^{13}C and ^{1}H NMR spectra of substituted dihydropyrroles prepared by the reaction of 2-aminooxazoles and maleimide

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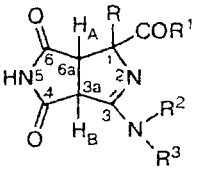
Substituted dihydropyrroles were characterized by ^{13}C and ^{1}H NMR spectra. The spectral patterns of these compounds and reversible hydrogen—deuterium exchange are discussed.

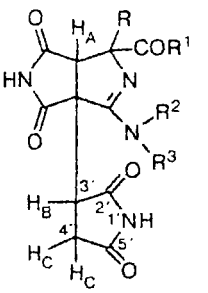
Key words: substituted dihydropyrroles, ^{13}C NMR spectroscopy, ^{1}H NMR spectroscopy, molecular structure, hydrogen—deuterium exchange.

The reaction of 2-aminooxazoles with maleimide has been reported to give,[1] among other products, compounds that have been identified as **1a—c** and **2a—c** based on the data from elemental analysis, hydrogen—deuterium exchange, and IR, UV, and ^{1}H NMR spectroscopy. In the case of the products of a similar reaction of 5-aminooxazoles,[2] unambiguous decision between structural isomers, 4,5-dihydro-3*H*-pyrroles and 2-aminoendoxotetrahydropyridine-3,4-dicarboximides, was possible only by using both ^{13}C and ^{1}H NMR spectroscopy, even if only one isomer was present. In this work, the structures of dihydropyrroles **1** and **2** were also confirmed by means of ^{13}C and ^{1}H NMR spectroscopy.



1a—c

a: R = R^1 = R^2 = R^3 = Me;
b: R = R^1 = Me, R^2 = R^3 = Et;
c: R = R^2 = R^3 = Me, R^1 = Et



2a—c

a: R = R^1 = R^2 = R^3 = Me;
b: R = R^2 = R^3 = Me, R^1 = Et;
c: R = R^1 = R^2 = Me, R^3 = Ph

The ^{1}H NMR spectra of compounds **1a,b** (Table 1) exhibit signals at about 1.1—1.6 ppm (R = Me) and 2.2—2.4 ppm (R^1 = Me), signals for the protons of the dialkylamino group, a CH_A—CH_B AB spectrum (J = 9.0 Hz), and a signal for NH. These data suggest that structure **1** is one of the possible alternatives. The spectra of compounds **2a—c** contain a singlet for the H_A proton and signals for the H_B and 2 H_C protons; this corresponds to an ABX spin system, which is degenerated to A_2X in some solvents. In addition, the nature of the solvent has an influence on the ^{1}H NMR chemical shifts of compounds **1** and **2**. Thus in DMSO the signal for H_B is observed in a lower field than the H_A signal,

Table 1. ^{1}H NMR spectra of dihydropyrroles **1** and **2**

Compound	Solvent	δ (J/Hz)					
		H_A	H_B	R	R^1	R^2, R^3	Other signals
1a	DMSO-d_6	3.82 (J_{H_A,H_B} = 9.0)	4.43	1.18	2.17	2.98	5.13 (br.s, 1 H, NH)
	C_5D_5N	4.42	4.42	1.52	2.28	3.02	
	C_5D_5N—C_6D_6 (1 : 1)	4.35 (J_{H_A,H_B} = 9.0)	4.18	1.50	2.24	2.93	
1b	$CDCl_3$	4.19	4.19	1.40	2.30	3.51 (q, CH_2); 1.13 (t, Me) ($J_{CH_2,Me}$ = 7.5)	
	DMSO-d_6	3.83 (J_{H_A,H_B} = 9.0)	4.43	1.18	2.20	3.4, 3.5 (both br.q, noneq. CH_2); 1.07 (t, Me)	
2a	C_5D_5N	4.55 (s)	4.25 (br.t)	1.58	2.38	3.22	2.97 (br.d, 2 H, H_C)
2b	C_5D_5N	4.51 (s)	4.25 (br.t)	1.57	0.95 (t, Me)	3.21	2.9 (m, 4 H, H_C and $\underline{CH_2}$Me)
2c	C_5D_5N	4.59 (s)	4.12 (br.t)	1.53	2.33	3.61 (s, Me); 6.55—7.38 (m, Ph)	2.93 (br.d, 2 H, H_C)

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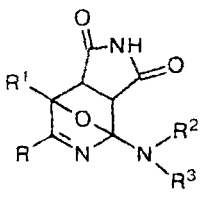
whereas in a C_5D_5N—C_6D_6 mixture these signals are displayed in the reverse order, as shown based on ^{13}C—^1H selective double resonance. The assignment of signals was also confirmed by selective deuteration (see below).

However, the identification of compounds **1a,b** based only on the data of ^1H NMR spectroscopy still seems ambiguous because other compounds, for example, the heterodiene adduct **3**, can account for about the same set of spectral parameters.[1] Therefore, the ^{13}C NMR method was used to confirm the structures of molecules **1a—c** and **2a—c**.

It can be seen from the results obtained (Table 2) that the presence of characteristic signals in the spectrum of ^{13}C—^1H double resonance and in the spectrum with complete proton decoupling allow the compounds in question to be identified as isomers with structure **1**. Indeed, the low-field region contains four signals and the medium region exhibits one signal. The signals in the lowest-field region belong to the C atoms of the carbonyl group COR^1, which is absent from heterodiene adducts **3**; the signals for the amide-type carbonyl groups are present at about δ 175.45—178.19 and those for the vinylic C(3) atoms are present in the region of δ 159.85—162.80. The signal with δ 74.71—81.53 corresponds to the C(1) atom, which is confirmed by the character of coupling with the H_A proton and with the protons of the methyl group (R) in the spectrum of **1a** (Table 3).



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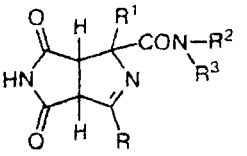
Comparison of the ^{13}C NMR spectra of compounds **1a—c** with the spectra of their structural analogs, compounds **4**,[2] shows that the signals for the C(6a) atoms in all these compounds are present in higher field than the signals for C(3a). However, the positions of the signals for C(3a) themselves are substantially different: in the case of compounds **1a—c**, they are shifted ~6 ppm upfield; the nature of the alkyl groups R^2 and R^3 virtually does not influence the signal positions. These differences between the chemical shifts of C(3a) can be due either to the fact that the β-effect of the amino group is less pronounced than that of Me or Ph or to the influence of the amino group on the imine—amine and keto—enol equilibrium in dihydropyrroles **1**, which is discussed below. Meanwhile, the variation of the ^{13}C chemical shifts for different orientations of substituents at C(1) is insignificant and does not exceed[2] 1 ppm.



4

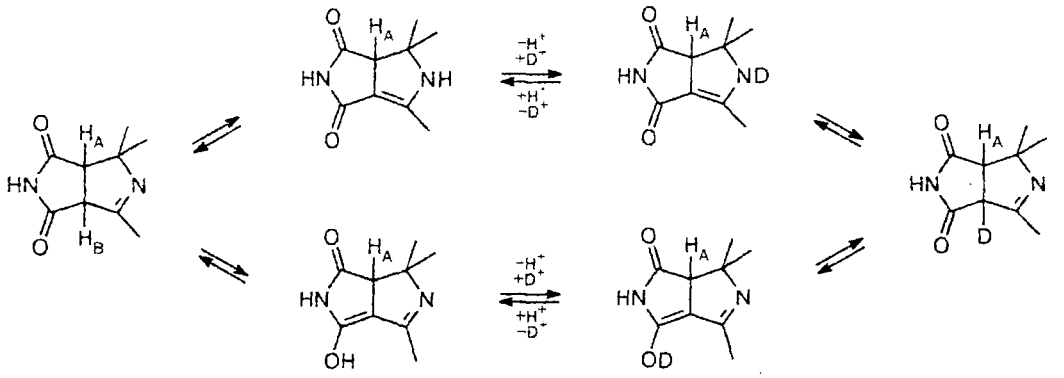
It was found that dihydropyrroles **1a,b**, like compounds **4** studied previously,[2] contain a mobile H_B atom, which can be reversibly replaced by deuterium, for example, on treatment with CD_3OD. Thus refluxing of **1a** in excess CD_3OD for 4 h results in 50% deuteration at H_B (according to ^1H NMR); this is much lower than the result attained for similar compounds **4**, which are deuterated by 75% even over a period of 1 h.[2] Refluxing of deuterated dihydropyrroles in CH_3OH is accompanied by replacement of deuterium by hydrogen, indicating that the reaction is reversible. This exchange is possible in terms of the tautomeric equilibrium (Scheme 1).

Undoubtedly, the difference between the rates of deuterium exchange is due to the effect of the amino group, which influences the electron density distribution in the N=C(3)—C(3a)—C(4)=O system (see

Table 2. ^{13}C NMR spectra of dihydropyrroles **1** and **2**

Compound	Solvent	δ										
		C(1)	C(3)	C(3a)	C(6a)	CO	C(4), C(6), C(2'), C(5')	C(3')	C(4')	R	R^1	R^2, R^3
1a	DMSO-d_6	80.20	160.94	53.97	50.14	209.45	175.45, 177.27	—	—	22.46	24.52	39.09
	C_5D_5N	81.53	161.12	54.76	50.87	209.51	175.95, 178.00	—	—	23.13	24.64	39.28
1b	C_5D_5N	81.41	159.85	54.94	50.74	210.80	177.00, 178.19	—	—	23.19	24.90	43.41 (CH_2), 13.23 (Me)
1c	AcOH	74.71	162.80	51.39	48.67	208.70	172.09, 175.00	—	—	22.19	8.04 (Me), 30.51 (CH_2)	41.44, 44.11 (noneq.)
2a	C_5D_5N—DMSO-d_6	78.80	160.46	66.41	53.06	210.85	176.30, 176.48, 176.85, 177.76	42.31	33.45	23.43	24.28	40.13
2b	C_5D_5N	79.59	160.63	67.32	54.21	213.40	176.79, 177.15, 177.94, 177.94	42.98	34.12	24.22	8.31 (Me), 29.50 (CH_2)	40.25
2c	C_5D_5N	79.96	160.70	67.87	53.54	209.87	176.36, 176.48, 176.73, 178.49	43.10	34.05	23.43	24.71	42.00 (Me), 126.88 (*p*-C), 128.04 (*o*-C), 129.31 (*m*-C), 147.82 (C—N)

Scheme 1



Scheme 1). This process might also be subject to an influence of the substituents R and COR[1].

It has been noted above that the signal of C(3a) in the ^{13}C NMR spectra of compounds **1a—c** is shifted upfield compared with the spectra of the structural analogs **4**.[2] Apparently, this shift is partially due to a lower contribution of structures in which C(3a) is a vinylic-type carbon atom (see Scheme 1).

In the spectra of compounds **2a—c**, the signal for C(3a) is not coupled with protons and is shifted ~11 ppm downfield relative to that in the spectra of compounds **1a—c** (the α-effect of the maleimide residue); the signals for C(6a) and C(3) are shifted by 2—3 ppm and by 1 ppm (β-effect).

Thus, the changes in the chemical shifts of the signals for the C(1), C(3), C(3a), and C(6a) atoms of compounds **2a—c** with respect to **1a—c** confirm the position of the maleimide residue in the dihydropyrrole molecules **2a—c**. These effects are nearly equal to those observed in the structural analogs of these compounds.[2]

The ^{13}C NMR spectra of compounds **2a—c**, unlike those of **1a—c**, exhibit two additional signals due to the carbon atoms of the amide type carbonyl groups (see Table 3).

Unlike the ^{13}C NMR chemical shifts, the spin—spin coupling constants of compounds **2a—c** are equal to those of the corresponding dihydropyrroles **1a—c**, except for $^{1}J_{C(6a),H_A}$, which decreases from 143 Hz in the spectrum of **1** to 135—139 Hz in the spectrum of **2**. The data in Table 2 demonstrate that the ^{13}C NMR chemical shifts, like ^{1}H NMR chemical shifts, depend on the nature of the solvent. In some experiments, this dependence was used to resolve close (having similar chemical shifts) signals in the ^{13}C NMR spectra. For example, in the spectrum of **2b** in C_5D_5N, two signals for the four C atoms of the carbonyl groups coincide (177.9 ppm), while in DMSO-d_6 the four signals are resolved (175.90, 176.14, 176.62, and 177.41 ppm).

The ^{13}C NMR signals for the C atoms attached directly to protons were identified based on the presence of the largest spin—spin coupling constant, while the signals for C atoms attached to proton-containing substituents were identified based on coupling with the protons of these substituents and the corresponding multiplicity. The $^{13}C—^{1}H$ heteronuclear selective double resonance was also used for the signal assignment. For example, irradiation at the frequency of the protons of the NMe_2 group in **1a** reduced the unresolved C(3) multiplet to a doublet.

The spectrum of the H_A and H_B protons in **1a—c** was brought into correlation with the signals of C(3a) and C(6a) by replacing H_B by deuterium. The high-resolution ^{13}C NMR spectra of the phenyl substituents, whose protons form a highly coupled spin system, have not been calculated; however, the signal multiplicity and approximate spin—spin coupling constants were

Table 3. Spin—spin coupling constants ($^{1}J_{^{13}C,^{1}H}$/Hz) in the ^{13}C NMR spectra of dihydropyrroles **1** and **2**

Compound	Solvent	$^{1}J_{C(6a),H_A}$	$^{1}J_{C(3a),H_B}$	$^{1}J_{R^1}$	$^{1}J_{R}$	$^{1}J_{NMe}$	$^{1}J_{C(3'),H}$	$^{1}J_{C(4'),H}$
1a[a]	DMSO-d_6	143	143	128	128	136	—	—
2a	DMSO-d_6—C_5D_5N	135	—	129	129	137	136	134
2b[b]	C_5D_5N	139	—	127 (CH_2), 129 (Me)	130	138	136	134
2c[c]	C_5D_5N	138	—	129	130	140	133	132

[a] $^{2}J_{C(6a),H_B} = 3$, $^{2}J_{C(3a),H_A} = 2$, $^{2}J_{C(1),R} = 4$, $^{2}J_{C(3),H_B} = 4$, $^{2}J_{C(1),H_A} = 4$, $^{2}J_{C(6),H_A} = 5$, $^{2}J_{C(4),H_B} = 7$, $^{3}J_{C(4),H_A} = 5$, $^{3}J_{C(6),H_B} = 3$, $^{3}J_{C(6a),R} = 3$, $^{3}J_{NMe,NMe} = 3$.
[b] $^{2}J_{C(1),R} = 4$, $^{2}J_{C(1),H_A} = 4$, $^{2}J_{CH_2,Me} = 3$, $^{3}J_{NMe,NMe} = 3$.
[c] $^{2}J_{C(1),R} = 4$, $^{2}J_{C(1),H_A} = 4$.

used as additional information in the assignment. Compounds **1a—c** are relatively unstable; therefore, high-resolution ^{13}C NMR spectra for dihydropyrroles **1b** or **1c** were not recorded.

Experimental

^{13}C NMR spectra were recorded on a Bruker WP-60 spectrometer (15.08 MHz) in the pulse mode using Me_4Si as the internal standard. Chemical shifts (±0.06 ppm) were determined from ^{13}C NMR spectra with complete proton decoupling and spin—spin coupling constants (±0.9 Hz) were found from high-resolution spectra without proton decoupling.[3] ^1H NMR spectra were recorded on a Tesla BS 497 spectrometer (100 MHz).

Syntheses of 1-acetyl-3-dimethylamino-1-methyl- (**1a**), 1-acetyl-1-diethylamino-1-methyl- (**1b**), 3-dimethylamino-1-methyl-1-propionyl- (**1c**), 1-acetyl-3-dimethylamino-3a-(2,5-dioxopyrrolidin-3-yl)-1-methyl- (**2a**), 3-dimethylamino-3a-(2,5-dioxopyrrolidin-3-yl)-1-methyl-1-propionyl- (**2b**), and 1-acetyl-3a-(2,5-dioxopyrrolidin-3-yl)-1-methyl-3-(*N*-methylanilino)-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-4,6-dione (**2c**) were described previously.[1]

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