We sought a thiocarbonyl reagent that could be introduced by simple acylation. A second consideration was that the intermediate radical species resulting from attack of tin at thione sulfur would not be stabilized at the α-carbon. Such α stabilization could allow abstraction of hydrogen from the trialkylstannane to compete effectively with alkyl carbon–oxygen bond homolysis. Dethiation (thiobenzoyl ester → benzyl ether) and collapse (dithiocarbonate ester → alcohol starting material) byproducts have been observed by using the α-benzylic- and α-thiol-stabilized species.[13a,14]

Treatment of thiophosgene with phenol gave phenyl chlorothionocarbonate.[15] Pyridine effectively catalyzed reactions of this thioacyl chloride with relatively unhindered alcohols, but 4-(dimethylamino)pyridine was required[16] for smooth conversion of nucleosides to their 2′-*O*-phenoxythiocarbonyl derivatives. Reductive cleavage of these compounds occurred readily when tri-*n*-butylstannane in toluene at 75 °C with α,α′-azobisisobutyronitrile as initiator was used.[17] No dethiation or alcohol byproducts were detected in cases we have examined. As seen in Table I, thioacylation (generally quantitative) and reductive cleavage (proceeds to completion in 3 h) give good overall yields of deoxygenation of isolated secondary alcohols (entries 4, 5). An epoxide function is tolerated (entry 5b).

Selective 3′ and 5′ protection was required for specific 2′-deoxygenation of ribonucleosides. Multistep procedures have been required previously,[7] but a hindered bifunctional disiloxane reagent became available recently.[18] Treatment of ribofuranosyl compounds (**1**) with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine gave the cyclic 3′,5′-trioxadisila derivatives (**2**, R = H) in over 90% yields (Scheme I). Thioacylation of **2** (R = H) gave the 2′-*O*-phenoxythiocarbonyl esters (**2**, R = $CSOC_6H_5$). Reductive cleavage of this function gave the 2′-deoxynucleosides protected as the cyclic 3′,5′-trioxadisila intermediates. Deprotection was effected by using tetra-*n*-butylammonium fluoride[19] to give the 2′-deoxynucleosides (**3**).

Adenosine (**1a**) was converted to 2′-deoxyadenosine (**3a**) in 78% overall yield by this sequence. This is superior to yields obtained in prior chemical syntheses of 2′-deoxyadenosine by any route.[3,6a,7,13b] Uridine (**1b**) was converted to 2′-deoxyuridine in 68% yield in this manner. This yield is higher, even, than routes involving O-2→2′ cyclonucleoside interconversions.[4,5] It clearly demonstrates the generality of the method since cyclonucleoside formation did not intervene. This was a concern since treatment of 5′-*O*-trityluridine with thiocarbonyldiimidazole in hot toluene was known to produce the 2,2′-anhydroarabino compound in over 85% yield.[20]

Finally, methyl β-D-ribofuranoside (**1c**) was subjected to this sequence. The product (**3c**) was converted into its crystalline 3,5-di-*O*-*p*-toluyl ester derivative[21] in 58% overall yield for the five steps. No cleavage of our thionocarbonate ester (**2c**, R = $CSOC_6H_5$) to starting alcohol was observed, in contrast to side reactions reported in an analogous application of the thiobenzoate and dithiocarbonate methods.[14]

The present sequence of reactions thus provides smooth and efficient access to 2′-deoxynucleosides from ribonucleosides, a process for which general methods were lacking. Demonstration of its applicability with nucleoside antibiotics and evaluation of the stereoselectivity of reduction will be reported with details of the present work.

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## Conformational Analysis of the C(6)–O(1)–C(5)–C(4) Fragment in Acetylcholine by $^{13}C$ NMR Spectroscopy

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The conformation of acetylcholine (ACh) is still a subject of interest.[1-3] Lately, changes in the Raman spectra of ACh halides (AChBr, AChCl, and AChI) on going from solid state to aqueous solution have been attributed to conformational differences in the choline fragment.[2] It has been suggested[4] that the conformational change could arise from rotation around the O(1)–C(5) bond (see Figure 1). It is known that the conformations adopted by ACh cation in the crystals of its halides differ essentially because of the fragment C(6)–O(1)–C(5)–C(4), which is trans in the crystal of its chloride ($\tau_1$ = 193°)[5] and gauche in the crystal of its bromide ($\tau_1$ = 79°)[6] and iodide ($\tau_1$ = 83°),[3] whereas in aqueous solution the conformational equilibrium appears to be independent of the counterion.[2,7,8] On the basis of the NMR acylation shift of the $CH_2O$ protons, Culvenor and Ham[8] proposed an essentially trans arrangement for this fragment. It follows that Raman and $^1H$ NMR spectroscopic techniques suggest a different conformational behavior as concerns $\tau_1$ for AChCl when moving from solid state to aqueous solution. In view of the biological importance of this angle,[9] the conformational features around the O(1)–C(5) bond would be better established in aqueous solution. In this communication, measurements of the vicinal C(6)–O(1)–C(5)–H coupling constant in the temperature range 10–70 °C suggest the trans-C(6)/C(4) conformation ($\tau_1 \sim 180°$) is preferred; however, a distorted gauche conformation ($\tau_1 \sim 90°$) also displays significant population. The population ratio ranges from 0.688/0.312 at 10 °C to 0.625/0.375 at 70 °C.

The proton-coupled $^{13}C$ NMR spectra were recorded at 25.2 MHz on a Varian XL-100-12 spectrometer, with a digital resolution of 0.12 Hz. The concentration of AChCl was about 1 M in $D_2O$ and a small amount of sodium 4,4-dimethyl-4-silapentane-1-sulfonate was added to generate the internal reference signal.

The $^{13}C(6)$ resonance displays a symmetrical pattern which can easily be identified as a quartet of triplets. The signal multiplicity allows the assignment of the larger coupling constant (6.9 Hz) to the two-bond $^{13}C(6)$–C(7)–H coupling and the smaller one (2.85 Hz at 70 °C) to the vicinal $^{13}C(6)$–O(1)–C(5)–H coupling. Cooling of ACh aqueous solution from 70 to 10 °C is accompanied by a change in $^3J_{^{13}C(6)-O(1)-C(5)-H}$ (from 2.85 to 2.55 Hz) (Table I) but not in $^2J_{^{13}C(6)-C(7)-H}$. We interpret this fact as indicative of the

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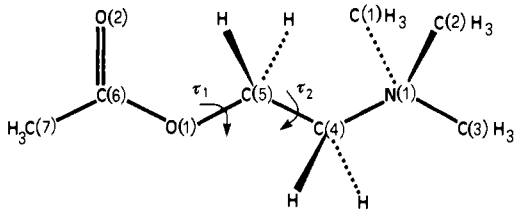


**Figure 1.** Atom and torsion-angle numbering in acetylcholine.

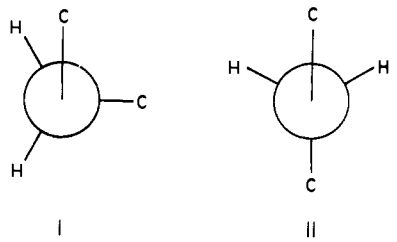


**Figure 2.** Suggested rotamers for the C(6)–O(1)–C(5)–C(4) fragment. Rotamer I: $\tau_1 \sim 90°$, rotamer II: $\tau_1 \sim 180°$.

**Table I.** Acetylcholine: $^3J_{^{13}C(6)\text{-}O(1)\text{-}C(5)\text{-}H}$ Values,[a] Fractional Rotamer Populations, and $\Delta G°$ Values at Different Temperatures for the Fragment C(6)–O(1)–C(5)–C(4)

| temp, °C | $^3J_{^{13}COCH}$, Hz | fractional rotamer population | | $\Delta G°$, cal/mol |
|---|---|---|---|---|
| | | $N_I$ | $N_{II}$ | |
| 10 | 2.55 | 0.312 | 0.688 | −443 |
| 30 | 2.66 | 0.335 | 0.665 | −412 |
| 50 | 2.78 | 0.360 | 0.640 | −368 |
| 70 | 2.85 | 0.375 | 0.625 | −347 |

[a] ±0.05 Hz. Consequently the rotamer populations $N$ and $\Delta G°$ values are accurate to ±0.010 and ±29 cal/mol, respectively.

occurrence of a conformational equilibrium between different rotamers.

The rotational isomerism of ACh cation in solution can be represented by an equilibrium of the two rotamers shown in Figure 2 on the following grounds. First, torsion angles C(6)–O(1)–C(5)–C(4) found in crystal structure of choline esters cluster round two values: 90 and 180°, except for two carbamoylcholine ions.[3] Second, formate and acetate esters of ethyl alcohol show a nearly identical value of $^3J_{^{13}COCH}$ (3.32 and 3.23 Hz, respectively[10,11]), thus suggesting that their conformational behavior is very similar. There is evidence derived from microwave spectroscopy[12] that ethyl formate exists in solution as a mixture of one trans and two distorted gauche rotamers, the relative C–O–C–C dihedral angles being approximately 85, 180, and 275°. Therefore, it seems reasonable to assume that, on rotation about the C–O axis, the energy of the ACh cation goes through two minima occurring at nearly 90 and 180°. The rotamer with $\tau_1 \sim 275°$ seems highly implausible, keeping the fragment O(1)–C(5)–C(4)–N in its more stable conformation ($\tau_2 \simeq 60°$)[7,8] due to the steric requirements of the C=O and $N(CH_3)_3$ groups. Since the internal rotation is sufficiently rapid, the observed $^3J_{^{13}COCH}$ value is a weighted average of the corresponding constants for the individual rotamers:

$$^3J_{^{13}COCH} = N_I\,{}^1/_2[^3J_{^{13}COCH}(30°) + {}^3J_{^{13}COCH}(150°)] + N_{II}{}^3J_{^{13}COCH}(60°) \quad (1)$$

where $N_I$ and $N_{II}$ are the fractional populations of rotamer I and II, respectively:

$$N_I + N_{II} = 1 \quad (2)$$

The coupling constant in rotamer I is given by the mean value $^1/_2[^3J_{^{13}COCH}(30°) + {}^3J_{^{13}COCH}(150°)]$, owing to the rapid interconversion of rotamer I with its mirror image.

The $^3J_{^{13}COCH}(30°)$, $^3J_{^{13}COCH}(60°)$, and $^3J_{^{13}COCH}(150°)$ values could be obtained from a Karplus-type relationship:

$$^3J_{^{13}C,H} = A\cos^2\varphi + B\cos\varphi + C \quad (3)$$

Such a relationship has received experimental[13-17] as well as theoretical[18] evidence. However, reported $^3J_{^{13}C,H}$ values exhibit a considerable scattering which has been attributed to structural parameters[14,17] (e.g., carbon hybridization, electronegative substituents, nuclei sequence in the coupling pattern). The coefficients $A$, $B$, and $C$ for the $^3J_{^{13}C,H}$ coupling transmitted via the specific nuclei sequence $^{13}C$–O–C–H have been determined as follows. $C$ is considered to be negligible, as a survey of the literature shows that when $\varphi$ approaches 90°, $^3J_{^{13}C,H}$ becomes undetectable.[14,15] The $A$ value (7.8 Hz) is derived from averaged $^3J_{^{13}COCH}$ couplings in methyl acetate[10,11] and formate.[10] Knowledge of $A$ and $C$ enables us to obtain $B$. A mean $B$ value of −1.8 Hz is computed from the values of vicinal $^{13}C$,H coupling constants (8.7 and 9.3 Hz) measured in nearly trans and trans arrangements ($\varphi$ = 158 and 180°) of the $^{13}C(0)$–O–C–H fragment in 2,5′-anhydro-2′,3′-isopropylideneuridine[16] and vinylene carbonate,[19] respectively. When eq 1-3 and the $^3J_{^{13}C(6)\text{-}O(1)\text{-}C(5)\text{-}H}$ values at different temperatures are employed, one obtains the population fractions reported in Table I.

Although the most stable conformation corresponds to the extended form of the fragment C(6)–O(1)–C(5)–C(4), rotamer I is also significantly populated. The free-energy difference between the two rotamers [$\Delta G° = -RT \ln (N_I/N_{II})$] is only 412 ± 29 cal/mol at 30 °C. This energy difference is of the order of magnitude of that found by microwave spectroscopy in ethyl formate between the trans and distorted gauche rotamers (200 cal/mol).[12] The slightly greater value agrees with the prediction by Roberts and co-workers[10] that in the acetate and formate esters of primary alcohols an increase of the size of the group attached to the α-carbon should cause an increase in the free-energy difference between the trans and the gauche rotamers.

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## NMR of Protons Coupled to $^{13}C$ Nuclei Only

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In this communication we describe a simple multinuclear multipulse sequence which enables the cancellation of signals arising from protons bonded to $^{12}C$ nuclei, allowing the observation of just those signals of protons coupled to $^{13}C$. The sequence will be useful in studying $^{13}C$-enriched compounds obtained, for instance, in the study of biosynthetic pathways either as an alter-

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