Table I. Oxidation of Aconitine with Potassium Permanganate

solvent(s)	time, h	oxonitine yield, %
CH_3COCH_3, CH_3COOH[a]	5	20–25
5% MeOH in CH_3COCH_3, CH_3COOH[a]	5	45
CH_3COCH_3, C_6H_5COOH[b]	5	20
15% CH_3COCH_3 in H_2O, CH_3COOH[a]	5	3
5% CH_3OH in H_2O, CH_3COOH[a]	2.5	6
CH_3COCH_3, H_2O (20:3)	1.5	13[c]
H_2O	1	20
0.40% CH_2O in H_2O	1	55

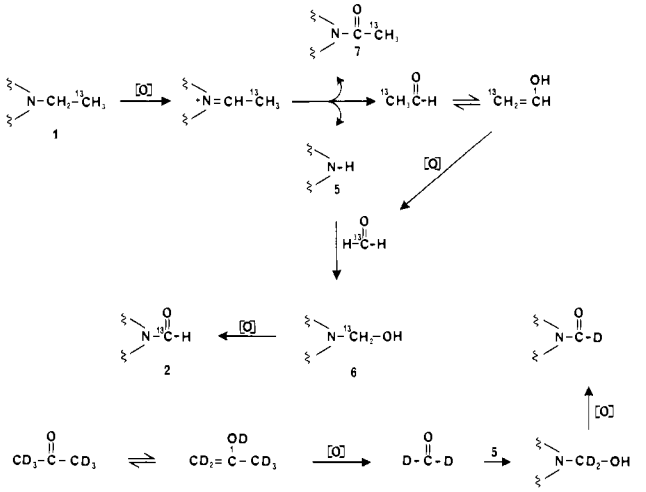
[a] Just sufficient acetic acid was added to bring the solution to about pH 6. [b] 5mg in 10 ml of acetone. [c] 60% of *N*-desethylaconitine.

3 H, s, CH_3O), 4.10 (1 H, d), 4.47 (2 H, m), 4.91 (1 H, d, C(14)-β-H); ^{13}C NMR ($CDCl_3$) δ 172.2, 166.1, 133.4, 129.7, 129.7, 128.7, 91.5, 89.7, 83.3, 81.3, 78.9, 78.9, 77.1, 74.1, 71.0, 61.1, 59.1, 57.7, 55.7, 55.7, 50.8, 49.3, 47.0, 43.8, 43.4, 40.8, 40.8, 34.8, 34.8, 21.4; in 60% yield. When the reaction was allowed to proceed for 1.5 h, we isolated oxonitine (**2**) in 13% yield along with *N*-desethylaconitine. As the reaction time increased, the yield of oxonitine increased and that of *N*-desethylaconitine decreased.

Treatment of *N*-desethylaconitine (**5**) with 0.4% formalin in methanol afforded **6** in quantitative yield; mp 200–202 °C; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, s, CH_3CO), 3.16, 3.30, 3.48, and 3.75 (each 3 H, s, CH_3O), 3.33 (2 H, s, NCH_2OH); ^{13}C NMR ($CDCl_3$) δ 172.2, 166.2, 133.3, 129.9, 129.8, 128.7, 91.5, 90.2, 89.3, 83.2, 81.7, 78.9, 78.9, 76.3, 74.2, 71.0, 60.9, 60.5, 59.1, 57.8, 55.9, 49.7, 49.2, 47.6, 44.9, 43.9, 42.9, 40.7, 35.5, 34.1, 21.4. Oxidation of **6** with aqueous $KMnO_4$ yielded oxonitine, mp 273–275 °C, in quantitative yield. From these results, we conclude that reaction of *N*-desethylaconitine (**5**) with the formaldehyde generated in situ from oxidation of solvent(s) furnishes intermediate **6**, which is subsequently oxidized to oxonitine. To test this mechanism and to locate the source of the *N*-formyl group of oxonitine, we systematically investigated the oxidation of aconitine using various solvent systems and established the role of each solvent used in this oxidation. Acetic acid can be replaced with other organic acids with no impact on the yield of oxonitine. However, the presence of a stronger acid decreases the rate of the reaction as well as the yield of oxonitine. At pH 3.5 the oxidation process is practically suppressed. During several experiments we observed that the presence of acid is not necessary and that the yield of oxonitine is higher in alkaline media. Experimental results presented in Table I demonstrate that the solvents acetone and methanol, as well as the acetaldehyde generated by oxidation of the *N*-ethyl group of aconitine, are the source of formaldehyde.

Fosse has reported[19] that oxidation of acetone with calcium permanganate solution in the presence of ammonia produces formaldehyde. We have observed similar results using $KMnO_4$. Oxidation of aconitine with $KMnO_4$ in hexadeuterated acetone afforded oxonitine mainly containing the –NCDO group,[20] a result that confirms that acetone is a source of the N–CHO group of oxonitine. Aconitine also afforded oxonitine in 20% yield when it was treated with aqueous $KMnO_4$. This result can be explained by cleavage of the *N*-ethyl group of aconitine to **5** and acetaldehyde. The latter is oxidized to formaldehyde in alkaline media as shown in Scheme I. Formaldehyde reacts with **5** to give compound **6**, which is immediately oxidized to oxonitine. In this reaction the CH_3 carbon of the *N*-ethyl group is the source of the N–CHO group of oxonitine. This fact was confirmed by oxidation of ^{13}C-labeled aconitine with aqueous $KMnO_4$ (Scheme I). This labeled compound ($^{13}CH_3CH_2N$) was prepared in a yield of 40% by treatment of **5** with $^{13}CH_3CH_2I$ in refluxing methanol for 90 min. The labeled aconitine was treated with aqueous $KMnO_4$ for 2 h to afford a 1:1 mixture of oxonitine (**2**) and the *N*-acetyl

Scheme I



derivative (**7**), which contained the ^{13}C label on the aldehyde carbon and on the methyl group, respectively.

In summary, the data presented here clearly demonstrate that acetone, methanol, or acetaldehyde is the source of the *N*-formyl group of oxonitine and that oxidation of aconitine to oxonitine takes place via intermediates **5** and **6**, as shown in Scheme I. Turner's results are ambiguous because the 6% incorporation of ^{14}C label in his product oxonitine probably resulted from the presence of some $>N-^{14}COCH_3$ as an impurity in his oxonitine sample. Wiesner's experimental results are correct, but since *N*-acetyldesethylaconitine is always formed along with oxonitine during oxidation of aconitine, the *N*-acyl aromatization product **3** would of course consist of a mixture of compounds bearing the >NCHO and $>NCOCH_3$ groups.

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Registry No. **1**, 302-27-2; **2**, 545-57-3; **4**, 2752-64-9; **5**, 3327-35-3; **6**, 82323-95-3.

(19) Fosse, F. *C. R. Hebd. Seances Acad. Sci.* **1936**, *202*, 445.

(20) A small amount of oxonitine containing the –NCHO group is also formed because of generation of a small amount of HCOH by oxidation of the $-NCH_2CH_3$ group of aconitine (Scheme I).

Intrinsic Steric $^2H/^1H$ Isotope Effects on ^{13}C Shieldings: Dihedral Angular Dependence of Shifts over Three Bonds in Saturated Systems

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Shielding changes produced by replacement of hydrogen with deuterium have been recognized for ^{13}C nuclei for many years,[1] and two types of isotope effects have been delineated:[2] "equilibrium" isotope shifts caused by perturbation of the relative populations of two (or more) equilibrating species and "intrinsic" isotope shifts involving a single species. The observed effects are largest for ^{13}C nuclei directly bonded to deuterons and are rapidly attenuated with increasing separation such that intrinsic effects in saturated systems are essentially zero over more than three bonds.[3] Typically, a deuterated carbon is shifted 0.3–0.6 ppm

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(2) (a) Saunders, M.; Kates, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 8071. (b) Anet, F. A. L.; Dekmezian, A. H. *Ibid.* **1979**, *101*, 5449.

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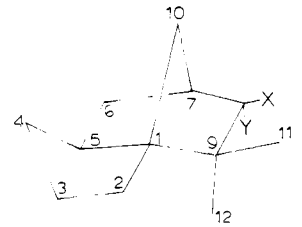
Table I. Deuterium-Induced Isotope Shifts for ^{13}C Nuclei in **1a–c**[a]

compd[b]	C-4	C-5	C-6	C-7	C-9	C-10	C-11
1a-d_x	0.076[c]	0.101	0.106	0.068	0.060	0.097	
1b-d_x	0.083[c]	0.103	0.111	0.107	0.016	0.092	
1c			0.024	0.111	0.119		0.076[c]

[a] Excluding one-bond effects (see text); all values measured at 50.3 MHz (4.7 T) in $CDCl_3$ and given in ppm (experimental error ±0.006 ppm) toward higher field; shifts less than 0.010 ppm are not listed. [b] Data listed for **1a** and **1b** partially deuterated at C-6, -7, and -11. [c] $J_{CCCD} \sim 1$ Hz.

while ^{13}C nuclei two or three bonds from the deuteron exhibit shifts of ca. 0.1 and 0.01 ppm, respectively. Consequently, ^{2}H substitution has been utilized to aid assignments of specific signals in ^{13}C spectra.[4] Anet and Dekmezian,[2b] however, have emphasized that long-range intrinsic isotope effects could be expected if a deuteron is spatially close to an observed nucleus, which could occur for vicinal ^{2}H–^{13}C interactions, but these have not received particular attention.[5] We report examples of the stereochemical dependence of vicinal deuterium-induced ^{13}C isotope shifts, a phenomenon of both theoretical interest[6] and practical significance for spectral assignments.

In our homoenolization studies of polycyclic ketones,[7] we found that **1a** undergoes exchange at three sites upon treatment with

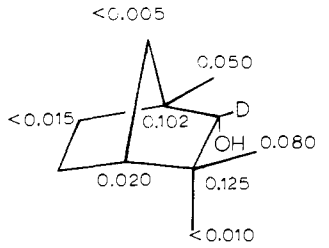


1a X,Y = O
b X = H, Y = OH
c X = D, Y = OH

t-BuO^-/*t*-BuOD at 185 °C, as expected from the behavior of related ketones.[7b] The ^{13}C spectra of partially deuterated samples of **1a**-d_x contained characteristic C–D triplets within the absorption patterns for C-6 (J_{CD} = 20.6 Hz), C-7 (J_{CD} = 22.8 Hz), and C-11 (J_{CD} = 19.5 Hz), with upfield isotope shifts of 0.365, 0.348, and 0.278 ppm, respectively. The C-6 and -7 patterns also had slightly broadened singlets 0.106 and 0.068 ppm upfield from the original signals arising from species bearing single deuterons at C-7 and -6, respectively. Furthermore, the patterns for C-5, -9, and -10, the remaining sp^3 centers geminal to deuterium, contained isotopically shifted components arising from two-bond interactions with ^{2}H at C-6, -11, and -7, respectively (see Table I).[8] However the absorption for another *methylene* carbon exhibited a similarly shifted component, appearing as a triplet, $J \sim 1$ Hz, which is strong evidence for a vicinal (three-bond) isotope shift. This methylene carbon must be C-4, and the enhanced vicinal shift (0.076 ppm) could be tentatively ascribed to the relative orientation of the 6-deuteron and C-4. Since preferential exo exchange was anticipated at C-6, by analogy with related systems,[7b] we expected most of the 6-deuterons to eclipse C-4, i.e., a dihedral angle ~0° for C_4–C_5–C_6–D (exo). Clearly **1a**-d_x has a vicinal interaction significantly larger than any reported heretofore for a saturated ^{13}C–C–C–D interaction.

For **1a** in $CDCl_3$, C-4 and -6 absorb at 33.05 and 33.22 ppm, respectively, and the multiplets for each are heavily overlapped in the spectra of the deuterated samples. This complication was removed by reduction ($LiAlH_4$) to the corresponding endo-alcohol **1b** for which C-4 and -6 appear at 33.30 and 29.07 ppm, respectively; the C-6 signal is shifted upfield by the γ-gauche effect of the endo-hydroxyl group.[9] The ^{13}C spectra of the corresponding **1b**-d_x samples revealed isotope shifts analogous to those for **1a**-d_x (Table I). In addition, **1a** was treated with $LiAlD_4$ to produce 8-exo deuterio alcohol **1c**. The ^{13}C spectrum of a 3:2 mixture of **1b** and **1c** gave the results collected in Table I; the upfield one-bond shift for C-8 is 0.489 ppm (J = 22.3 Hz). The key feature was the fact that the absorption for C-11 closely resembled that for C-4 in **1a**-d_x and **1b**-d_x; its isotopically shifted component appeared as a triplet, $J \sim 1$ Hz, 0.076 ppm upfield from the normal signal.

With this evidence for a dependence of vicinal D–^{13}C isotope shifts on the dihedral angle, the isotope shifts for *endo*-fenchol-*2-exo*-d_1 (**2**) were determined by examination of a 3:2 mixture



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of **2** and *endo*-fenchol. An upfield one-bond isotope shift of 0.528 ppm (J = 22.1 Hz) was found as well as the longer range effects indicated with formula **2**. Fenchol was chosen because of the several carbons vicinally located with respect to a 2-exo-deuteron, and a clear stereochemical dependence of the vicinal isotope shift was revealed. For the exo-8-methyl carbon, $\theta \sim 0°$ and the vicinal shift is 0.080 ppm while for C-10, $\theta \sim 30°$ and the shift is 0.050 ppm; for the remaining cases, $\theta \geq 90°$ and the isotope shifts are ≤0.020 ppm. Thus, as Anet has suggested,[2b] longer range isotope shifts induced in ^{13}C spectra by ^{2}H are dependent on the spacial proximity of the interacting nuclei. The fact that the magnitude of three-bond isotope shifts can closely approach those of two-bond effects requires that results from deuterium labeling for spectral assignments be applied with due caution although vicinally shifted components can be distinguished from geminal effects if $\theta \sim 0$ or 180° for which $J_{CCCD} > J_{CCD}$. Perhaps the present results can aid the theoretical interpretations of isotope shifts in general, but it must be noted that the stereochemical dependence of deuterium-induced isotope shifts in ^{19}F spectra has been found to be quite different,[10] with maximal vicinal shifts found for orientations that maximize the separation between ^{2}H and ^{19}F.

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Registry No. **1a**, 82414-82-2; **1b**, 82414-83-3; **1c**, 82414-84-4; **2**, 82414-85-5.

(3) Unsaturated systems including both neutral and cationic species exhibit longer range effects. As leading references see: Ernst, L.; Eltamany, S.; Hopf, H. *J. Am. Chem. Soc.* **1982**, *104*, 299. Aydin, R.; Günther, H. *Ibid.* **1981**, *103*, 1301.

(4) Stothers, J. B. In "Topics in ^{13}C NMR Spectroscopy"; Levy, G. C., Ed.; Wiley: New York, 1974; Vol. 1, pp 234–238. Wehrli, F. W.; Wirthlin, T. "Interpretation of ^{13}C NMR Spectra"; Heyden & Sons: London, 1976; pp 107–110. Abraham, R. J.; Loftus, P. "Proton and Carbon-13 NMR Spectroscopy"; Heyden & Sons: London, 1978; pp 145–148.

(5) (a) With the important exception of the isotope shifts induced through oxygen by exchange of hydroxyl protons with deuterons. (Pfeffer, P. E.; Valentine, K. M.; Parrish, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 1265. Pfeffer, P. E.; Parrish, F. W.; Unrich, J. *Carbohydr. Res.* **1980**, *84*, 13. These references illustrate the utility in examinations of a wide variety of carbohydrate structures). (b) Aydin, R.; Günther, H. *Z. Naturforsch., B* **1979**, *34B*, 528.

(6) Batiz-Hernandez, H.; Bernheim, R. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1967**, *3*, 63. Jamieson, C. J. *J. Chem. Phys.* **1977**, *66*, 4983. Raynes, W. T. *Nucl. Magn. Reson.* **1979**, *8*, 12.

(7) (a) See, for example: Cheng, A. K.; Ghosh, A. K.; Sheepy, I.; Stothers, J. B. *Can. J. Chem.* **1981**, *59*, 3379. (b) Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. In "Rearrangements in Ground and Excited States"; Mayo, P. de, Ed.; Academic Press: New York, 1980; Vol. 1, pp 410–437.

(8) Isotope-shifted components would be expected for the carbonyl absorption through two- and three-bond interactions with ^{2}H at C-7 and C-6, but only a broadened singlet ($\Delta\nu_{1/2} \sim 4$ Hz) was observed presumably because of a combination of unresolved C–D spin coupling and opposite signs for the isotope shifts.[1]

(9) For closely related systems see: Stothers, J. B.; Tan, C. T.; Teo, K. C. *Can. J. Chem.* **1976**, *54*, 1211.

(10) Lambert, J. B.; Greifenstein, L. G. *J. Am. Chem. Soc.* **1973**, *95*, 6150; **1974**, *96*, 5120.