^{13}C NMR CHEMICAL SHIFT ASSIGNMENTS OF ALKYL CHAINS OF HISTAMINE ANALOGOUS ω-AMINOALKYLHETEROCYCLES AND BICYCLIC DERIVATIVES

Martin POHL, Wolf-Dieter BLOEDORN, Clemens MUGGE and Jurgen LIEBSCHER*

Fachbereich Chemie,
Humboldt-Universitat Berlin, Hessische Str. 1-2, D-10115 Berlin, Germany

Received August 9, 1993
Accepted October 12, 1993

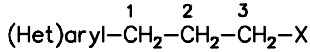
ω-Aminoalkylheterocycles and aromatics as well as bicyclic azolodiazepine derivatives were investigated by means of CH-COSY and INADEQUATE experiments. The ^{13}C NMR shifts of all carbon atoms of the aminopropyl and aminobutyl moieties could be assigned. The benzylic position of the ω-aminopropyl moieties appears most upfield rather than more downfield like erroneously reported in the literature.

ω-Aminoalkylheterocycles with alkyl chains longer than two carbon atoms such as compounds *I* are homologues and analogues of the naturally occurring histamine. They can be prepared by traditional ring closure reactions[1]. Recently a variety of new compounds *I* could be synthesized by ring chain transformation reactions[2 – 10]. By derivatization of the ω-amino group of homohistamine *I* (Het)aryl = 4-imidazolyl, X = NH_2) to quanidine moieties highly active H_2-receptor antagonists, such as Impromidine[11], were obtained[12 – 15]. This transformation can be conducted via bicyclic derivatives *II* (refs[12 – 15]), e.g. *IIa*. ^{13}C NMR data of ω-aminoalkylheterocycles *I* were repeatedly reported[2 – 9], but without a full assignment of the signals of the alkyl side chain (for a ^{13}C signal assignment in a branched aminopropylisoxazole see ref.[16]. By one exception *IIa* (ref.[12]), the same holds true for bicyclic derivatives *II* (ref.[17]). In the former report[12] the central CH_2 group (position 2) of *IIa* was assigned to the most upfield ^{13}C signal.

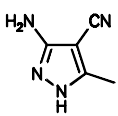
We report now on detailed 2D-NMR experiments which reveal that the previous assignments[12] were erroneous and allow to assign the ^{13}C NMR shifts of all carbon atoms of ω-aminoalkylheterocycles *I* and bicyclic derivatives *II*. A number of ω-functionalized alkylbenzenes and heterocycles *I* as well of bicyclic derivatives *II* were in-

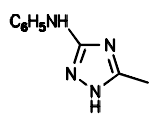
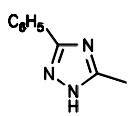
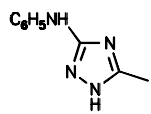
* The author to whom correspondence should be addressed.

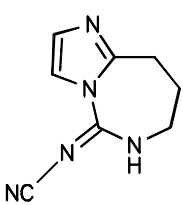
vestigated by ^{1}H NMR and by the CH-COSY method (Table I). The assignment of the proton signals was possible based on the signal splitting and chemical shifts. The CH_2 group at position 2 appears most upfield as a multiplet. The two other methylene groups are pseudo triplets with the CH_2 group next to the electronegative heteroatom (position 3) found most downfiled. As far as the substituent on nitrogen in vicinity of position 3 in bicyclic derivatives *IIc* is chiral ($-CH(CH_3)C_6H_5$) the spectra are more complex because of the diastereotopic CH_2 protons. In the aminobutyl compound *Ih* the CH_2 group at position 3 shows a multiplet because of the neighbourhood of an additional methylene group.



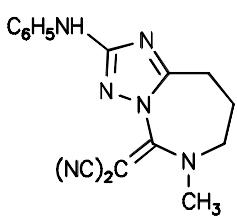
I

	(Het)aryl	X
a	C_6H_5	NH_2
b	C_6H_5	OH
c	C_6H_5	Cl
d	C_6H_5	H
e		$NHCH_3$

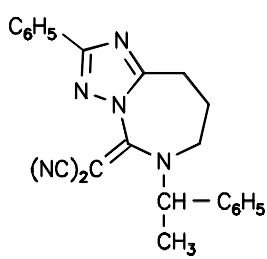
	(Het)aryl	X
f		$NHCH_3$
g		NH - CH - C_6H_5 (CH$_3$)
h		CH_2NHCH_3



IIa



IIb



IIc

Based on the proton chemical shifts, CH-COSY experiments were used to assign the ^{13}C signals. An unambiguous correlation between the highest field shifted inner CH_2 protons (position 2) and the medium shifted ^{13}C signal was found. This proves the location of the carbon signal of position 2 of compounds *I* (*Ih* excepted) and *II* at

TABLE I
Proton and ^{13}C NMR chemical shifts (in ppm, δ-scale) compounds *Ia* – *Ih* and *IIa* – *IIc*. Solvent CD_3SOCD_3

Compound	^1H NMR			^{13}C NMR		
	CH_2-1	CH_2-2	CH_2-3	CH_2-1	CH_2-2	CH_2-3
Ia	2.53[a]	1.63[a]	2.57[a]	32.6	34.8	41.1
Ib	2.65	1.78	3.49	31.8	34.5	60.3
Ic	2.71	2.01	3.59	32.2	33.7	44.5
Id(ref.[18])	2.52	1.57	0.87	37.3	24.1	13.5
Ie	2.52	1.71	2.47	24.3	27.8	50.7
If	2.65	1.78	2.49	24.0	27.5	50.9
Ig	2.87[a]	1.90[a]	2.57[a]	25.5	27.2	46.8
Ih[b]	2.63	1.70	1.45	26.0	25.3	28.7
IIa	2.92	2.01	3.20	23.9	28.3	42.1
IIb	3.05	2.30	3.40	22.1	27.2	51.2
IIc	3.06	1.48/1.92	3.17	22.3	27.3	41.9

[a] Measured in $CDCl_3$. [b] Other signals of CH_2–N: ^1H 2.46 and ^{13}C 51.2.

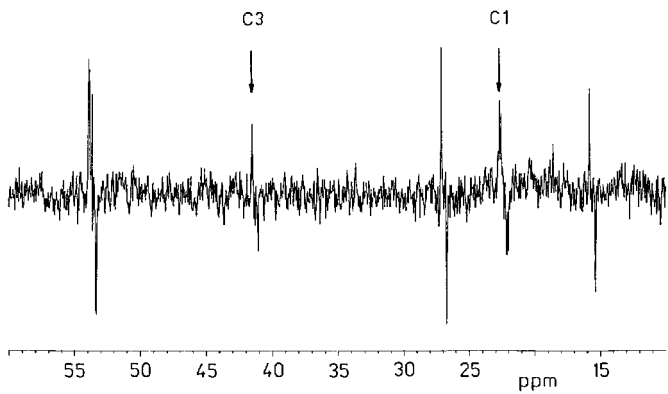


FIG. 1
INADEQUATE spectrum of *IIc*

medium shift of the three propylene ^{13}C signals rather than at the most upfiled position, like erroneously reported before[12]. An unambiguous assignment of the most upfiled signal was possible by an 1D-INADEQUATE NMR spectrum of the bicyclic compound *IIc* (see Fig. 1), which shows the connectivity of CH_2 at position 1 with the ring carbon atom of the triazole ring (two $^1J(^{13}C,^{13}C)$ splittings). Consequently the most downfield signal belongs to the CH_2 group in position 3 (or 4 in *Ih*) next to the heteroatom. The location of the benzylic CH_2 signal (position 1) in compounds *I* and *II* is caused by both, a typical γ-effect of the heteroatom X and the influence of the heterocycle. In all compounds *I* and *II* the same sequence 1 < 2 < 3 of ^{13}C NMR chemical shifts is found (*Id* X = H excepted), but the shift differences between position 1 and 2 sometimes becomes relatively small (e.g. *Ic*). An analogous sequence of the ^{13}C NMR shifts is found in the aminobutyl compound *Ih* but the additional CH_2 group at position 2 gives rise to the sequence (2 < 1 < 3 < 4).

Most presumable the assignment of ^{13}C NMR shifts of ω-functionalized propyl and butyl substituents can also be applied to other compounds *I* and *II* reported in the literature[2 – 10, 12 – 15].

EXPERIMENTAL

Compounds *Ia – Ic* were purchased from Aldrich. The following compounds were prepared according to literature procedures: *Ie* (ref.[5]), *If – Ih* (ref.[2]), *IIb* and *IIc* (ref.[17]). Compound *IIa* was supplied by Dr A. Buschauer, Freie Universitat Berlin. All spectra were recorded at ambient temperature on a Bruker AM 300 spectrometer operating at 300.13 and 75.46 MHz for ^1H and ^{13}C, respectively. As solvent CD_3SOCD_3 was used with sample concentrations of 0.1 mol l^{-1}. The $^{13}C–^1H$ heteronuclear correlation experiment was carried out with proton decoupling in F_1 CHCORRD (ref.[19]) and standard parameters. The INADEQUATE experiments[20] were performed with an one bond coupling optimization (^1J(C,C) = 50 Hz) without refocussing. The following parameters were used: evolution time for J(C,C): 0.01 (2 × D2) s, repetition time: 10 s, digital resolution: 0.1 Hz/pt.

We thank Prof. Dr A. Buschauer for supplying a sample of the bicyclic homohistamine derivative IIa and the Fonds der Chemischen Industrie for financial support.

REFERENCES

1. Elz S., Schunack W.: Z. Naturforsch., B *42*, 238 (1987).
2. Liebscher J., Patzel M., Kelboro Y. F.: Synthesis *1989*, 672.
3. Liebscher J., Patzel M., Bechstein U.: Synthesis *1989*, 967.
4. Patzel M., Liebscher J., Andreae S., Schmitz E.: Synthesis *1990*, 1071.
5. Patzel M., Liebscher J.: J. Heterocycl. Chem. *28*, 1257 (1991).
6. Patzel M., Liebscher J.: Arch. Pharm. *324*, 963 (1991).
7. Radics U., Liebscher J., Ziemer B., Rybakov Y.: Chem. Ber. *125*, 1389 (1992).
8. Radics U., Liebscher J., Pätzel M.: Synthesis *1992*, 673.
9. Patzel M., Liebscher J.: J. Org. Chem. *57*, 1831 (1992).
10. Bohrisch J., Patzel M., Mugge C., Liebscher J.: Synthesis *1991*, 1153.

11. Buschauer A.: J. Med. Chem. *32*, 1963 (1989).
12. Buschauer A., Schunack W.: J. Heterocycl. Chem. *21*, 753 (1984).
13. Buschauer A., Kramer I., Schunack W.: Arch. Pharm. *319*, 434 (1986).
14. Elz S., Schunack W.: Arch. Pharm. *320*, 185 (1987).
15. Buschauer A.: Arch. Pharm. *321*, 415 (1988).
16. Dannhardt G., Grobe A., Gussmann S., Obergrusberger R., Ziereis K.: Arch. Pharm. *321*, 163 (1988).
17. Pohl M., Bechstein U., Patzel M., Liebscher J., Jones P. G.: J. Prakt. Chem. *334*, 630 (1992).
18. Pretsch E., Seibl J., Simon W., Clerc T.: *Tabellen zur Strukturaufklarung organischer Verbindungen mit spektroskopische Methoden*, p. C40. Springer, Berlin 1986.
19. Wilde J. A., Bolton P. H.: J. Magn. Reson. *59*, 343 (1984).
20. Bax A., Freeman R., Kempsell S. P.: J. Am. Chem. Soc. *102*, 4849 (1980).