreover, a flattening of the ribose ring was shown to enhance $J_{2'3'}$ and to lower the sum $J_{1'2'} + J_{3'4'}$.

A flattening of the ribose ring in the adduct **2a**, relative to adenosine (1) in $Me_2SO$, is evidenced by an important increase in $J_{2'3'}$ ($\Delta J_{2'3'} = 3.1$ Hz) and a decrease in the sum $J_{1'2'} + J_{3'4'}$ ($\Delta\sum = -2.8$ Hz). This flattening is confirmed by an examination of a Dreiding molecular model which shows that the maximum value of the dihedral angle $\phi_{2'3'}$ is about 20°.

It can be noted that protonation of $N_1$ of adenosine tends to reduce the population of the type S conformer since addition of trifluoroacetic acid results in a decrease in $J_{1'2'}$ and an increase in $J_{3'4'}$.

In the case of the ether **3a**, the vicinal $^3J_{3'4'}$ coupling constant is low enough to be resolved neither in the $H_{3'}$ nor in the $H_{4'}$ signals, so that the dihedral angle $\phi_{3'4'}$ is near 90°. This fact together with the great value of $J_{1'2'}$ indicates that the type S conformer is strongly favored in the ether **3a**, the ratio N/S being about 20/80, in spite of the fact that in the S conformation the picryl ether group is in a quasi-axial orientation.

**Conformation of the Picryl Ring in the Ether 3a.** The conformation of the picryl ring in **3a** may also be established from $^1H$ NMR data. The chemical shift of $H_{1'}$ in **3a**-$H^+$ is close to that observed in 1-$H^+$. This fact and the well-known anisotropy of the aromatic ring allow us to exclude a conformation where the picryl ring would lie in the vicinity of the ribose $C_{1'}$ carbon; i.e., the bonds $H_{3'}$–$C_{3'}$ and $O_{3'}$–$C_{1''}$ cannot be antiparallel. Inspection of a Dreiding molecular model suggests that the dihedral angle $\phi_{H_{3'}-C_{1''}}$ may take values between ±60° relative to the zero position where the two aforementioned bonds are parallel.

Previous studies on picryl ethers have shown that in solution, as in the solid state, the ortho nitro groups lie out of the aromatic plane whereas the ether oxygen is conjugated with the ring.[12,13,20,32] A similar situation probably prevails in **3a**; however, the equivalence of both sides of the picryl ring observed in $^1H$ and $^{13}C$ spectra implies that rotation around the $O_{3'}$–$C_{1''}$ bond is rapid on the NMR time scale.

## Conclusion

Evidence has been presented that the opening of the dioxolane ring of the spiro complex **2a** occurs exclusively at the $O_{2'}$ oxygen to yield 3′-*O*-(2,4,6-trinitrophenyl)-adenosine (**3a**). As suggested by space-filling molecular models, the formation of the isomeric ether **4a** might be disfavored because of a strong steric interaction between the adenine moiety and the *o*-nitro groups of its picryl ring. Such a steric strain does not exist in **3a**, which would explain the observed stereoselectivity. On this basis, one might anticipate this behavior to be dependent on the nature of the base, making it of interest to look at the decomposition of spiro adducts derived from pyrimidine nucleosides.

## Experimental Section

**Material.** The spiro complex **2a** was prepared according to the procedure described by Azegami and Iwai.[3] 3′-*O*-(2,4,6-Trinitrophenyl)adenosine (**3a**) was prepared by adding, in portions, 500 mg of the orange sodium salt of **2a** to 25 mL of a vigorously stirred aqueous solution of hydrochloric acid (0.1 M). The reaction gave a quantitative yield of **3a** as yellow crystals

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(30) R. Wagner and W. Von Philipsborn, *Helv. Chim. Acta*, **54**, 1543 (1971).

(31) C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, **95**, 2333 (1973).

(32) C. M. Grammaccioli, R. Destro, and M. Simonetta, *Acta Crystallogr., Sect. B*, **B24**, 129 (1968).

which were filtered off, washed with water, and dried; mp 225 °C.

**NMR Spectra.** $^1H$ and $^{13}C$ spectra were recorded on a Varian XL-100-12 WG spectrometer. $^1H$ and $^{13}C$ shifts were measured with $Me_4Si$ as an internal reference. $^1H$ spectra (100 MHz, 5-mm tubes, $^1H$ lock) were studied by using the CW mode. $^{13}C$ spectra (25.17 MHz, 10-mm tubes, $^2H$ lock) were collected by using the Fourier transform technique. The instrument was equipped with a 620 L-100-16 K on-line computer. Spectral widths of 5000 or 2500 Hz were used (digital resolution 1.25 or 0.68 Hz/point). The sample concentration was about 0.33 M.

**Acknowledgment.** We are indebted to Dr. J. Y. Lallemand for the $^1H$ spectra of **3a** recorded at 250 MHz with a CAMECA instrument.

**Registry No.** 1, 58-61-7; 1-$H^+$, 18475-49-5; **2a**, 74792-78-2; **3a**, 50827-00-4; **3a**-$H^+$, 74684-32-5.

# Synthesis of 19-Norprogesterone and 19-Nordeoxycorticosterone

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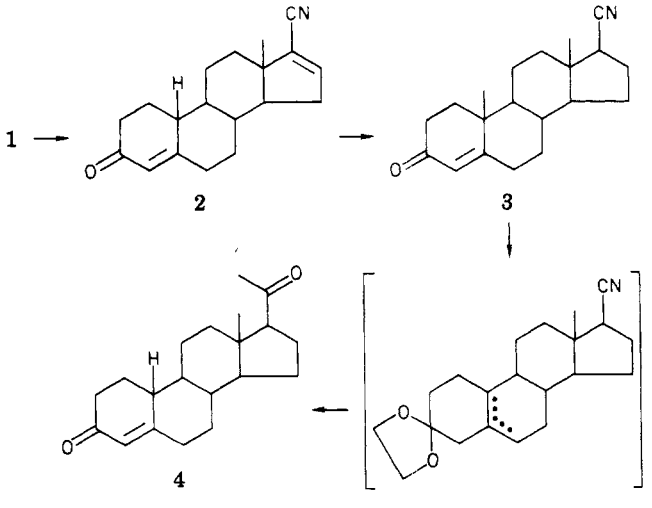
19-Norprogesterone was obtained by a synthesis similar to the one used for the transformation of androst-4-ene-3,17-dione to progesterone. 19-Norandrost-4-ene-3,17-dione was converted to its 17-cyanohydrin and dehydrated and the 16,17 double bond catalytically reduced. The 3-ketone was protected by ketalization with ethylene glycol and the crude product was reacted with methylmagnesium iodide to give the desired 19-norprogesterone in an overall yield of 15%. The starting material for 19-nordeoxycorticosterone was 19-norandrost-4-ene-3,17-dione 3-ethylene ketal which was transformed via a Wittig reaction and hydrolysis to 17β-formyl-19-norandrost-4-en-3-one and 3-oxoestr-4-en-17-al 3-ethylene ketal. Reaction of the keto aldehyde with propane-1,3-dithiol gave the bis(thioketal), the anion of which was treated with formaldehyde. The resulting 19-nordeoxycorticosteroid 3,20-bis(thioketal) was hydrolyzed to the desired 19-nordeoxycorticosterone in an overall yield of 10%.

17-Hydroxy-17-cyanoestr-4-en-3-one (1)[1] was dehydrated with phosphorus oxychloride in pyridine to give the conjugated nitrile **2**. Selective catalytic reduction with palladized charcoal gave 17β-cyanoestr-4-en-3-one (**3**) which was ketalized with ethylene glycol. The crude produce was reacted with methylmagnesium iodide and hydrolyzed to yield the desired 19-norprogesterone[2] (**4**) in a yield of 15% (from estr-4-ene-3,17-dione) (Scheme I).

Since we were unable to even approximate the published[3] yields for the Serini reaction on 17β-hydroxy-20,21-diacetoxy-19-norpregn-4-en-3-one to give 19-nordeoxycorticosterone acetate, we searched for another route to the desired 19-nordeoxycorticosterone. The following sequence, shown in Scheme II, led to the desired product. The known[1] 3-ethylene ketal of estr-4-ene-3,17-dione (**5**)[4] was reacted with (methoxymethylene)triphenylphosphonium chloride under Wittig conditions[5] to give the $\Delta^{5(6)}$ and $\Delta^{5(10)}$ mixture of 17-ξ-(methoxymethylene)-estr-4-en-3-one 1,2-ethanediyl acetal (**6**).[6] Hydrolysis with dilute perchloric acid gave 3-oxoestr-4-ene-17β-carboxaldehyde (**7**) and also the 3-oxoestr-4-en-17-al 3-(1,2-ethanediyl acetal) (**8**), a product arising from trans-

Scheme I




acetalization. The mixture of these two compounds was treated with propane-1,3-dithiol to give 3-oxoestr-4-ene-17-carboxaldehyde 3,20-bis(1,3-propanedithiylacetal) (**9a**). The anion of the thioacetal **9a**, produced with *n*-butyllithium, was alkylated with formaldehyde to give 21-hydroxy-19-nordeoxycorticosterone 3,20-bis(1,3-propanedithiyl acetal) (**9b**). Deacetalization with mercuric chloride and calcium carbonate gave the desired 19-nordeoxycorticosterone (**10**)[7] in an overall yield of ca. 10% (from **5**).

Another, albeit aborted, approach to 19-nordeoxycorticosterone (**10**) was initiated by the acetoxylation of

(1) P. de Ruggieri, *Gazz. Chim. Ital.*, 87, 795 (1957).

(2) For previous preparations of 19-norprogesterone see, e.g., J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6118 (1958); A. Bowers, R. Vilotti, J. A. Edwards, E. Donot, and O. Halpern, *ibid.*, 84, 3204 (1962).

(3) A. Sandoval, G. H. Thomas, C Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 77, 148 (1955).

(4) For an analysis of the ratio of $\Delta^{5(6)}$ and $\Delta^{5(10)}$ of a cyclic 3-(1,2-ethanediyl acetal) see F. T. Bond, W. Weyler, B. Brunner, and J. E. Stemke, *J. Med. Chem.*, 19, 255 (1976).

(5) S. Danishefsky, K. Nagasawa, and K. N. Wang, *J. Org. Chem.*, **40**, 1989 (1975).

(6) This product is a mixture of the two 17(20) double bond isomers as shown by the splitting of the 18-methyl and of the methoxy NMR signals.

(7) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 4117 (1953).

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