Unusual Schmidt Rearrangement of 7,7a,8,9,10,12-Hexahydro benzo[*h*]pyrrolo[1,2-*b*]-isoquinoline-7,10-dione

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The reaction of 7,7a,8,9,10,12-hexahydrobenzo[*h*]pyrrolo [1,2-*b*]isoquinoline-7,10-dione **2** with sodium azide in sulfuric acid afforded the unexpected cyano derivative **5**. The proposed structure for **5** is supported by ^{13}C nmr, ^{1}H nmr and HMBC spectra.

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A common way to promote carbon-to-nitrogen rearrangement reactions [1] is to place a strong electron-withdrawing group on a nitrogen atom. The use of organic azides in organic synthesis lead to the formation of the aminodiazonium ion as in the Steiglitz rearrangement [2] or the iminodiazonium ion, as an intermediate in the Schmidt reaction [3]. This last rearrangement is well documented and some variations such as the intermolecular and intramolecular reactions of alkyl azides with ketones have been reported [4]. The formation of nitriles [5] accompanied with the formation of lactams has been reported in the Schmidt reaction of ketones.

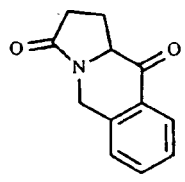
While investigating the Schmidt rearrangement of 1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline-3,10-dione (compound **1**) [6], we were intrigued by the behaviour of compound **2**, where a naphthyl group replaced the phenyl group of compound **1**.

The Schmidt rearrangement was carried out on compound **2** under the same conditions (concentrated sulfuric acid/sodium azide/0°) as for compound **1**. We did not obtain the lactams **3** or **4** but the unexpected cyano derivative **5** as the major product of the reaction.

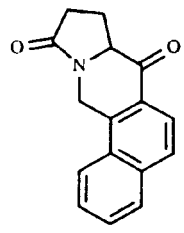
A postulated mechanism is outlined in Scheme 2. Addition of the hydrazoic acid afforded the iminodiazonium intermediate [7] **6** after loss of water. Then, the departure of nitrogen gave the nitrenium compound **7**. Bond breaking generated the nitrile group and the unstable carbocation **8** which immediately reacted with the more electron-rich ring of the naphthyl moiety affording the tetracyclic compound **5** with a nitrile group on the naphthyl moiety. The intermediate **6** could rearrange along two different alkyl-migration pathways, but did not afford lactams **3** or **4**.

The proposed structure for compound **5** is supported by infrared and mass spectral data and by proton and carbon-13 nmr data. The infrared spectrum shows absorptions at

Scheme 1



1



2

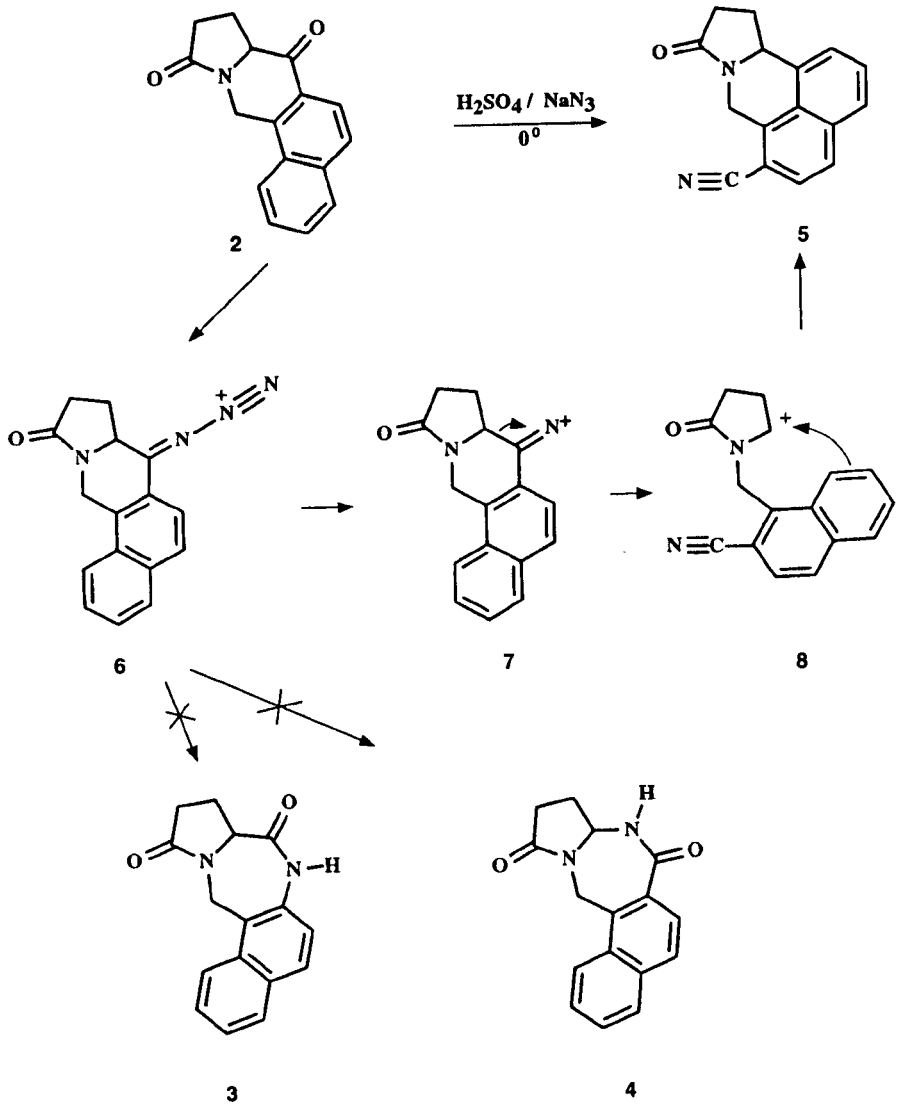
2240 and 1675 cm^{-1} for the nitrile group and the lactam, respectively. The mass spectrum (chemical ionization with ammonia) indicates a molecular peak at 249 (M^++1) and the mass spectrum (EI) a peak at 247 (M^+-1); (247.0866 found, 247.0871 calculated for $C_{16}H_{11}N_2O$ in hrms); the M^+-1 peak is characteristic of a nitrile group [8]. A detailed nmr study was undertaken.

The ^{13}C nmr spectrum of compound **5** consists of sixteen resolved signals. Beyond confirming the presence of an amide function (δ = 172.8 ppm), the multiplicities of the individual carbons, determined using the DEPT pulse sequence [9], indicated three methylene (C_7, C_{10}, C_{11}), six methine (C_1, C_2, C_3, C_4, C_5 C_{11a}) and seven non-protonated resonances (C_{3a}, C_6, C_{6a}, C_9, C_{11b}, C_{11c}, CN). Moreover the two signals at about 105 and 117 ppm are indicative of an aromatic carbon bearing a nitrile group [10].

The 400 MHz ^{1}H nmr spectrum showed five aromatic and seven aliphatic protons; they constitute AMKXY, AMX and two AM spin systems which are analyzed as first-order. At this point, compound **5** was identified as a tetrahydro-7*H*-benzo[*de*]pyrrolo[2,1*a*]isoquinolin-9-one based on the above spectral arguments, with an undetermined position for the nitrile group.

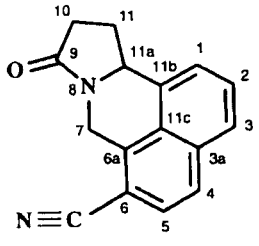
The complete ^{1}H and ^{13}C chemical shifts assignment

Scheme 2



of the compound **5**, and therefore the location of the nitrile function, was done using inverse detection techniques [11]. The one-bond proton-carbon chemical shift correlation was obtained from the heteronuclear multiple quantum coherence (HMQC) sequence [12], while long-range connectivities were obtained using a heteronuclear multiple quantum bond connectivity (HMBC) experiment [13]. From the HMBC contour plot, the H-7 resonance showed a correlating peak with the quaternary carbon located at 105 ppm. As a consequence, the CN group is β to the methylene C-7. The HMBC contour plot of compound **5** is reported in Figure 1 where the long range connectivity is indicated for proton H-7.

Scheme 3



5

The ^1H and ^{13}C chemical shifts and the proton-proton coupling constants are listed in table 1 and 2, respectively.

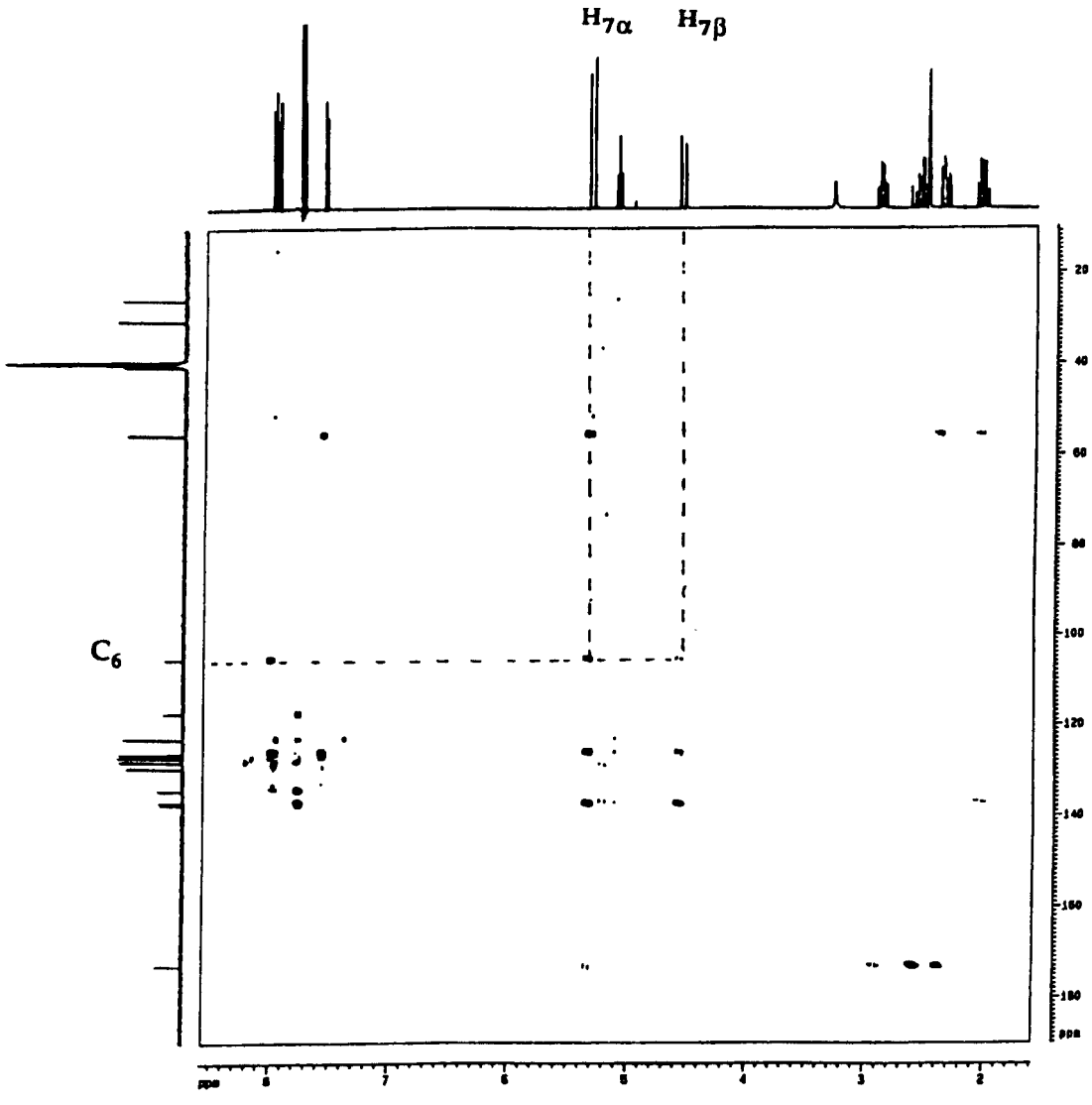


Figure 1

Table 1

Proton and Carbon NMR Chemical Shifts of **5** in DMSO-d_6

Position	δ ^{13}C (ppm)	Multiplicity	δ ^{1}H (ppm)
1	122.9	CH	7.57
2	129.3	CH	7.76
3	126.3	CH	7.96
3a	134.2	C	–
4	127.9	CH	8.00
5	127.0	CH	7.77
6	105.3	C	–
6a	137.2	C	–
7	40.5	CH_2	5.33 (β) and 4.57(α)
9	172.8	C	–
10	30.4	CH_2	2.58 (β) and 2.36 (α)
11	25.9	CH_2	2.89 (β) and 2.05 (α)
11a	55.4	CH	5.11
11b	136.9	C	–
11c	126.0	C	–
CN	117.3	C	–

Table 2

^{1}H-^{1}H Coupling Constants (Hz) of 5

Group	^{2}J	^{3}J	^{4}J
H-1, H-2		7.2	
H-1, H-3			1.3
H-1, H-11a			1.3
H-2, H-3		8.4	
H-4, H-5		8.6	
H-7α, H-7β	-17.5		
H-10α, H-10β	-16.7		
H-10α, H-11α		9.6	
H-10α, H-11β		9.6	
H-10α, H-11a			1.3
H-10β, H-11α		3.0	
H-10β, H-11β		9.6	
H-11α, H-11a		7.6	
H-11β, H-11a		7.7	
H-11α, H-11β	-12.4		

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 297 spectrophotometer. The mass spectra were obtained on a Nermag 10C apparatus and on a Varian VG analytical 70-S.

6-Cyano-9,10,11,11a-tetrahydro-7*H*-benzo[*de*]pyrrolo[2,1-*a*]isoquinolin-9-one (**5**).

The ketone **2** [14] (3.76 g, 1.5 mmoles) was dissolved in concentrated sulfuric acid (24.3 ml) and chloroform (15 ml) and the mixture cooled using an ice-bath. Sodium azide (2.14 g, 3.3 mmoles) was added portionwise and after the addition the mixture was stirred for 3 hours at room temperature. After cooling at 0°, ice (300 g) was added followed by dropwise addition of a 10% solution of sodium hydroxide until a *p*H 7 was reached. After extraction with dichloromethane (3 x 100 ml), drying over magnesium sulfate, and evaporating under reduced pressure, a solid was obtained. This solid was purified by flash chromatography on silica gel (230-400 mesh) using dichloromethane:methanol (99:1, v/v) as eluent, yield 1.21 g, 32%, mp 170-172° (ethanol); ir (potassium bromide): 2240 (CN), 1675 (CO) cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.21; H, 4.98; N, 11.34.

NMR Spectroscopy.

All nmr experiments reported were performed using a Bruker AMX-400 spectrometer in DMSO-d_6 solutions. Chemical shifts were measured in parts per million relative to tetramethylsilane. Resonance multiplicities for ^{13}C were established *via* the acquisition of DEPT spectra. The HMQC spectrum was obtained using a pulse sequence (INVBTP in the operating Bruker software) which includes the bilinear rotational decoupling (BIRD) [15] pulse to invert the magnetization of the proton not coupled to ^{13}C. The HMQC spectrum was collected with 2K x 512 data points (t2 x t1) and 8 scans per t1 increment. Spectral widths of 2800 and 14000 Hz were employed in the F_2 (^1H) and F_1 (^{13}C) domains respectively. Data were processed using shifted sine bell functions for weighting in both dimensions. The delay Δ_1 was set to 3.4 ms, while Δ_2 was empirically optimized to 400 ms. The HMBC spectrum was obtained using a standard pulse sequence (INV4LPLRND in the operating Bruker software). The spectral widths were 2800 Hz (F_2) and 18000 Hz (F_1) while the delays Δ_1 and Δ_2 were set to 3.4 and 90 ms, respectively.

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