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STRUCTURE DETERMINATION OF A TRANS-OCTAHYDROINDOLE DERIVATIVE OBTAINED BY CONSECUTIVE COUPLING OF A ß-ACETAMIDO RADICAL WITH α-CHLOROACRYLONITRILE AND CYCLISATION

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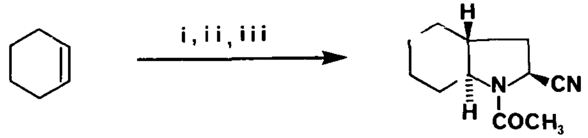
Summary: The determination of the structure of 1-acetyl-octahydroindole-2-carbonitrile by NMR spectroscopy, X-ray diffraction and computerized conformational analysis is described.

We have prepared 1-acetyl-octahydroindole-2-carbonitrile (1) by acetamidomercuration of cyclohexene, followed by reductive coupling of the mercurial with α-chloroacrylonitrile and ring closure under basic conditions [1)].



1

i) CH_3CN, $Hg(NO_3)_2$, 20°C, then NaCl; ii) $CH_2{=}C(CN)Cl$, $NaBH_4$, EtOH, - 15°C $\longrightarrow$ + 15°C; iii) NaH, DMF, 0°C

From mechanistic considerations one would assume that the relative configuration of the three asymmetric centers at C 01, C 03 and C 04 (numbering of Fig. 1, see below) should be as shown in 1, i.e. having a trans ring juncture and cis hydrogen atoms at C 01 and C 04.

The hydrogen atom at C 01 (H 011) gives rise to a sharp doublet at δ = 4.90 ppm in the 270 MHz ^{1}H NMR spectrum at 100°C in DMSO-d_6 (These conditions were used to eliminate complications due to the existence of rotamers at 25°C). This can be attributed to a dihedral angle close to 90° between this hydrogen and hydrogen H 021 at C 02 [2)]. The trans connection of the rings could not be proven from the NMR spectrum [3)].

We then applied the SCRIPT program developped by Cohen 4) to our problem. This program allows the automatic generation of energy minimized conformers from a set of topological and geometric parameters using a strain energy minimization criterion. We could show, that only in the configuration shown in 1 conformers with dehedral angles close to 90° between H 011 and H 021 or H 022 could exist 5).

Ultimate structure proof came from X-ray analysis 6). Single crystals of 1 were obtained from ethyl acetate. The compound crystallizes in the non-centrosymmetric space group P n a 2_1 with 4 molecules in the unit cell. The cell dimensions are: a = 11.414 Å, b = 14.179 Å, c = 6.402 Å, V = 1036.1 Å^3, D_m = 1.28 g/cm^3, D = 1.232 g/cm^3. In all, 1377 unique reflections were used in the analysis, the structure was refined to a weighted R-value of 0.034. The coordinates of the atoms and their isotropic temperature coefficients are listed in the table. An ORTEP plot and a view of the crystal lattice along the crystallographic c-axis showing 4 unit cells are shown in Fig. 1 and 2.

Table Coordinates and Isotropic Temperature Coefficients of the Atoms of 1

Atom	X	Y	Z	B
O1	.4265 (2)	.1756 (2)	-.3984 (4)	5.2 (1)
N1	.3049 (2)	.1395 (2)	-.1356 (5)	3.2 (1)
N2	.3364 (3)	-.0832 (2)	-.3322 (6)	5.7 (1)
C01	.3791 (3)	.0585 (2)	-.0793 (6)	3.3 (1)
C02	.3445 (3)	.0357 (2)	.1450 (6)	3.4 (1)
C03	.2150 (3)	.0613 (2)	.1420 (6)	2.8 (1)
C04	.2144 (3)	.1555 (2)	.0271 (5)	2.8 (1)
C05	.0890 (3)	.1772 (3)	-.0397 (7)	4.0 (1)
C06	.0142 (3)	.1842 (2)	.1578 (7)	4.4 (1)
C07	.0202 (3)	.0964 (3)	.2938 (6)	4.1 (1)
C08	.1468 (3)	.0679 (2)	.3457 (6)	3.7 (1)
C09	.3433 (3)	.1972 (2)	-.2904 (6)	4.1 (1)
C10	.2777 (4)	.2891 (2)	-.3176 (6)	5.8 (1)
C11	.3563 (3)	-.0217 (3)	-.2236 (6)	3.9 (1)
H011	.4639 (19)	.0790 (16)	-.1052 (43)	2.8 (6)
H021	.3597 (21)	-.0261 (16)	.1865 (44)	2.6 (7)
H022	.3890 (22)	.0849 (19)	.2540 (47)	4.2 (8)
H031	.1704 (20)	.0161 (16)	.0467 (41)	2.1 (6)
H041	.2443 (20)	.2065 (16)	.1509 (46)	3.2 (6)
H051	.0829 (22)	.2305 (18)	-.1040 (43)	3.9 (7)
H052	.0589 (27)	.1268 (18)	-.1353 (57)	5.5 (9)
H061	-.0620 (23)	.2030 (18)	.1078 (53)	5.1 (8)
H062	.0422 (24)	.2460 (22)	.2506 (45)	6.2 (9)
H071	-.0165 (25)	.0448 (19)	.2158 (49)	5.0 (10)
H072	-.0226 (31)	.1113 (24)	.4283 (69)	8.0 (11)
H081	.1432 (19)	.0054 (16)	.4164 (44)	3.4 (6)
H082	.1888 (20)	.1132 (15)	.4427 (45)	2.8 (6)
H101	.1905 (42)	.2713 (40)	-.4273 (98)	19.6 (20)
H102	.2641 (25)	.3179 (19)	-.1994 (51)	5.6 (8)
H103	.3181 (26)	.3235 (20)	-.4055 (56)	7.3 (9)

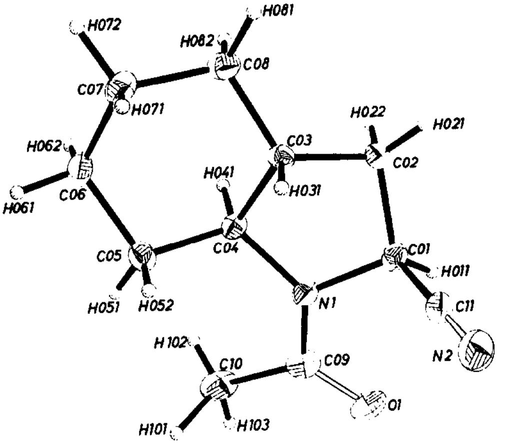


Fig. 1: ORTEP plot of 1

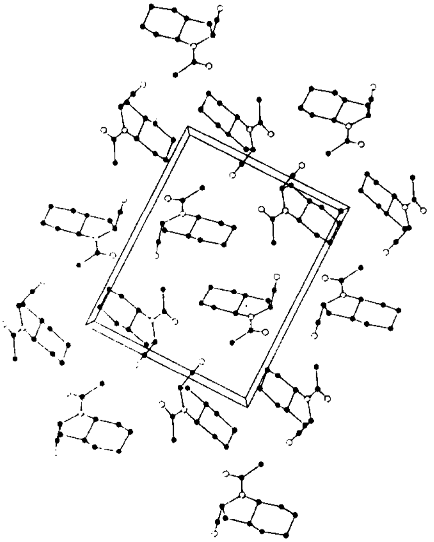


Fig. 2: Projection along the crystallographic c-axis

The analysis clearly demonstrates the configuration for this compound as shown in 1. The five-membered ring has a twisted envelope conformation; C 01 is lying 0.252 Å above and C 02 0.458 Å below the plain of the other three atoms. As a consequence of the steric strain due to the trans ring juncture, the hybridisation of nitrogen atom N 1 is not exactly sp^2, which causes it to be positioned 0.114 Å above the plain of its ligands. The sum of the bond angles around it (358.1°)differs markedly from 360°. The six-membered ring shows a largely undisturbed chair conformation.

In the crystal, only the anti isomer of the amide bond is present; upon solution in DMSO it equilibrates to a mixture containing 40 % syn and 60 % anti isomer at 25°C as shown by NMR 9).

Acknowledgement: We are indebted to Dr. H.-W. Fehlhaber for recording and interpreting the NMR spectra.

References and Notes

1) R. Henning and H. Urbach, *Tetrahedron Lett.*, (1983)

2) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

3) Proton H 041 shows up as a doublet of triplets with J_1 = 3Hz and J_2 = 13 Hz.

4) N. C. Cohen, P. Colin and G. Lemoine, *Tetrahedron* **37**, 1711 (1981).

5) For the configuration shown in **1** the program generates two conformers of approximately equal energy corresponding to the rotamers of the amide bond. The dihedral angle H 011-C 01-C 02-H 021 is calculated to be -86.1° for the syn- and -88.1° for the anti-isomer. The isomer having a trans relationship between H 011 and H 041 has dihedral angles of 39.2° for H 011-CO1-C 02-H 021 and 161.9° for H 011-C 01-C 02-H 022, which makes the signal of H 011 in the NMR a triplet$^{1)}$.

6) The analysis was carried out with a computer driven Nicolet single crystal diffractometer using Mo-K_{α} radiation.(θmax. = 28°; 1066 reflections with intensities $> 1\sigma$ (I); R_1 (unweighted)=0.100; the weighting scheme was restricted to the counting statistics; anisotropic temperature factors for all nonhydrogen atoms were used in the least squares refinement). The structure was solved with the direct phase determination method$^{7)}$ using the SHELXTL program$^{8)}$, which was also used for all the other calculations.

7) G. Germain, P. Main and M. M. Woolfson, *Acta Cryst. B.*, **26**, 274 (1970), G. Germain and M. M. Woolfson, *ibid.*, **24**, 91 (1968).

8) G. M. Sheldrick: SHELXTL, an integrated system for solving, refining and displaying crystal structures from diffraction data, University of Goettingen, 1981.

9) The rotamers show the following characteristic absorptions:

syn-**1**: δ = 5.03(d.J=7.3Hz, H 011); 2.88(dt,J_1=3Hz, J_2=13Hz, H 041)
anti-**1**: δ = 4.80(d.J=7.3Hz, H 011); 3.05(dt,J_1=3Hz, J_2=13Hz, H 041).

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