An Anomalous Reaction of 7-Chloro-2-hydrazono-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine with Sodium Acetate and 1,1'-Carbonyldiimidazole

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The addition of 7-chloro-2-hydrazono-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine **3** to a mixture of sodium acetate and 1,1'-carbonyldiimidazole **1** at room temperature gave, in moderate yields, carbonyl-1,1'-bis[7-chloro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ylidene hydrazone] **7** instead of the expected 2-acetylhydrazono-7-chloro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine **4**.

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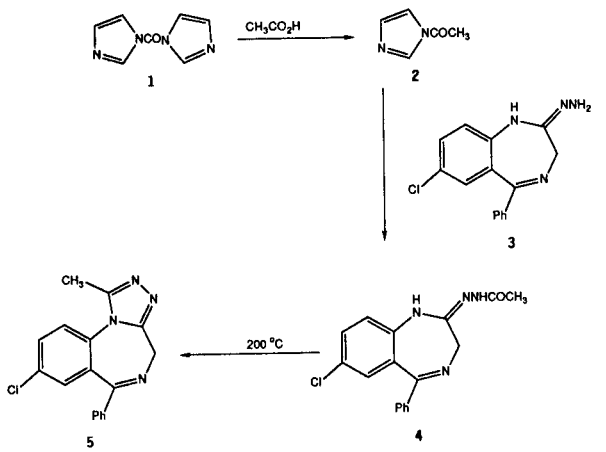
In the course of screening acylating agents for their potential in introducing the radionuclide carbon-11 ($t_{1/2}$ = 20 minutes) into alprazolam (8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine) **5**, the use of sodium acetate and 1,1'-carbonyldiimidazole was tested [1].

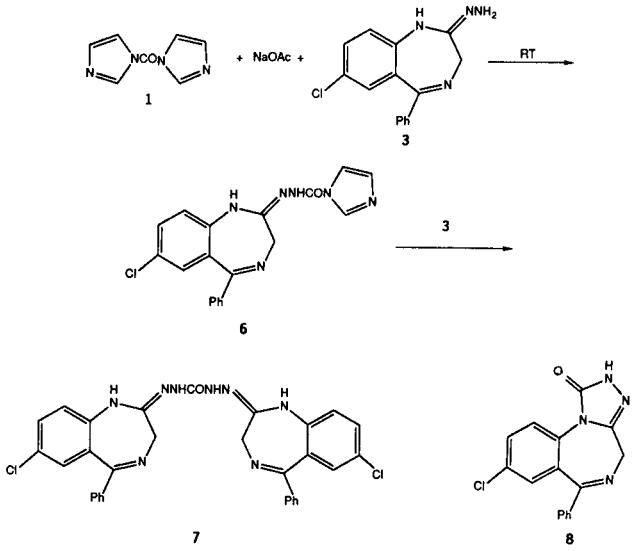
Hsi [2] had reported that carbon-14 labelled alprazolam **5** could be efficiently synthesized from thermal cyclization of the carbon-14 acylated amidrazone **4**. The latter was obtained from the reaction of carbon-14 *N*-acetylimidazole **2**, and hydrazine **3**. The key intermediate, namely the acetyl imidazole **2**, was formed *in situ* from carbon-14 acetic acid and 1,1'-carbonyldiimidazole **1** (Scheme I).

Scheme I



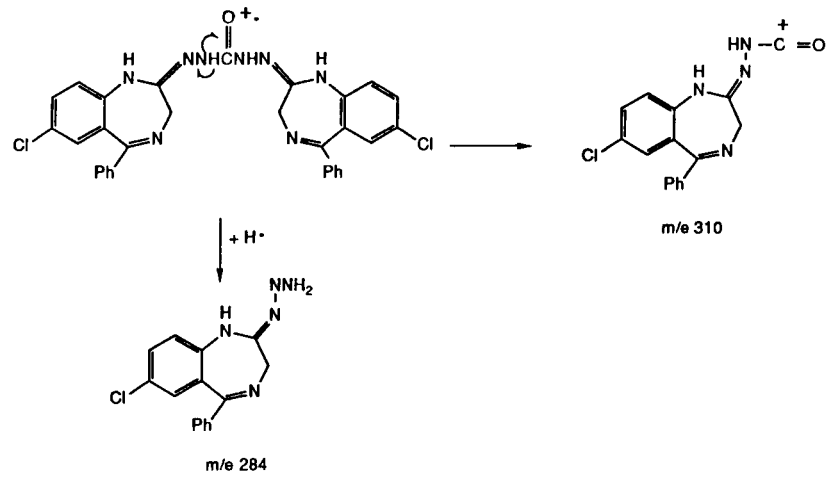
In an attempt to prepare the acylated amidrazone **4**, the precursor amidrazone **3** was added directly to a mixture of sodium acetate and 1,1'-carbonyldiimidazole at room temperature. A solid product (mp 216-219°) was isolated in 45-58% yield which was not the expected product **4** (mp 199-200° [3]). The product was assigned structure **7** (Scheme II) based on the following spectral and analytical data. Its infrared spectrum showed the absence of an amide II stretching vibration at 1560 cm^{-1} in contrast to the acylated amidrazone **4** which shows a very prominent amide II band [4]. The absence of this prominent band may be due to a nullification of the C-N stretching as a further result of the symmetrical nature of **7**. The proton

Scheme II



nmr spectrum (DMSO-d_6) of the product showed the absence of the acetyl protons at δ 2.0, a characteristic resonance signal for compound **4**. Also, the C_3 methylene protons of the diazepine ring appeared at δ 4.3 as a very broad singlet instead of a sharp singlet at δ 4.4. The ^{13}C nmr spectrum (DMSO-d_6) indicated the pressence of a carbonyl resonance signal at δ 168.8 as compared to δ 174.8 for the acetylated amidrazone **4**. This upfield shift in the carbonyl signal is in accordance with the substitution of the methyl group by an amino moiety and is commonly seen with urethanes [5]. Furthermore, when the reaction depicted in Scheme II was repeated with carbon-13 enriched acetate, carbon-13 nmr analysis indicated the absence

Scheme III



of carbon-13 enrichment in the isolated product **7**. Elemental analysis was in agreement with the proposed structure **7**, hence excluding not only formation of compound **4**, but also that of imidazolide **8** which could possibly arise from the reaction of amidrazone **3** and 1,1′-carbonyldiimidazole [6,7]. Interestingly, the mass spectrum (EI and CI mode) showed no molecular ion at m/z 594. The absence of a molecular ion can be attributed to a rapid fragmentation of the urethane N-CO bond to give a 310 and 284 m/z fragments as shown in Scheme III. Indeed, a base peak at 310 m/z and a 284 m/z fragment of 33% abundance were obtained in the EI mode.

Attempts at thermal cyclization of the isolated compound **7** to produce alprazolam **4** led to extensive degradation as evidenced by tlc analysis and tar formation.

Although the use of 1,1′-carbonyldiimidazole with acetic acid is well documented [2], it seems that activation of the sodium acetate with 1,1′-carbonyldiimidazole to form *N*-acetylimidazole **2** did not occur, at least at room temperature. Rather, the 1,1′-carbonyldiimidazole reacted with the amidrazone **3** to give the intermediate **6** which further reacted with a second amidrazone molecule to form product **7** (Scheme II).

Interestingly, on the other hand, the mixed carbonic anhydride of acetic acid and isobutyl chloroformate can be readily produced from either sodium acetate or the parent acid. Indeed, using the mixed anhydride method, compound **4** could be prepared from carbon-13 or carbon-14 sodium acetate, in reaction times as short as 5 minutes at temperatures which varied from −45° to 25°. Cyclization of the appropriate acylated amidrazone provided alprazolam **5** labelled with either carbon-13 or carbon-14 [3].

EXPERIMENTAL

Melting points were determined using a Fisher Johns melting point apparatus and are reported uncorrected. Infrared (ir) spectra were recorded on a Perkin Elmer 1430 ratio recording spectrophotometer. Proton and carbon-13 nmr spectra were obtained using a Varian VXR300 nmr spectrometer using tetramethylsilane as an internal reference. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA, USA. Mass spectra were recorded on a Varian MAT CH-5 mass spectrometer at 70 eV (EI) and methane for CI.

Carbonyl-1,1′-bis[7-chloro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepin-2-ylidene hydrazone] (**7**).

A suspension of sodium acetate (28.8 mg, 0.352 mmole) and 1,1′-carbonyldiimidazole (57.0 mg, 0.352 mmole) in anhydrous THF (5.0 ml) was vigorously stirred for 10 minutes at room temperature. The above solution was next added to a cooled (0°) solution of 7-chloro-2-hydrazono-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine (**3**) [3] (100.0 mg, 0.352 mmole) in THF (2.0 ml). The mixture was allowed to stir for 2 hours after which the volume was reduced *in vacuo* to approximately 3 ml. Diethyl ether was added dropwise to precipitate the sodium imidazole that had formed. The salt was removed by vacuum filtration (pale pink powder, mp 281° dec (lit [8] 284° dec). Addition of more ether to the filtrate caused the rapid precipitation of a solid which was filtered to give product **2** as an off-white amorphous powder (122.3 mg, 58% yield), mp 216-219° dec. Chromatography (10% methanol/chloroform, Whatman K6F 250μ silica plates) revealed a pure substance **7**; ir (potassium bromide): 1630, 1475, 1390, and 1230 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 300 MHz δ 4.2-4.4 (4H, brs, C_3H_2, $C_{3'}H_2$), 7.1-7.6 (16H, m, aromatic); ^{13}C-nmr (DMSO-d_6): 300 MHz δ 168.8 (-NH-CO-NH-); ms: (EI 70 eV) m/z (% relative intensity) 312 (33.4), 310 (100), 309 (53.6), 297 (13.5), 295 (41.4), 286 (6.8), 284 (19.3), 275 (95.2); ms: (CI) m/z (% relative intensity) 312 (3.7), 311 (4.0), 310 (10.9), 309 (12.2), 286 (2.8), 284 (6.8), 275 (14.4), 253 (15.6), 149 (100).

Anal. Calcd. for $C_{31}H_{24}N_8Cl_2O\cdot\frac{1}{2}H_2O$: C, 61.59; H, 4.17; N, 18.54. Found: C, 61.57; H, 4.15; N, 18.44.

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REFERENCES AND NOTES

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