HETEROCYCLES, Vol. 53, No. 3, 2000, pp. 697 - 702, Received, 19th October, 1999

CHEMISTRY OF HETEROCYCLIC PSEUDOBASIC AMINO- CARBINOLS. PART 37.[1] CORRECTION OF A STRUCTURE - A NEW HETEROCYCLIC RING SYSTEM

Csaba Szántay*[a,b], Lajos Szabó[a], Csaba Szántay Jr[c]., Gábor Tárkányi[c], and Mátyás Czugler[b]

[a]Department of Organic Chemistry, Technical University, Gellért tér 4, H-1521 Budapest, Hungary, [b]Chemical Research Center of the Hungarian Academy of Sciences, [c]Gedeon Richter Ltd., Spectroscopic Research Center, P.O.Box 27, H-1475 Budapest, Hungary

Abstract - A previously published structure (**1**) and the rationalization of its formation must be corrected. The modified structure of the new heterocyclic ring system can be depicted as **2**.

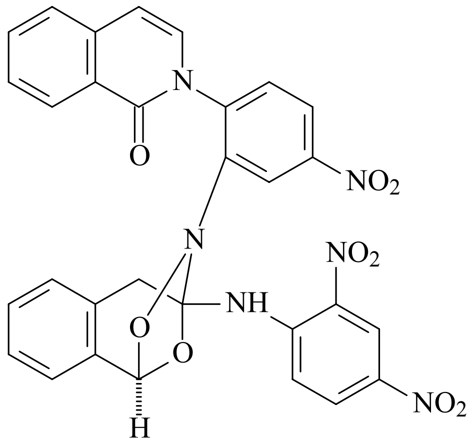
1 INTRODUCTION

In 1965 we disclosed [2,3] a new type of heterocyclic ring system (**1**) (Scheme), assumed at the time to have been formed through 1,3-dipolar cycloadditon. Since the proposed structure had only been supported by degradation, elementary analyses and IR spectra, we decided to reinvestigate the compound after 35 years by using up-to-date methods, namely NMR and X-Ray, which unambiguously gave the correct structure as **2** instead of **1** (the denoted skeletal positions correspond to the AUTONOM numbering, with primes serving to facilitate the unambiguous presentation of NMR results - see below).

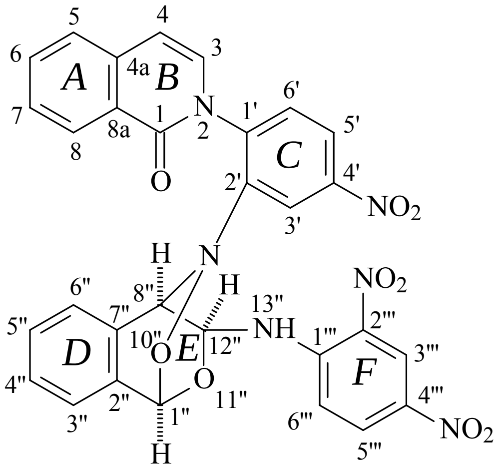
RESULTS AND DISCUSSION

2.1 NMR spectroscopy

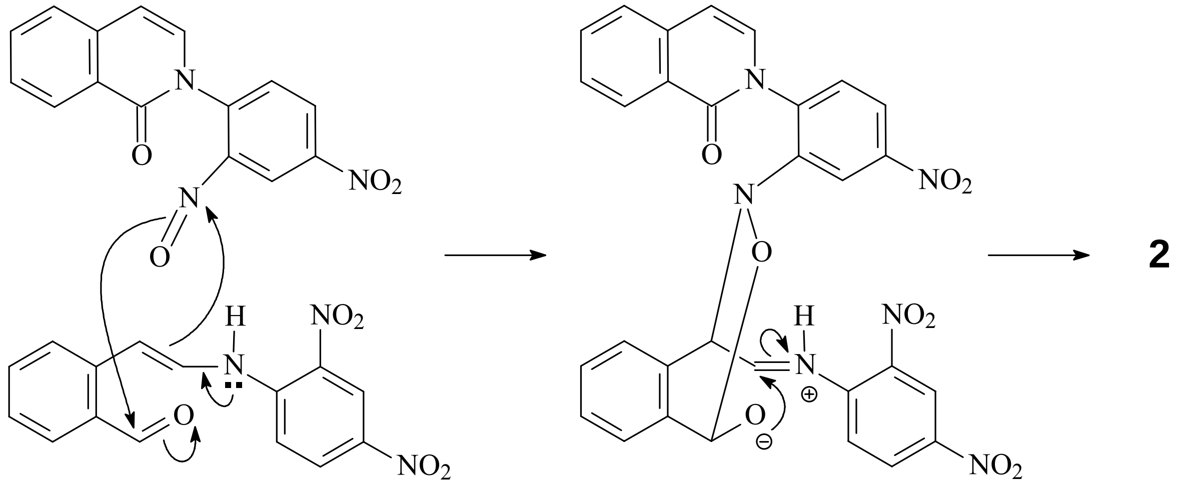
The constitution of **2** follows readily from the number of aliphatic units present in the ^{1}H and ^{13}C NMR spectra. A more detailed study based on the concerted use of standard high-field one- and two-dimensional (2D) NMR methods, 2D ^{1}H-^{1}H and ^{13}C-^{1}H shift correlation (DQFCOSY, NOESY, HSQC, HMBC)[4] and selective 1D NOE (DPFGSE-NOE)[5], led to a complete verification of this structure as well as the full



1



2



Scheme

assignments given in the Table.

The most intriguing problem with regard to this structure comes from its high degree of potential conformational freedom as well as some ambiguity regarding the relative configuration of C(12’’). In addition, the NMR spectra turned out to contain a major and a minor set of signals in a 4:1 molar ratio (only the major signals are listed in the Table). The relevant signal pairs proved to be connected by a magnetization transfer process in the NOE experiments, showing that the two species belong to a two-site chemical exchange system whose forward and backward exchange rates are slow on the chemical shift timescale (the exchange broadening of ^{1}H signals was negligible at 500 MHz and 30 °C) but fast on the relaxation timescale. On raising the temperature to 50 ^{o}C, no perceivable move toward coalescence was observed, indicating that the two species are separated by a particularly large energy barrier.

With regard to the major species the interunit NOEs between the "southern" and "northern" parts of the molecule revealed a spatial proximity between rings *A/B* and *E* (see underlined NOE connections in the Table), no doubt stabilized by π-π interactions. The ensuing geometry (Figure) turned out to be fully consistent with the solid-phase structure obtained from the X-Ray study (see below), and is only accommodated by H-3 being on the same face as H-4.

The geometry of the main species, energy-minimized through molecular modeling calculations using an AM1 semiempirical method[6] is shown in the Figure. Severe spectral congestion together with magnetization transfer operating between the major and minor sites rendered experimental investigations toward the identity of the minor species unduly demanding. Nevertheless we can speculate that the large energy barrier between the two species might be due to the minor form also being stabilized by π-π interactions, and to that effect three possible candidates immidiately suggest themselves in which the relative orientations of the *A/B* and *F* rings are different from the major species. Our preliminary calculations have shown that all such conformers, as well as others in which π-π interactions were assumed to form between other "southern" and "northern" rings, gave significantly higher energies than the major form shown in the Figure.

2.2 X-Ray studies

Seeking for further corroboration we performed X-Ray studies as well, which unambiguously proved the correctness of structure (**2**). The obtained data have the depository number at Cambridge Crystallographic Centre: CCDC 117955.

2.3 Mechanism

As a consequence of the structure modification it is necessary to change the rationalization[2] of the formation of **2**. We can safely assume that the key step of the process is a cycloadditon according to the Scheme. However, we have no facts in our hands to draw a conclusion whether the process is synchronised or stepwise.

Without a detailed investigation we can assume that the structure of substituted derivatives[3] should to be corrected accordingly.

Table ^{1}H and ^{13}C NMR chemical shifts, characteristic ^{1}H-^{1}H coupling constants and ^{1}H-^{1}H NOE connections for compound **2.**[a]

Position	^{1}H (δ)	$J_{H,H}$(Hz)	NOE (H)	^{13}C (δ)
1’’	6.82 s		3’’,13’’,3’	94.0
12’’	5.78 dd	$J_{12'',8''}=2.1$ $J_{12'',13''}=8.7$	8’’,6’’’,6’’,13’’	78.0
8’’	4.76 d	$J_{12'',8''}=2.1$	12’’,6’’,6’’’,13’’	60.0
7’’				128.0
6’’	7.16 d		8’’,5’’,12’’	115.3
5’’	7.41 td		4’’,6’’	129.4
4’’	7.51 td		5’’,3’’	129.2
3’’	7.69 d		1’’,4’’,3’	121.5
2’’				134.8
13’’	9.09 d	$J_{12'',13''}=8.7$	12’’,8’’,3	
1’’’				145.1
2’’’				130.4
3’’’	8.68 d	$J_{3''',5'''}=2.7$	5	123.2
4’’’				136.4
5’’’	7.87 dd	$J_{3''',5'''}=2.7$ $J_{6''',5'''}=9.5$	6’’’,8,7	129.7
6’’’	7.10 d	$J_{6''',5'''}=9.5$	5’’’,12’’	115.3
1				161.5
3	7.25 d	$J_{4,3}=7.3$	4,13’’	131.8
4	6.47 d	$J_{4,3}=7.3$	3,5	106.0
4a				136.7
5	7.47 d		4,3’’’	126.3
6	7.55 td		5,7	132.5
7	7.39 td		6,8,5’’’	126.9
8	8.12 d		7,5’’’	127.0
8a				125.2
1’				146.9
2’				136.7
3’	7.11 d	$J_{3',5'}=2.6$	1’’,3’’	115.6
4’				146.0
5’	7.95 dd	$J_{6',5'}=8.7$	6’	120.4
6’	7.59 d	$J_{6',5'}=8.7$	5’	131.8

[a] Relatively weak NOEs are denoted with small characters; underlined characters indicate NOEs connecting the southern and northern parts of the molecule.

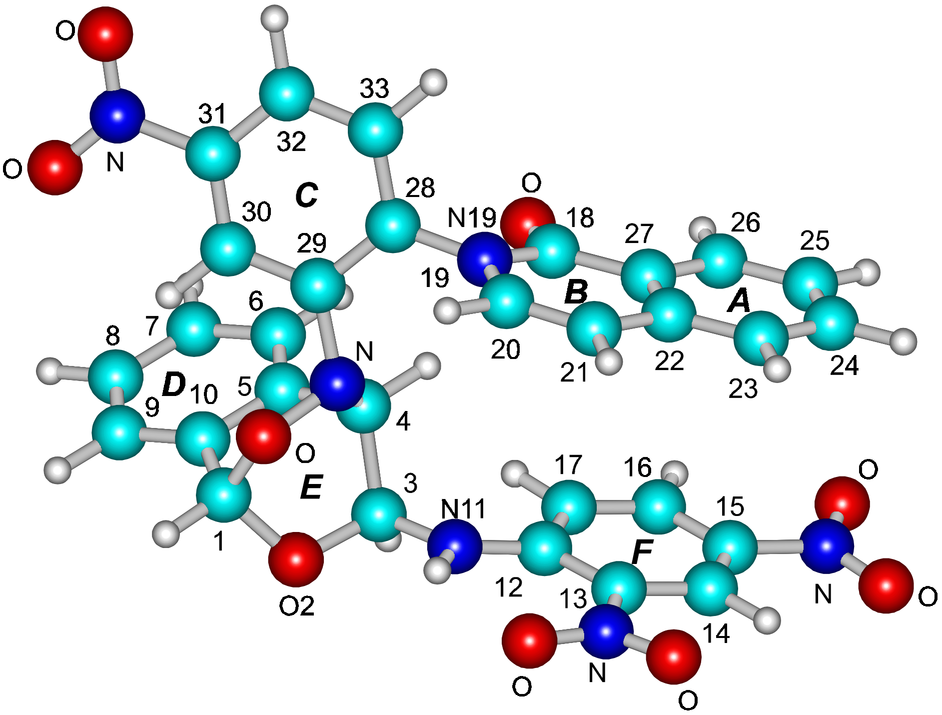


Figure. The preferential geometry of compound (**2**), as calculated by AM1 semiempirical energy minimization.

Conclusion

According to the above studies we must replace the originally proposed structure (**1**) with the correct structure (**2**), and at the same time the reaction sequence leading to **2**.

3 EXPERIMENTAL

The melting point is uncorrected. IR spectra were recorded on a Perkin-Elmer 1000 spectrophotometer. All ^{1}H and ^{13}C NMR spectra were recorded on a Varian $^{\mathrm{UNITY}}$*INOVA* 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) with internal deuterium lock in DMSO-d$_6$ at 30 °C. Chemical shifts are given relative to δ_{TMS}=0.00 ppm. All pulse programs were run by using the standard spectrometer software package and utilizing its pulsed field gradient facility. NOEs were measured in non-degassed samples with a 0.8 s mixing time. MS data were obtained on a VG-TRIO-2 (EI, 70 eV) and a Finnigan MAT 95SQ (FAB) spectrometer.

2-{2-[12-(2,4-Dinitrophenylamino)-10,11-dioxa-9-azatricyclo[6.2.2.0^{2,7}]dodeca-2,4,6-trien-9-yl]-4-nitrophenyl}isoquinolin-1(2*H*)-one (2): The compound was prepared as described earlier.[2] After recrystallization from nitromethane the mp of the yellow crystals rose to 242-244 °C. *IR* (KBr, cm^{-1}):

3369 cm^{-1} (NH), 1658 (C=C), 1651 (C=O), 1531, 1523, 1333 (NO_2), 1066 (C-O-C), 1614, 761, 742 (Ar). *MS* (EI) *m/z* (rel. %): 397 (30), 322 (18), 265 (48), 219 (29), 183 (100), 153 (51), 128 (26), 91 (74), 76 (43), 63 (67), 51 (81); (FAB): [MH$^+$]=609.

ACKOWLEDGEMENTS

We thank Mr. J. Brlik and Dr. B. Hegedűs for the MS and IR data.

REFERENCES

1. For part 36 see: D. Korbonits, G. Horváth, P. Kiss, K. Simon, and P. Kolonits, *Chem. Ber*., 1990, **123**, 493.
2. Cs. Szántay and L. Szabó, *Chem. Ber*., 1965, **98**, 1013.
3. Cs. Szántay and L. Szabó, *Chem. Ber*., 1965, **98**, 1023.
4. S. Braun, H.-O. Kalinowski, and S. Berger, ‘100 and More Basic NMR Experiments, A Practical Course’, 2nd ed.,VCH, New York, 1996.
5. K. Stott, J. Keeler, Q. N. Van, and A. J. Shaka, *J. Magn. Reson.*, 1997, **125**, 302.
6. M. J. S. Dewar, E. Dewar, E. G. Zoebisch, Eamonn F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc*., 1985, **107**, 3902.