Perhydro-1,3-diazepine-2,4-diones by Cyclization of 4-Ureidobutyric Acids with Thionyl Chloride: A Reinvestigation

Roland Heckendorn [a] and Tammo Winkler [b]

[a] Novartis Pharma AG, Research Department, Therapeutic Area Nervous System, CH-4002 Basel, Switzerland
[b] Novartis Crop Protection AG, Spectroscopy Department, CH-4002 Basel, Switzerland

Received December 8, 1998

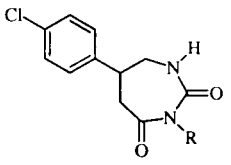
Dedicated to the memory of William Bencze

The structures of the previously reported aryl-perhydro-1,3-diazepine-2,4-diones are shown to be pyrrolidinone carboxamide derivatives by nmr spectroscopy.

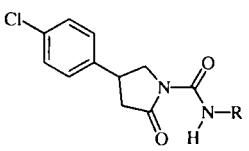
J. Heterocyclic Chem., **37**, 111 (2000).

Perhydro-1,3-diazepine-2,4-diones are rare [1] and can only be prepared by special methods [2]. We were intrigued, therefore, by the recent report in this journal describing their preparation by cyclization of 4-ureidobutyric acids with thionyl chloride [3], since, in our experience, ring closure leading to a five membered ring is always favored over that leading to a seven membered ring for entropic and steric reasons [4]. The reported spectral data [3], however, soon showed that the claimed seven membered ring structures **1a-f** are in fact the five membered pyrrolidinone carboxamides **2a-f**. This is shown in the present paper by an nmr spectroscopic investigation.

Scheme 1



1 a-f



2 a-f

R

a C_6H_5
b CH_2CH_3
c CH_2CH_2Cl
d $CH(CH_3)_2$
e $CH_2CH_2CH_3$
f H

Results and Discussion

We repeated the preparation of the ethyl derivative **5b** by following exactly the procedure given in [3] (see Scheme 2).

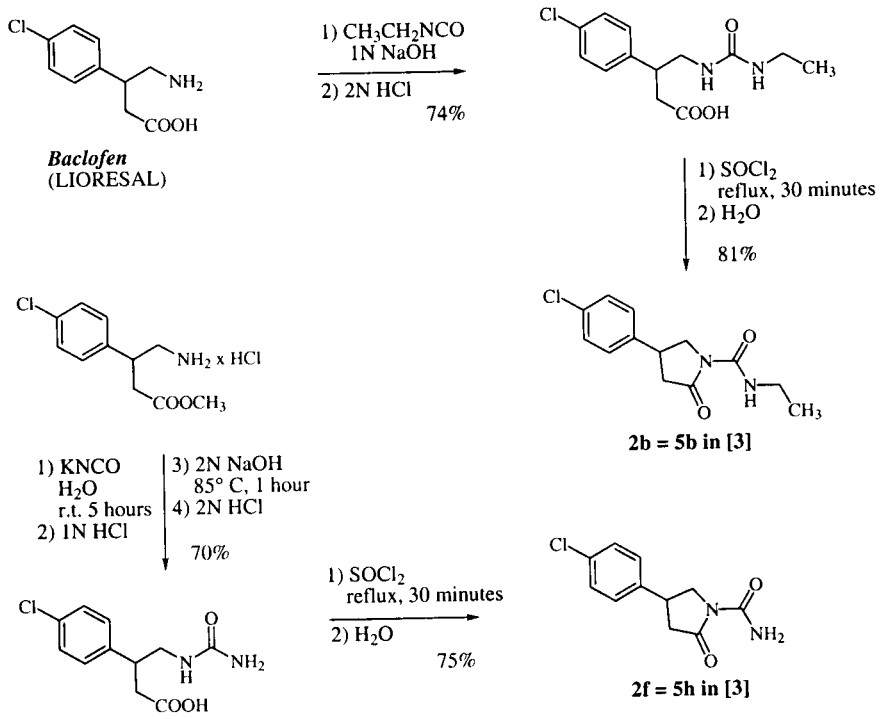
The product obtained has the same mp, ^{1}H- and ^{13}C-nmr spectra as reported for **5b** in [3]. To begin the structure assignment, a quick estimation of the ^{13}C-nmr chemical shifts of the heteroring starting from the data of the known compound **3** [5] (Scheme 3) and correcting for the acyl substituent with the data of **4** [6] indicates already that **5b** in [3] is in reality the pyrrolidinone **2b** (calculated versus observed shifts: C(3) δ 40.0 versus 40.7, C(4) 35.9 versus 35.4, and C(5) 52.6 versus 51.8 ppm).

The pyrrolidinone structure is corroborated by two nmr correlation experiments, namely a H,H-COSY and an inversely detected GHMBC, summarized in Scheme 4. The COSY (Figure 1) shows a crosspeak between the NH proton and the CH_2 protons of the ethyl group, *i.e.*, the CH_2 protons couple with the NH proton. This indicates that the ethyl group is not attached to a ring N-atom, but to a side chain NH moiety. Likewise, in the GHMBC experiment, no crosspeak is observed between the CH_2 protons of the ethyl group and the amide CO of the ring (at 175.3 ppm). Such a crosspeak would definitely be observed if the ethyl group were attached to the imide N-atom of the seven membered ring. This crosspeak would be caused by a vicinal C,H coupling. For example, a strong crosspeak is observed between the CH_2 protons of the ethyl group and the urea CO (at 152.4 ppm). A secondary result of the GHMBC (and a fully coupled ^{13}C-nmr spectrum yielding the $^1J_{CH}$ coupling constants) is the reassignment of the chemical shifts of the phenyl and the pyrrolidinone C-atoms as given in the Experimental.

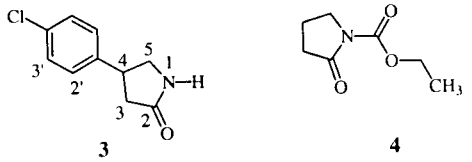
To sum up, it was proved above that **5b** in [3], reported to have structure **1b**, has in reality structure **2b**. In addition, a comparison of its nmr data with that of **5a**, **c-e** and **h** in [3] shows that the ^{1}H and ^{13}C-nmr chemical shifts of the 4-chlorophenyl and hetero rings as well as that of the urea CO are only slightly different from one derivative to the other. All compounds **5** in [3] are, therefore, not the perhydro-1,3-diazepine-2,4-diones (**1a-f**) but the pyrrolidinones (**2a-f**).

Compounds with structure **1f** and **2f** are both reported in [3]. We, therefore, repeated the preparation of **5h** in [3], claimed to have structure **1f**. Thereby, we used exactly the reaction conditions (see Scheme 2) described in [3]. The product obtained has the same mp, ^{1}H- and ^{13}C-nmr spectra as **5h** in [3] proving the identity of the reaction product. The spectra of the reaction product, as stated above, are very

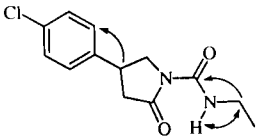
Scheme 2



Scheme 3



Scheme 4

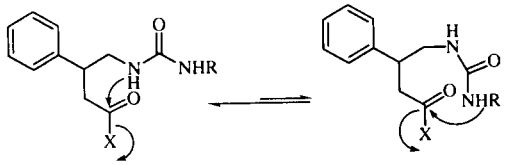


2D nmr correlations used in the structure assignment of 2b. The double-headed arrow indicates a COSY correlation, and the single-headed arrows indicate GHMBC correlations. No GHMBC correlation is observed between the CH_2 protons of the ethyl group and the amide CO (C(2)).

similar to those of **2b** (with the exception of the absence of the ethyl group of course) showing that **5h** in [3] possesses structure **2f** and not **1f**. The ^{13}C-nmr spectra of **5h** and **10** in [3] (structure **2f** in this paper) are also identical (the solvent for **5h** in [3] is erroneously given as dimethyl-d_6 sulfoxide), whereas the ^1H-nmr spectrum of **10** in [3] (structure **2f** in this paper) differs by a constant amount (*ca.* 0.11 ppm) from that of **5h** in [3], probably due to a referencing error. The spectra of **2f** in dimethyl-d_6 sulfoxide were also recorded for this paper: They are distinctly different from those in deuteriochloroform (see data in the Experimental).

Regarding the reported ring closure reaction, one should take into consideration that, whenever a substrate contains nucleophilic centers in 5- and in 7-position to an electrophile, the formation of the 5-membered heterocycle is strongly favored especially for conformational reasons (Scheme 5).

Scheme 5



favorable conformation unfavorable conformation

In conclusion, we have shown that the desired perhydro-1,3-diazepine-2,4-diones (**1a-f**) were not synthesized by the procedure described in [3], quite in agreement with our opening statement. In view of the expected pharmacological activity of these seven membered ring systems, however, it would be very worthwhile to look for a more successful route to these compounds.

EXPERIMENTAL

The ^1H-nmr spectra were obtained on a Varian Unity 500 (MHz) spectrometer equipped with a 5 mm gradient inverse detection probe (^1H 90° pulse width = 6.9 μsec, ^{13}C decoupler pulse width = 16 μsec) at 25°. The GHMBC [7] spectra were acquired as 2048 x 128 points. The data were linear predicted to 256 points in F1 and then zero filled to 2048 x 512 points prior to Fourier transformation. The long-range delay was optimized to 8 Hz (63 msec) and an interpulse delay of 1.5 seconds was used.

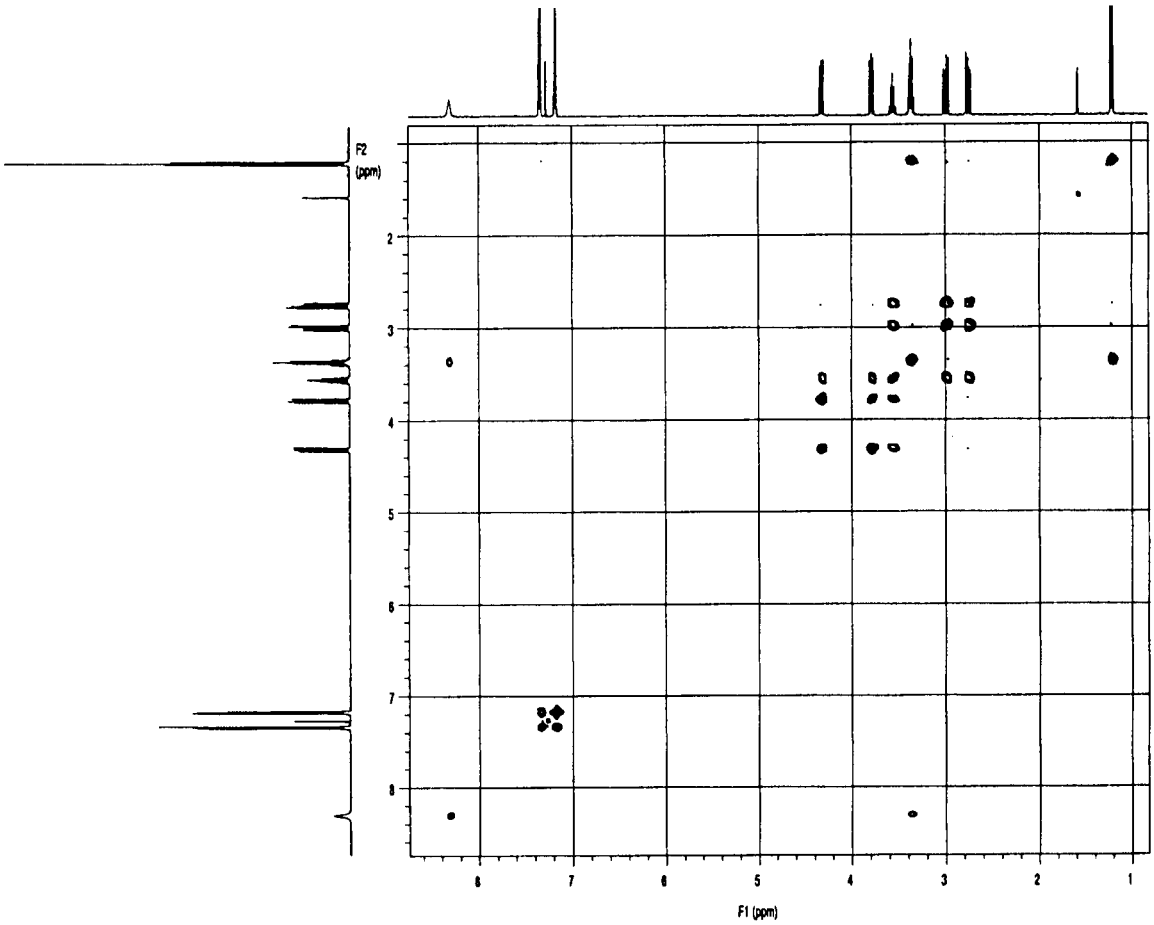


Figure 1 COSY of **2b**

The ^{13}C-nmr spectra were measured with a Varian XL 300 (MHz) spectrometer at room temperature. The compounds **2b** and **2f** were prepared by following exactly the experimental procedure described in [3].

4-(4-Chlorophenyl)-2-oxo-pyrrolidine-1-carboxylic acid ethylamide **2b** [3].

This compound was obtained as colorless crystals melting at 102-103° (lit [3]:106°) after recrystallization from dichloromethane/hexane. ^{1}H-nmr (deuteriochloroform): 8.30 (b, NH), 7.33 and 7.17 (AA'XX' system, H-3'/H-5' and H-2'/H-6' respectively), 4.31 (dd, J = 11.2 and 8.2, H-5), 3.78 (dd, J = 11.2 and 7.9, H-5), 3.56 (m, H-4), 3.36 (m, CH_2CH_3), 2.99 (dd, J = 17.3 and 8.7, H-3), 2.75 (dd, J = 17.3 and 9.2, H-3), 1.21 (t, CH_3); ^{13}C-nmr (deuteriochloroform, multiplicities and J_{CH} from the coupled spectrum): 175.3 (b, C-2), 152.4 (tb, urea CO), 139.1 (b, C-1'), 133.2 (tt, C-4'), 129.1 (dd, C-3' and C-5'), 128.0 (ddd, C-2' and C-6'), 51.8 (tm, $^1J_{CH}$ = 148, C-5), 40.7 (tm, $^1J_{CH}$ = 134, C-3), 35.4 (dm, C-4), 34.7 (tqd, $^2J_{CNH}$ = 3, CH_2CH_3), 14.9 (qtd, CH_3).

4-(4-Chlorophenyl)-2-oxo-pyrrolidine-1-carboxylic acid amide **2f** [3].

This compound was obtained as colorless crystals melting at 152-153° (lit [3]: 156°) after recrystallization from ethylacetate. ^{1}H-nmr (deuteriochloroform): 8.18 (b, NH), 7.34 and 7.18 (AA'XX' system, H-3'/H-5' and H-2'/H-6' respectively), 5.30 (b, NH), 4.32 (dd, J = 11.2 and 8.2, H-5), 3.79 (dd, J = 11.2 and 7.9, H-5), 3.59 (m, H-4), 3.02 (dd, J = 17.4 and 8.6, H-3), 2.77 (dd, J = 17.4 and 9.2, H-3); ^{1}H-nmr (dimethl-d_6 sulfoxide; the five spin system of the pyrrolidinone ring shows higher order character even at 500 MHz): 7.75 (b, NH), 7.41 (b, NH), 7.39 and 7.37 (AA'BB' system, H-3'/H-5' and H-2'/H-6' respectively), 4.11 (H-5), 3.60 (H-4), 3.54 (H-5), 2.90 (H-3), 2.80 (H-3). ^{13}C-nmr (deuteriochloroform): 175.3 (C-2), 153.1 (urea CO), 138.9 (C-1'), 133.3 (C-4'), 129.1 (C-3' and C-5'), 128.0 (C-2' and C-6'), 51.6 (C-5), 40.5 (C-3), 35.4 (C-4); ^{13}C-nmr (dimethl-d_6 sulfoxide): 175.5 (C-2), 152.6 (urea CO), 140.3 (C-1'), 131.6 (C-4'), 129.1 (C-2' and C-6'), 128.6 (C-3' and C-5'), 51.3 (C-5), 39.9 (C-3), 34.9 (C-4).

Acknowledgements.

We thank D. Strub for supplying Baclofen (Lioresal ®) and the corresponding methylester.

REFERENCES AND NOTES

[1a] V. E. Marquez, J. A. Kelley, J. S. Driscoll, *J. Org. Chem.*, **45**, 5308 (1980); [b] A. Brandner, *Synthesis* 973 (1982); [c] S. A.

Avetisyan, S. L. Kocharov, L. V. Azaryan, A. A. Karapetyan, Yu. T. Struchov, *Chem. Heterocyclic Compd.* (Engl Transl.) **31**, 28 (1995).

[2] A. R. Katrizky and C.W. Rees, *"Comprehensive Heterocyclic Chemistry"*, Ed. W. Lwowsky, Pergamon Press, Oxford, 1984 Vol. **7**, pp 605-607.

[3] J. Guillon, P. Sonnet, M. Boulouard, P. Dallemagne, H. Miel, M. Daoust, S. Rault, *J. Heterocyclic Chem.* **35**, 535 (1998).

[4] Examples from our laboratory are: [a] I. Sigg, G. Haas, T. Winkler, *Helv. Chim. Acta* **65**, 275 (1982); [b] G. Rihs, I. Sigg, G. Haas, T. Winkler, *Helv. Chim. Acta* **68**, 1933 (1985); [c] Y. P. Auberson, T. Winkler, *Synthesis* 470 (1994) (in this example, a six membered ring is preferred over a seven membered one).

[5] ^{13}C-nmr (dimethyl-d_6 sulfoxide): 175.8, 141.8, 131.1, 128.8, 128.4, 48.4 (C-5), 39.1 (C-4), 37.6 ppm (C-3). W. Bencze, unpublished results.

[6] SpecInfo Spectrum No. STCC-83275-657D, Chemical Concepts GmbH, Weinheim, Germany.

[7] C. Griesinger, H. Schwalbe, J. Schleucher, M. Sattler, in "Two-Dimensional NMR Spectroscopy, Applications for Chemists and Biochemists, 2nd Ed., Ed. W. R. Croasmun and R.M. K. Carlson, VCH Publishers, New York 1994, p. 457 and references cited therein.