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Mechanism of the Backbone Rearrangement of Amino Steroids. A Carbon-13 and Tritium Nuclear Magnetic Resonance Spectroscopic Study of Isoconessine, Neoconessine, and the Corresponding Polydeuterated and Polytritiated Species

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Considerable effort has been devoted in the early 1970's to investigation of the mechanism of the backbone rearrangement of steroids.[4] Deuterated reagents were used in a number of cases,[4] but unitl recently[5] no appropriate technique was available for the structural analysis of the complex polylabeled molecules. We report herein carbon-13 and tritium NMR spectroscopic evidence concerning the mechanism of the backbone rearrangement of conessine (1) into isoconessine (2)[6] and into neoconessine (4).[7]

Conessine (1) treated with D_2SO_4 or $THSO_4$ at 0 °C afforded as expected an isotopic mixture of polydeuterated isoconessine **2**-d_x or polytritiated isoconessine **2**-t_x, respectively (Scheme I). Comparison of the 400-MHz ^1H and 62.86-MHz ^{13}C NMR spectra of **2** and **2**-d_x led to the conclusion that a mixture of 17 deuterium atoms attached to 9 carbon centers were incorporated into **2**-d_x in agreement with mass spectroscopic results (**2**, $M^{+\cdot}$ at *m/e* 356; **2**-d_x, $M^{+\cdot}$ from *m/e* 365 to 373).

Interpretation of the 61.4-MHz proton-decoupled deuterium NMR spectrum of **2**-d_x was extremely difficult as a result of the broad overlapping deuterium signals. However, the 106.7-MHz proton-decoupled tritium NMR spectrum[8] of labeled isoconessine (**2**-t_x) exhibited in C_6D_6 solution 12 resolved signals (Figure 1). The radioactivity of **2**-t_x formed during the reaction from $THSO_4$ (35 Ci) was 1.2 Ci (0.75 g of **2**-t_x). The ^3H spectrum required overnight accumulation on 10 mCi of compound. Integration of the tritium NMR spectrum and its comparison with the 400-MHz proton spectrum of **2** and **2**-d_x afforded evidence that the 12 resolved signals of **2**-t_x correspond to the partial incorporation of 17 tritium atoms.

As a result of the multiple partial labeling, carbon–deuterium spin–spin coupling, and the deuterium-induced isotope shifts, the ^{13}C NMR spectrum of **2**-d_x was highly complex. Therefore, the ^{13}C NMR spectrum of **2**-d_x was recorded at 62.86 MHz with simultaneous proton and deuterium decoupling and without any lock system for field stabilization. Under these experimental conditions a ^{13}C NMR spectral comparison between **2** and **2**-d_x afforded interpretable results. The spectrum of **2**-d_x exhibited considerably reduced intensity for 12 resonances with respect to the spectrum of **2**. The carbon signals of relatively low intensity correspond to the nine labeled sites and to the quaternary centers C_5, C_8, and C_9 which are in a highly deuterated environment. Carbon-13 chemical shift assignment for isoconessine (**2**), based on steroidal models,[9] on spin-echo methods,[10] and on chemical shift rules,[9] is given in Table I which contains data for the di-*N*-cyano derivative **3** of isoconessine which was also prepared by the action of BrCN on **2** or on **2**-d_x.[6]

Table I. Carbon-13 NMR Chemical Shifts[a]

	iso-conessine (**2**)	di-*N*-cyano-isoconessine (**3**)	neo-conessine (**4**)
C-1	*29.5*[b]	*28.7*[b]	35.5
C-2	29.1	30.6	30.8
C-3	59.2	53.9	67.3
C-4	*43.0*	*43.9*	*43.5*
C-5	33.0	33.0	43.8
C-6	*33.3*	*33.2*	*32.8*
C-7	*28.3*[b]	*27.9*[b]	*29.2*[b]
C-8	131.2[c]	131.4[c]	133.0[c]
C-9	128.4[c]	128.6[c]	128.1[c]
C-10	*51.7*[d]	*51.1*[d]	*53.1*[d]
C-11	*27.0*[b]	*27.0*[b]	*27.8*[b]
C-12	33.3	32.1	33.3
C-13	48.3	50.8	48.9
C-14	*46.9*[d]	*46.1*[d]	*47.4*[d]
C-15	*28.0*[b]	*27.5*[b]	*29.8*[b]
C-16	27.5	26.1	27.2
C-17	55.9	56.8	55.8
C-18	70.0	62.8	70.3
C-19	*27.5*	*26.8*	*16.5*
C-20	63.3	59.5	63.5
C-21	14.0	13.6	14.1
NMe	40.0		40.0
2 × NMe	41.5		44.7
NC–N-Me		36.7	
NC–N-**Me**		*e*	

[a] ^{13}C NMR chemical shifts (δ) were measurd in C_6D_6 solution and are given for $\delta(Me_4Si) = 0$. Signals of relatively low intensity in the spectrum of **2**-d_x, **3**-d_x, and **4**-d_x are italic. Upfield isotope shifts of 0.2 ± 0.1 ppm in agreement with the signal assignments were observed for the following signals: **2**-d_x and **3**-d_x (C_2, C_3, C_{12}, C_{13}, and C_{16}); **4**-d_x (C_3, C_{12}, C_{13}, and C_{16}). [b-d] Assignments may be reversed within vertical columns. [e] This chemical shift was not measured.

Thus all the hydrogen atoms attached to C_1, C_4, C_6, C_7, C_{10}, C_{11}, C_{14}, C_{15}, and C_{19} are labeled in **2**-d_x and presumably in **2**-t_x while the other sites do not show incorporation. (Deuterium incorporation at rates varying between 50% and 80%, based on integration of the 400-MHz ^1H NMR spectrum of **2** and **2**-d_x, could be determined at the carbon atoms indicated.[11]) This conclusion is also in agreement with a tentative analysis of the tritium NMR spectrum of **2**-t_x in which the 1.0–1.3-ppm region may contain three axial tritons and the 1.6–2.2-ppm region three equatorial and six allylic tritons. The tritium atoms attached to C_{15} are probably distributed between these two spectral regions. The tentative assignment of the tritons are based on the known chemical shift differences between axial and equatorial protons in cyclohexane systems.[12] The pro-

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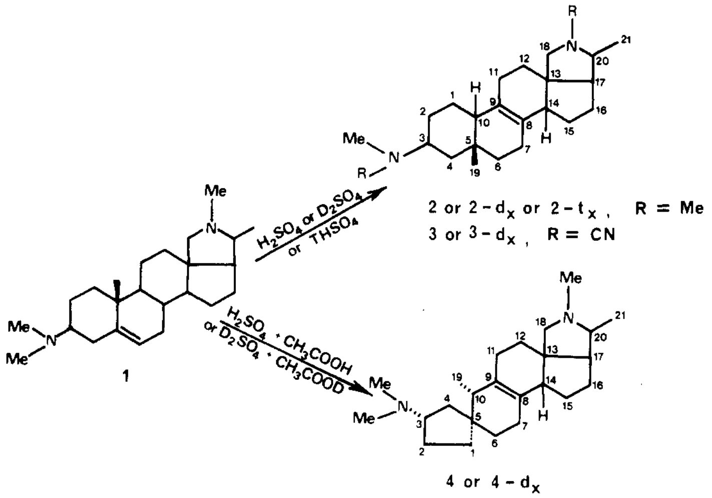
Scheme I



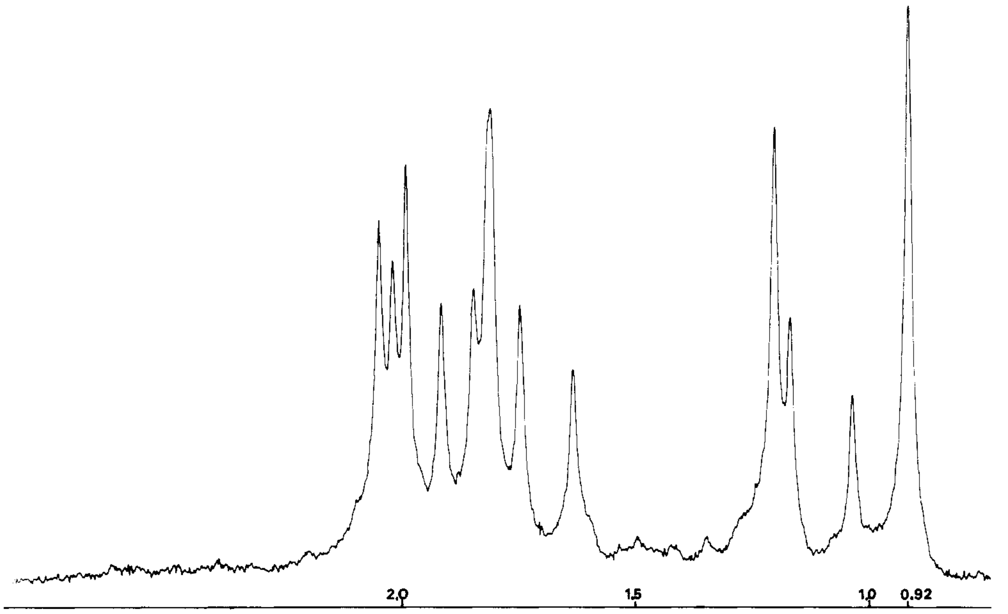


Figure 1. Proton-decoupled 106.7-MHz tritium NMR spectrum of chromatographically >95% pure 2-t_x in C_6D_6 solution. Chemical shift scale is given with respect to the C-19 methyl protons taken to be 0.92 ppm from the ^{1}H NMR spectrum of 2 in C_6D_6.

ton-coupled tritium NMR spectrum of 2-t_x was not recorded.

A similar investigation has been carried out on neoconessine 4-d_x obtained after treatment of conessine 1 with D_2SO_4 + CH_3COOD.[7] In this case, during the reaction only 15 deuterium atoms were incorporated (4, $M^{+\cdot}$ at m/e 356; 4-d_x, $M^{+\cdot}$ from m/e from 362 to 371) corresponding to eight carbon sites (Table I). It appears from the spectral study that the deuterium-bearing carbon sites for 4-d_x are C_4, C_6, C_7, C_{10}, C_{11}, C_{14}, C_{15}, and C_{19} (signals of relatively low intensity in the spectra of 2-d_x, 3-d_x, and 4-d_x are italicized in the Table).

The chemical shift similarity between 2 and 4 as far as carbons from C_{12} to C_{18} are concerned affords evidence that the stereochemistry of the C/D ring junction is identical in both compounds. Previously, a 14β-H stereochemistry was determined[13] for isoconessine (2), but the problem had not been investigated for neoconessine (4).

In the light of these results the following mechanism may be considered for the backbone rearrangement: the reaction starts by the formation of a carbocation at C_5 in equilibrium with the Δ^4 and Δ^5 olefins. This is followed by the migration of the C_{19} methyl group from C_{10} to C_5 (the mechanism leading to the labeling of the C_{19} methyl group has already been discussed[14]). It appears that the carbocation C_{10}^+ is not favored with respect to C_5^+ and the step $C_5^+ \rightarrow C_{10}^+$ is slow. This is reflected by the incorporation of deuterium or tritium at C_4 which must be the consequence of the C_3 stereochemistry of the amino group of 1.[15] In contrast to these results, during the backbone rearrangement of 3α-amino-5-pregnen-20-one no incorporation has taken place at C_4.[5]

In the presence of CH_3COOD, neoconessine 4-d_x is obtained, resulting from an attack of acetic acid on C_5^+.[7] The 3β stereochemistry of the amino group creates favorable conditions for the migration of the C_1–C_{10} bond.[16] No incorporation takes place at C_1. From carbocation C_{10}^+ isoconessine (2) or neoconessine (4) is formed according to the same mechanism: the charge is transferred from

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C_{10} toward C_{14}, and the intermediate tertiary carbocations are in equilibrium with the corresponding trisubstituted olefins. The interconversion between C_{10}^+, C_9^+, C_8^+, and C_{14}^+ proceeds by 1,2 hydrogen shifts or by a protonation–deprotonation mechanism. The reactions afford the thermodynamically favored products **2** and **4**, both with a 14β-H stereochemistry.[13]

Experimental Section

Isoconessine,[6] di-*N*-cyanoisoconessine,[6] and neoconessine[7] were prepared by the literature procedures. The corresponding polydeuterated species were obtained by using the same methods except that sulfuric acid and acetic acid were replaced by D_2SO_4 and by CH_3COOD, respectively. These reagents were obtained from Merck, Germany.

Tritiated sulfuric acid was prepared by the literature procedure[17] by using oleum 20%. Isoconessine-t_x was obtained from tritiated sulfuric acid and conessine in the same way as the nonlabeled compound.[6]

^1H and ^2H NMR spectra were recorded at 400 and 61.4 MHz, respectively, on a Bruker WM-400 spectrometer. The ^3H NMR spectrum was recorded at Saclay on a Bruker spectrometer operating at 106.7 MHz. The carbon-13 NMR spectra were obtained on a Bruker WM-250 spectrometer. For the spectrum of the deuterated materials simultaneous proton and deuterium decoupling was used without any lock system for field stabilization. During these experiments a delay time of 20 s was employed.

Mass spectra were recorded at Gif on a MS-50 spectrometer. Measurement of the radioactivity was carried out using standard procedures.

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Solvent Nucleophilicity of 2,2,2-Trifluoroethanol–Ethanol Mixtures[1]

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Recently a scale of solvent nucleophilicities (N_{KL}) was developed[2] on the basis of the specific rates of solvolysis of the triethyloxonium ion at 0.0 °C. It was proposed that this scale had an important advantage over a scale based upon an initially neutral substrate such as methyl *p*-toluenesulfonate[3] in that for a series of commonly used aqueous–organic solvents the contribution to the linear free-energy relationship (LFER) which is governed by solvent influence upon the leaving group is reduced by approximately one order of magnitude.[2] Accordingly, errors in either the value chosen to scale the influence of solvent properties upon the initial state to transition-state variation within the leaving group (*m* value) or the *Y* scale used as a measure of these solvent properties (solvent-ionizing power in the case of an initially neutral substrate), as introduced into the two-term (extended) Grunwald–Winstein equation[4] (eq 1), have minimal influence upon the calculated solvent nucleophilicity values (*N*).

Table I. Solvolysis Data for Triethyloxonium Hexafluorophosphate at 0.0 °C and *tert*-Butyldimethylsulfonium Trifluoromethanesulfonate at 50.0 °C in TFE–EtOH Mixtures

%EtOH (v/v)	log $(k/k_0)_{Et_3O^+}$ [a]	Y^+ [b]	N_{KL}
100	0.598	0.196	0.49
90	0.567		
80	0.405	0.061	0.37
70	0.191	−0.020	0.20
60	−0.051	−0.043	−0.03
50	−0.168	−0.126	−0.10
40	−0.421	−0.221	−0.30
30	−0.714	−0.334	−0.53
20	−0.915	−0.406	−0.69
10	−1.173	−0.513	−0.89
0	−2.173	−0.510	−1.89

[a] Decimal logarithm of the specific rate of solvolysis of Et_3O^+ at 0.0 °C relative to the specific rate of solvolysis in 80% aqueous ethanol (74×10^{-5} s^{-1}). [b] Decimal logarithm of the specific rate of solvolysis of *t*-BuS^+Me_2 at 50.0 °C relative to the specific rate of solvolysis in 80% aqueous ethanol (8.9×10^{-6} s^{-1}).

$$\log (k/k_0) = lN + mY \tag{1}$$

The *l* value governing the influence of solvent nucleophilicity on the specific rate of solvolysis (*k*) of a substrate in a given solvent relative to the specific rate of solvolysis in 80% (v/v) aqueous ethanol (k_0) was assigned a value of unity for the triethyloxonium ion, and a scale of Y^+ values based upon the specific rate of solvolysis (*k*) of the *tert*-butyldimethylsulfonium ion[5] relative to its specific rate of solvolysis in 80% (v/v) aqueous ethanol (k_0) was developed (eq 2) for use within eq 1.

$$\log (k/k_0)_{t\text{-BuS}^+\text{Me}_2} = Y^+ \tag{2}$$

Ethanol–2,2,2-trifluoroethanol (TFE) mixtures are virtually isodielectric, but the nucleophilicity of ethanol is considerably greater than that of TFE, and the solvent nucleophilicity of the mixtures will vary considerably with composition. Three solvent nucleophilicity values (*N*) for TFE–EtOH mixtures based on methyl *p*-toluenesulfonate and *tert*-butyl chloride solvolysis[6] have recently been supplemented[7] to cover the full range of composition, with *Y* values based on *p,p′*-dichlorobenzhydryl chloride solvolysis[8] being used.

In order to compare *N* values[6,7] with N_{KL} values for TFE–EtOH mixtures, we have measured the specific rates of solvolysis of the triethyloxonium ion and the *tert*-butyldimethylsulfonium ion for those TFE–EtOH compositions for which Kaspi and Rappoport[7] tabulate *N* values.

Swain, Kaiser, and Knee[5] used the chloride gegenion in their solvolysis studies of the *tert*-butyldimethylsulfonium ion. Since it has been shown[9] that, in aprotic solvents such as acetonitrile, chloride ion can promote a bimolecular

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