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Z- AND *E*-CONFORMERS OF *N*-CHLOROACETYLCYTISINE

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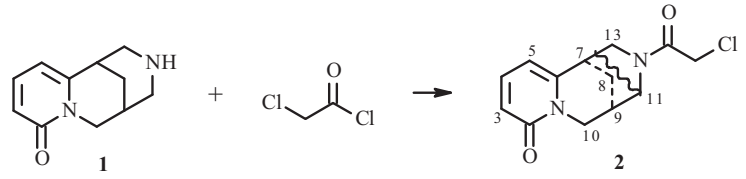
N-*Chloroacetylcytisine was synthesized by acylation of (–)-cytisine. Stable* Z- *and* E-*conformers with respect to rotational isomerism around the* N-*12–CO bond were found in PMR spectra at room temperature. The point at which PMR resonances of the* Z- *and* E-*conformers coalesced upon heating was measured. The transition barrier between the conformers was estimated.*

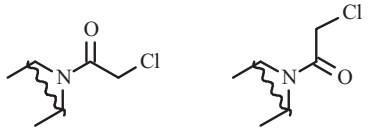
Keywords: cytisine, *Z*- and *E*-conformers of *N*-chloroacetylcytisine, PMR spectroscopy.

Structural features of cytisine derivatives have recently become very significant [1–5]. Cytisine itself has an exceedingly rigid and sterically constrained structure that is well-known, e.g., from x-ray data. However, we encountered a strange phenomenon in PMR spectra of acylated cytisines. Certain spectral lines were doubled whereas some disappeared from the spectrum [1]. The PMR spectrum displayed temperature dependence typical of spectra of molecules with several conformations of similar energy. This provided an impetus, along with the previous results [1], to study the stereochemical dynamics of acylated cytisine derivatives.

In continuation of research in this area, we studied the reaction of (–)-cytisine and chloroacetylchloride. The reaction was carried out without an HCl acceptor and also in the presence of pyridine (Py) or Et_3N. The yield of *N*-chloroacetylcytisine without an HCl acceptor was only 35%. The reaction in Py gave the target product in 77.6%. The yield of the final product was better (98%) for reaction of the (–)-cytisine:$ClCH_2COCl$:Et_3N in a 1:1.2:1.2 ratio in $CHCl_3$ at room temperature.



An analysis of the PMR spectrum of *N*-chloroacetylcytisine (**1**) in DMSO-d_6 at room temperature showed that most resonances in it were doubled. The reason for this doubling was the well-known rotational isomerism around the N-12–CO amide bond [1, 4, 6]. Conjugation of the carbonyl with the planar N atom leads to two rotational conformations that are designated [4] as the *Z*- and *E*-conformers.



2 (*Z*) **2** (*E*)

A series of *N*-acylcytisines that also showed *Z*- and *E*-conformers in the PMR spectra has been reported [1]. However, spectra were recorded in $CHCl_3$ at room temperature in that work, i.e., under conditions where a large number of very broad and overlapping resonances was observed. This did not allow several resonances to be assigned. Also, the samples could not be heated to the coalescence point and the barrier height could not be estimated because of the low boiling point of $CHCl_3$.

Herein we report spectra of **2** in DMSO-d_6 in the temperature range from ambient to 150°C. Table 1 lists the assignments of resonances with SSCC at room temperature. Figure 1 shows the PMR spectrum of **2** at room temperature and +150°C.

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TABLE 1. PMR Spectral Data for *N*-Chloroacetylcytisine (**2**) in DMSO-d_6 at Room Temperature (HMDSO = 0 ppm, J/Hz)

C atom	*Z*-conformer	*E*-conformer
3	6.088 (J = 6.8, 1.3)	6.161 (J = 6.8, 1.3)
4	7.256 (J = 9.0, 6.8)	7.291 (J = 9.0, 6.8)
5	6.137 (J = 9.0, 1.3)	6.166 (J = 9.0, 1.3)
7	3.109 (Tr. m)	3.109 (Tr.m)
8α	1.82–1.95	1.82–1.95
8β	1.82–1.95	1.82–1.95
9	2.415	2.415
10α	3.582* (J = 15.7, 6.6, 1.3)	3.594* (J = 15.7, 6.6, 1.3)
10β	4.048 (J = 15.7)	4.048 (J = 15.7)
11α	3.260 (J = 13.2, 2.5, 1.3)	2.824 (J = 13.2, 2.7, 1.3)
11β	3.887 (J = 13.2, 2.1, 2.1, 2.0)	4.415 (J = 13.2, 2.7, 2.2, 2.2)
13α	2.863 (J = 12.8, 2.4)	3.380 (J = 13.4, 2.1)
13β	4.249 (J = 12.8, 3.4, 1.6, 1.6)	3.754 (J = 13.4, 3.4, 1.7, 1.7)
CH_2Cl	4.232** (J = 13.1)	3.733** (J = 13.1)
	4.233*** (J = 13.1)	3.966*** (J = 13.1)

Chemical shifts marked by asterisks may have an alternate assignment.

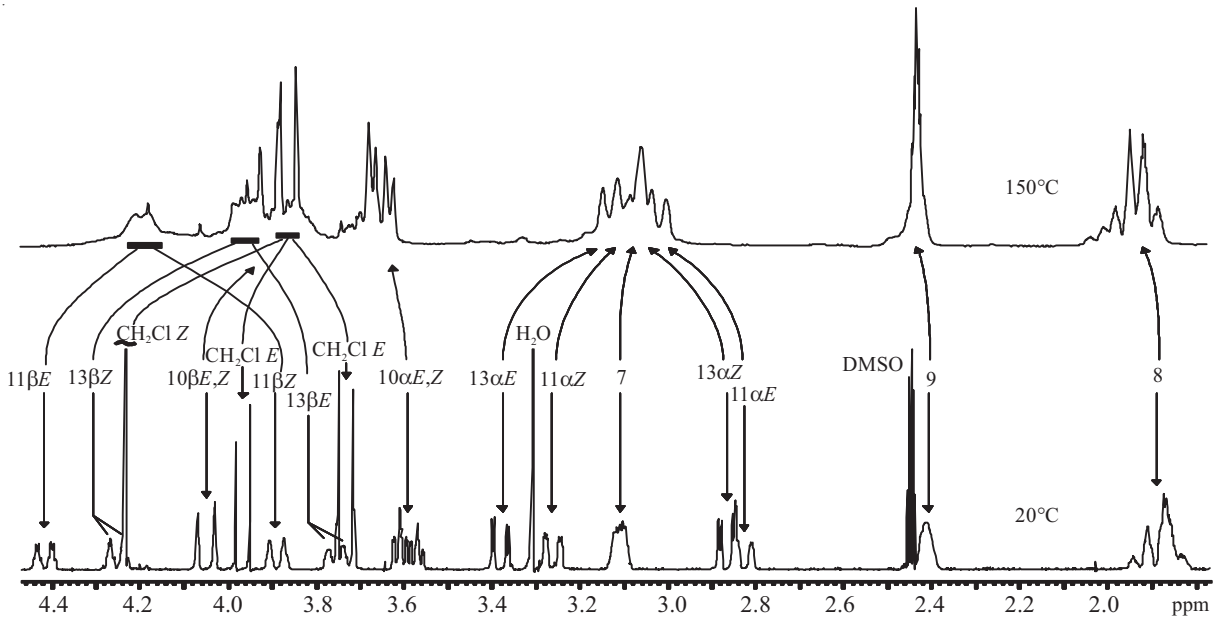

Fig. 1. PMR spectrum of the aliphatic part of *N*-chloroacetylcytisine at room temperature and +150°C.

Practically all resonances from protons of the saturated part of **2** were individualized at 20°C. The exception was only the pair of H-8 methylene protons, the four resonances of which appeared as before as one common multiplet. Resonances from the *Z*- and *E*-conformers and protons H-7, H-9, and H-10β could not be determined. The resonance of H-10β appeared as one well resolved doublet with ^{1}H integrated intensity. Therefore, this proton was insensitive to isomerism around the N–CO bond.

The resonance of H-10α at room temperature gave two sets of the "ddd" type with similar intensities that were shifted relative to each other by 0.012 ppm (Fig. 1). However, it first transformed into one slightly broadened "dd" set (J = 15.4 and 6.3 Hz) upon heating the sample to 45°C and then changed at 65°C to one "ddd" set with practically the initial values of the constants: 15.5, 6.4, and 1.2 Hz. Methylene protons H-11 and H-13 appeared as eight well resolved resonances of the two conformers [4].

We observed in the range 4.2–4.4 ppm resonances of equatorial (β-orientation) protons H-11 and H-13 oriented *cis* to the carbonyl. On the other hand, these methylene pairs in the α-orientation resonated at very strong field (2.82–2.86 ppm).

Polarization had a weaker effect on methylene protons oriented *trans* to the carbonyl. Resonances of these protons were intermediate between the aforementioned resonances.

The chloromethylene protons (CH_2Cl) appeared as two pairs of resonances of the AB-type. The *E*-conformer gave two distinct doublets (J = 13.1 Hz) at 3.73 and 3.97 ppm. Resonances of the *Z*-conformer were also two doublets. However, they had practically the same chemical shifts. Therefore, the outer components of their resonances were very weak whereas the central ones gathered into one unresolved singlet. The ratio of the amplitudes of the double central component and the very weak outer component was about 70:1. This corresponded to a difference in the chemical shifts of about 4 Hz (or 0.01 ppm) with a SSCC of about 13 Hz [7].

Upon heating, i.e., with accelerated exchange between the *Z*- and *E*-conformations, resonances of identical protons but from different conformers coalesced (averaged). This was already described above for H-10α resonances. For all other resonances, it can be stated only that they started to broaden significantly at 65°C and several resonances disappeared at 85–100°C. Averaged resonances were observed only above 100–120°C for most protons. However, the dynamics of individual resonances could not be followed in more detail because of the large number of overlapping and coalescing pairs.

The PMR spectrum at 150°C showed several unresolved multiplets. The assignments of the resonances of these multiplets to protons of the averaged molecule were obvious from the integrated intensities and average position between the corresponding resonances in the room-temperature spectrum. For example, the 3H multiplet at 2.95–3.20 ppm in the spectrum at 150°C was the fusion of five components from three protons (H-7 and axial protons H-11 and H-13) in the range 2.8–3.4 ppm of the room-temperature spectrum.

A complicated portion of the spectrum in the range 3.6–4.2 ppm at 150°C consisted of six protons: equatorial protons H-11 and H-13, methylene pairs H-10, and the chloromethyl protons. Three principal groups could be identified in this portion. The ratio of their integrated intensities was 1:3.5:1.5. The 1.5 H multiplet at 3.60–3.75 ppm consisted of proton H-10α and remnants of a still not fully averaged doublet for the chloromethyl methylene (3.733 ppm at room temperature). As mentioned above, the resonance of H-10α converts to its averaged shape already at 65°C. It practically does not change as the temperature is raised further. Only the small SSCC (1.3 Hz) with proton H-11α is lost and a very slight strong-field shift (~0.05 ppm) can be seen in its resonance at 150°C.

The 1H broad doublet at 4.15–4.22 ppm should naturally be assigned to equatorial proton H-11β, the pair of resonances at strongest field for a single proton of the *Z*- and *E*-conformers. The central group of this cluster, a multiplet at 3.76–4.00 ppm with 3.5H integrated intensity, should be assigned to the H-10β protons (which remain practically unchanged as the temperature is changed), H-13β, and the not fully averaged chloromethyl group.

The transformation of resonances in the aromatic part of the spectrum could be followed in more detail. Spectra were recorded in the temperature range 25–85°C in steps of 5°C. Two resonances of this proton are clearly visible in the spectrum at +25°C, that of the *Z*-conformer at 7.256 ppm and of the *E*-conformer at 7.291 ppm. The envelopes of the two "dd" resonances at first diminished upon heating whereas a single broad envelope for the H-4 resonance (coalescence point) was observed at 55°C. Only one "dd" resonance for the H-4 proton was seen at 85°C and higher. The barrier to rotation around the N-12–CO bond could be approximately estimated as ~15–17 kCal/mol according to a simplified Eyring formula [8] according to the difference in chemical shifts of this resonance in the *Z*- and *E*-conformers (0.035 ppm or 14 Hz) and the temperature at which coalescence was observed.

The relative population of the *Z*- and *E*-configurations at room temperature could be estimated as ~4:3 from the intensities of the resonances of the *Z*- and *E*-isomers. The Boltzmann equation under these conditions could be used to calculate approximately that the energy of the *Z*-conformer was very slightly more favorable by ~0.2 kCal/mol.

Thus, continued research on steric features of cytisine derivatives related to placement of substituents on N-12 led to preparation of *N*-chloroacetylcytisine. Its PMR spectra at various temperatures were studied. PMR spectroscopy showed that two rotational isomers around the N-12–CO bond were present in DMSO-d_6 solution. These had similar energies and an insignificant transition barrier between them. This could lead to peculiarities in the PMR spectra, i.e., doubling of some and disappearance of other spectral lines, at temperatures close to ambient.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer Model 2000 Fourier-IR spectrometer (pressed KBr pellets). The IR spectrum of **1** had absorption bands at (KBr, ν, cm^{-1}) 3021, 2977, 2949, 2894, 1639, and 801. PMR spectra were recorded in DMSO-d_6 on a Unity Plus spectrometer at operating frequency 400 MHz with HMDSO internal standard (0 ppm). Variable temperature experiments were carried out using the standard heating block of this NMR spectrometer.

Acylation of Cytisine by Chloroacetylchloride. A. A solution of cytisine (100 mg, 0.526 mmol, 1.0 equiv.) and Et_3N (0.05 mL, 0.632 mmol, 1.2 equiv.) in dry $CHCl_3$ (10 mL) was stirred at room temperature, treated with chloroacetylchloride (0.1 mL, 0.632 mmol, 1.2 equiv.), stirred for 1 h at room temperature, washed with water (2 × 5 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated. The residue was recrystallized from hexane to give white needle-like crystals, mp 198°C, yield 98%.

B. A solution of cytisine (1.9 g, 0.01 mol, 1.0 equiv.) and pyridine (1.0 mL, 0.012 mol, 1.2 equiv.) in dry $CHCl_3$ (25 mL) was stirred at room temperature, treated with chloroacetylchloride (0.9 mL, 0.012 mol, 1.2 equiv.), stirred at room temperature for 1 h, washed with water (2 × 5 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated. The solid was purified by column chromatography ($CHCl_3$:MeOH, 9:1). Yield 77.6%.

C. A solution of cytisine (1.9 g, 0.01 mol, 1.0 equiv.) in dry $CHCl_3$ (25 mL) was stirred at room temperature, treated with chloroacetylchloride (0.9 mL, 0.012 mol, 1.2 equiv.), stirred for 1 h at room temperature, washed with water (2 × 5 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated. The solid was purified by column chromatography ($CHCl_3$:MeOH, 9:1). Yield 35%.

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