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INVESTIGATION OF THE STEREODIRECTION OF THE RITTER REACTION. CRYSTALLINE AND MOLECULAR STRUCTURES OF N-(2-PHENETHYL)-4-METHYLPIPERID-4-OL AND N-(2-PHENETHYL)-4-METHYL-4-ACETAMIDO-PIPERIDINE

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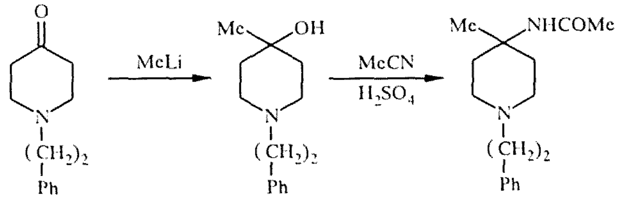
The stereodirection of the Ritter reaction of N-(2-phenethyl)-4-methylpiperid-4-ol to the corresponding amide has been studied. X-ray analysis has shown that the reaction occurs with retention of the configuration about atom C_4 of the piperidine ring. Attempts are made to explain the stereodirection of the reaction.

In continuation of a study of the application of the Ritter reaction to a series of piperid-4-ols [1] it was of interest to look at the effect of alkyl groups in the piperidine ring on the reaction stereodirection, in particular that of a 4-methyl group on the Ritter reaction of N-(2-phenethyl)-4-methyl-piperid-4-ol (II) to N-(2-phenethyl)-4-methyl-4-acetamido-piperidine (III).

Reaction of N-(2-phenethyl)piperid-4-one (I) with methyllithium gave alcohol II which was converted to III using acetonitrile in the presence of excess concentrated sulfuric acid at 50-60°C.



I II III

According to chromatographic data II and III are obtained as single isomers. To determine their steric structures an x-ray structural investigation was undertaken. It was found that both the 4-hydroxy and 4-acetamido substituents were orientated axially relative to the piperidine ring. This stereodirection of the Ritter reaction can be related to its expected mechanism.

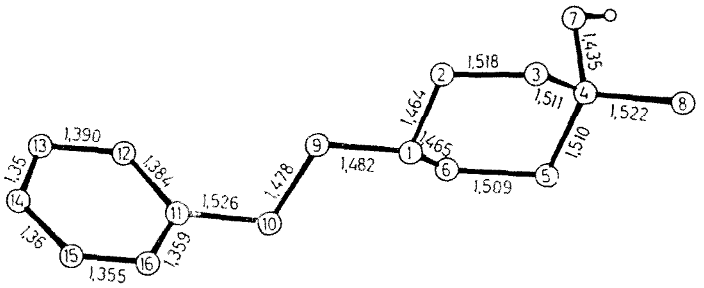


Fig. 1. Geometry of one of the individual molecules in II with average values of bond lengths for the two molecules.

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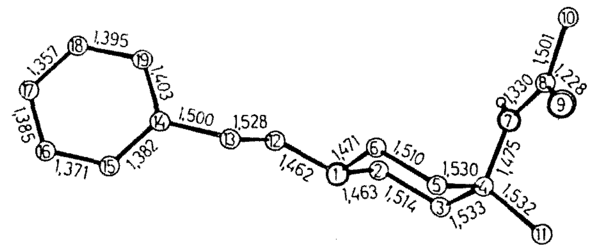
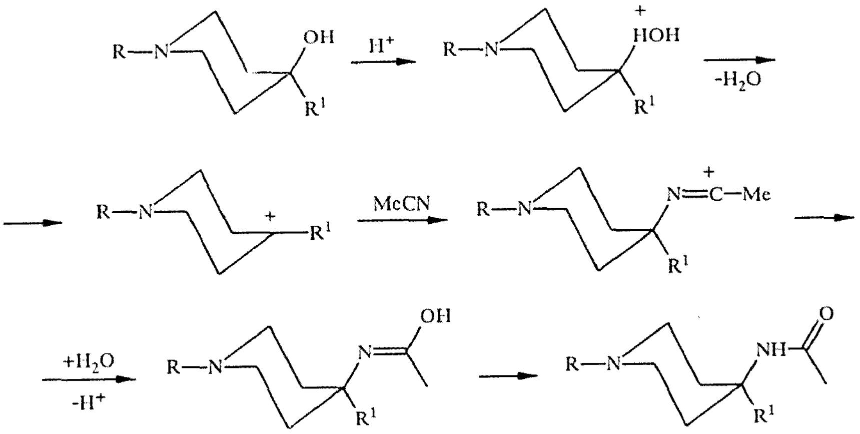


Fig. 2. Geometry of III with bond lengths.

In the presence of concentrated sulfuric acid the reaction of 4-alkyl(aryl)piperid-4-ols [1] occurs via an $S_N{}^1$ monomolecular nucleophilic substitution mechanism [2] to form a carbocation which undergoes attack of the nucleophile to form the thermodynamically more stable product having equatorial Me or Ph groups.



R=$(CH_2)_2$Ph; R^1=Me, Ph

Figure 1 shows the geometry of one of the individual molecules of II with the average bond length values for both molecules and Figure 2 the geometry of III with bond lengths. In Tables 1 and 2 there are given the valence angles for II and III respectively.

The aim of this work was a determination of the structure and conformation of II and III. Hence the observed spread of some geometrical parameters, arising from the modest quality of the monocrystals, was not analyzed. None the less, the x-ray investigation clearly answered the question as to whether the configuration about C_4 of the piperidine heterocycle was retained under Ritter reaction conditions.

In both molecules of II the piperidine ring has a slightly distorted chair conformation. The displacements of atoms N_1 and C_4 from the mean plane of the remaining four ring atoms are −0.685 and 0.626 Å in molecule A and −0.675 and 0.670 Å in B respectively. The displacements of C_9, C_8, and O_7 from the mean piperidine plane are −0.659, 0.484, and 2.031 Å in molecule A and −0.689, 0.589, and 2.036 Å in B, i.e. in both molecules A and B of II the 1-phenethyl and 4-Me substituents occupy equatorial positions and the 4-OH group axial ones.

In molecules A and B of II the 1-phenethyl substituent has an extended conformation (torsional angle $N_1C_9-C_{10}C_{11}$ of 170° in A and −173° in B). However, the mutual orientation of the piperidine and the phenyl rings are significantly different (dihedral angle between the mean piperidine plane and the Ph ring being 85° in A and 18° in B). This may be related to the different orientation of the Ph group and the ethyl fragment in these molecules (torsional angle $C_9C_{10}-C_{11}C_{12}$ in A and B being 63 and −55° respectively), caused overall by the different crystalline environment of the individual molecules.

Crystals of II are stabilized by intermolecular hydrogen bonding. Via the bonds $O_{7B}-H\cdots O_{7A}$ ($O\cdots O$ 2.830(4), O−H 0.82, $H\cdots O$ 2.07 Å, $O-H\cdots O$ 154°) and $O_{7A}-H\cdots O_w$ ($O\cdots O$ 2.778(5), O−H 0.76, $H\cdots O$ 2.04 Å, $O-H\cdots O_w$ 166°) the two crystallographically individual molecules and the solvated molecule of water form a repeating pattern which forms an infi-

TABLE 1. Valence Angles in II

Angle	ω (deg.)	
	molecule A	molecule B
$C_{(2)}N_{(1)}C_{(6)}$	108,8(3)	109,5(4)
$C_{(2)}N_{(1)}C_{(9)}$	106,7(3)	112,6(4)
$C_{(6)}N_{(1)}C_{(9)}$	112,8(3)	108,4(4)
$N_{(1)}C_{(2)}C_{(3)}$	111,9(3)	111,3(4)
$C_{(2)}C_{(3)}C_{(4)}$	113,0(4)	111,3(4)
$C_{(3)}C_{(4)}C_{(5)}$	109,0(4)	107,6(4)
$C_{(3)}C_{(4)}O_{(7)}$	107,2(3)	110,7(4)
$C_{(3)}C_{(4)}C_{(8)}$	110,9(4)	109,2(4)
$C_{(5)}C_{(4)}O_{(7)}$	109,6(3)	105,3(4)
$C_{(5)}C_{(4)}C_{(8)}$	112,0(4)	113,8(4)
$O_{(7)}C_{(4)}C_{(8)}$	108,0(4)	110,1(4)
$C_{(4)}C_{(5)}C_{(6)}$	112,4(4)	113,2(4)
$C_{(5)}C_{(6)}N_{(1)}$	111,1(3)	110,8(4)
$N_{(1)}C_{(9)}C_{(10)}$	114,5(4)	114,1(5)
$C_{(9)}C_{(10)}C_{(11)}$	110,4(4)	116,5(5)
$C_{(10)}C_{(11)}C_{(12)}$	121,4(5)	124,2(5)
$C_{(10)}C_{(11)}C_{(16)}$	119,7(5)	117,7(5)
$C_{(12)}C_{(11)}C_{(16)}$	118,9(5)	118,0(5)
$C_{(11)}C_{(12)}C_{(13)}$	120,3(6)	119,7(5)
$C_{(12)}C_{(13)}C_{(14)}$	118,7(7)	121,2(6)
$C_{(13)}C_{(14)}C_{(15)}$	119,8(8)	119,5(6)
$C_{(14)}C_{(15)}C_{(16)}$	121,3(7)	120,6(7)
$C_{(15)}C_{(16)}C_{(11)}$	121,0(6)	120,9(6)

TABLE 2. Valence Angles in III

Angle	ω (deg.)	Angle	ω (deg.)
$C_{(2)}N_{(1)}C_{(6)}$	109,1(2)	$N_{(7)}C_{(8)}O_{(9)}$	123,8(2)
$C_{(2)}N_{(1)}C_{(12)}$	109,9(2)	$N_{(7)}C_{(8)}C_{(10)}$	115,8(2)
$C_{(6)}N_{(1)}C_{(12)}$	112,8(2)	$O_{(9)}C_{(8)}C_{(10)}$	120,3(2)
$N_{(1)}C_{(2)}C_{(3)}$	112,2(2)	$N_{(1)}C_{(12)}C_{(13)}$	114,3(2)
$C_{(2)}C_{(3)}C_{(4)}$	113,4(2)	$C_{(12)}C_{(13)}C_{(14)}$	112,8(2)
$C_{(3)}C_{(4)}C_{(5)}$	108,1(2)	$C_{(13)}C_{(14)}C_{(15)}$	120,5(2)
$C_{(3)}C_{(4)}N_{(7)}$	107,8(2)	$C_{(13)}C_{(14)}C_{(15)}$	122,0(3)
$C_{(3)}C_{(4)}C_{(11)}$	110,6(2)	$C_{(15)}C_{(14)}C_{(19)}$	117,5(3)
$C_{(5)}C_{(4)}N_{(7)}$	110,1(2)	$C_{(14)}C_{(15)}C_{(16)}$	121,4(3)
$C_{(5)}C_{(4)}C_{(11)}$	111,1(2)	$C_{(15)}C_{(16)}C_{(17)}$	121,0(3)
$N_{(7)}C_{(4)}C_{(11)}$	109,2(2)	$C_{(16)}C_{(17)}C_{(18)}$	118,6(3)
$C_{(4)}C_{(5)}C_{(6)}$	113,2(2)	$C_{(17)}C_{(18)}C_{(19)}$	121,4(3)
$N_{(1)}C_{(6)}C_{(5)}$	110,9(2)	$C_{(14)}C_{(19)}C_{(18)}$	120,1(3)
$C_{(4)}N_{(7)}C_{(8)}$	125,7(2)		

nite band along c through hydrogen bonds: $O_w-H_A\cdots N_{1A}$ (x, −y, −0.5 + z) ($O_w\cdots N$ 2.993(4), O−H 0.82, H−N 2.20 Å, $O_w-H\cdots N$ 162°) and $O_w-H_B\cdots N_{1B}$ (x, 1 − y, −0.5 + z) ($O_w\cdots N$ 2.850(5), O_w-H 0.84, $H\cdots N$ 2.02 Å, $O_w-H\cdots N$ 174°).

In III the piperidine ring also has a slightly distorted chair ring conformation (displacements of N_1 and C_4 from the mean plane of C_2, C_3, C_5, and C_6 being −0.686 and 0.630 Å respectively). The displacements of C_{12}, C_{11}, and N_7 from the mean piperidine plane are 0.422, −0.674, and 1.558 Å), i.e. the 1-phenethyl and 4-Me substituents occupy equatorial and the 4-amido substituents axial positions with respect to the piperidine ring. The 1-phenethyl fragment has an extended conformation (torsional angle $N_1C_{12}-C_{13}C_{14}$ of −165°) and the dihedral angle between the mean piperidine plane and the Ph ring, specifying their mutual orientation, is 97°.

TABLE 3. Coordinates of Non-Hydrogen Atoms ($\times 10^4$) in II and their Equivalent Isotropic Thermal Factor Values (Å^2)

Atom	*x/a*	*y/b*	*z/c*	B_{iso}^{eq}
		Molecule A		
$N_{(1)}$	2675	925(3)	3968	4,0(1)
$C_{(2)}$	3931(5)	1654(3)	4270(4)	4,5(1)
$C_{(3)}$	5046(5)	1081(4)	3862(4)	4,6(1)
$C_{(4)}$	4593(5)	842(3)	2640(3)	4,1(1)
$C_{(5)}$	3240(5)	174(3)	2338(4)	4,6(1)
$C_{(6)}$	2189(5)	807(4)	2770(4)	4,8(1)
$O_{(7)}$	4419(4)	2010(2)	2099(3)	4,5(1)
$C_{(8)}$	5684(6)	139(4)	2295(5)	5,9(1)
$C_{(9)}$	1686(5)	1563(3)	4420(4)	4,8(1)
$C_{(10)}$	314(6)	930(4)	4201(5)	6,2(2)
$C_{(11)}$	-543(5)	1537(4)	4866(4)	5,4(1)
$C_{(12)}$	-956(7)	2724(5)	4690(5)	7,4(2)
$C_{(13)}$	-1722(7)	3263(6)	5319(6)	8,9(2)
$C_{(14)}$	-2058(8)	2565(10)	6106(6)	9,1(3)
$C_{(15)}$	-1638(7)	1392(8)	6261(5)	8,7(2)
$C_{(16)}$	-898(5)	881(5)	5660(4)	6,4(2)
O_w	3739(4)	1527(2)	-140(3)	4,6(1)
		Molecule B		
$N_{(1)}$	2137(4)	6503(3)	3689(3)	4,6(1)
$C_{(2)}$	2827(5)	5360(3)	4125(4)	5,0(1)
$C_{(3)}$	4211(5)	5264(3)	3920(4)	4,6(1)
$C_{(4)}$	4074(5)	5325(3)	2705(4)	4,4(1)
$C_{(5)}$	3289(6)	6473(3)	2255(4)	5,4(1)
$C_{(6)}$	1940(6)	6564(4)	2500(4)	5,4(1)
$O_{(7)}$	3246(4)	4345(2)	2127(3)	5,0(1)
$C_{(8)}$	5490(6)	5269(5)	2549(5)	7,7(2)
$C_{(9)}$	781(6)	6629(5)	3881(5)	6,9(2)
$C_{(10)}$	843(6)	7082(5)	4958(5)	7,7(2)
$C_{(11)}$	-490(5)	7095(4)	5251(5)	5,4(1)
$C_{(12)}$	-1690(6)	7674(5)	4623(5)	6,8(2)
$C_{(13)}$	-2817(5)	7710(5)	5002(6)	7,1(2)
$C_{(14)}$	-2802(6)	7185(5)	5937(6)	7,2(2)
$C_{(15)}$	-1650(8)	6585(7)	6538(5)	8,9(2)
$C_{(16)}$	-506(5)	6554(5)	6194(5)	6,9(2)

The crystalline structure of III is stabilized by weak intermolecular hydrogen bonding $N_7-H\cdots O_9$ (0.5 + x, 1 — y, 0.5 + z) (N···O 3.002(3), N—H 0.80, H···O 2.22 Å, N—H···O 165°) as a result of which the molecules form a chain along ac.

Hence the results of [1] and this work clearly show that the configuration about the piperidine ring C_4 position is retained under Ritter reaction conditions independently of the relative volumes of the Me or Ph substituents at position 4.

EXPERIMENTAL

TLC was carried out on Polygram Sil G/UV-254 plates using methanol—chloroform (1:5).

N-(2-Phenethyl)-4-methylpiperid-4-ol (II). A solution of I (10.0 g, 0.05 mole) in absolute ether (100 ml) was added dropwise with stirring to a solution of methyllithium which had been prepared from methyl iodide (10.0 g, 0.07 mole) and lithium (1.4 g, 0.2 mole) in absolute ether (300 ml). The product was stirred for 5 h at 20°C and basified with aqueous potassium hydroxide. The ether layer was separated, washed with water, and dried with magnesium sulfate. After evaporation of solvent II (6.4 g, 55%) was obtained as a viscous oil with bp 149-150°C at 2 mm Hg and R_f 0.42.

TABLE 4. Coordinates of Non-Hydrogen Atoms ($\times 10^4$) in III and their Equivalent Isotropic Thermal Factor Values ($Å^2$)

Atom	*x/a*	*y/b*	*z/c*	B_{iso}^{eq}
$\mathrm{N}_{(1)}$	1381	1439(2)	6493	3,6(1)
$\mathrm{C}_{(2)}$	1621(4)	2230(2)	7661(3)	4,0(2)
$\mathrm{C}_{(3)}$	-392(4)	2827(2)	7482(3)	4,4(2)
$\mathrm{C}_{(4)}$	-1323(4)	3378(2)	5985(3)	3,8(2)
$\mathrm{C}_{(5)}$	-1361(4)	2555(2)	4799(3)	3,9(2)
$\mathrm{C}_{(6)}$	711(4)	1997(2)	5070(3)	3,9(2)
$\mathrm{N}_{(7)}$	43(3)	4294(1)	5941(2)	3,1(2)
$\mathrm{C}_{(8)}$	-212(4)	4947(2)	4803(3)	3,6(2)
$\mathrm{O}_{(9)}$	-1642(3)	4862(1)	3628(2)	4,7(2)
$\mathrm{C}_{(10)}$	1372(5)	5833(2)	5031(3)	5,1(3)
$\mathrm{C}_{(11)}$	-3522(5)	3802(3)	5778(4)	6,1(3)
$\mathrm{C}_{(12)}$	3328(4)	838(2)	6769(3)	4,1(2)
$\mathrm{C}_{(13)}$	3295(5)	33(2)	5566(3)	4,6(2)
$\mathrm{C}_{(14)}$	5056(4)	-764(2)	6046(3)	4,0(2)
$\mathrm{C}_{(15)}$	4660(4)	-1847(2)	6173(3)	4,1(2)
$\mathrm{C}_{(16)}$	6248(5)	-2588(2)	6619(3)	5,2(3)
$\mathrm{C}_{(17)}$	8314(5)	-2272(3)	6978(3)	5,4(3)
$\mathrm{C}_{(18)}$	8741(4)	-1212(3)	6863(3)	5,9(3)
$\mathrm{C}_{(19)}$	7148(5)	-449(3)	6387(3)	5,4(3)

N-(2-Phenethyl)-4-methyl-4-acetamidopiperidine (III). Concentrated sulfuric acid (5 ml) was added with stirring to a mixture of II (2.0 g, 0.01 mole) and acetonitrile (2.0 g, 0.03 mole) so that the temperature did not exceed 60°C. Stirring was continued at room temperature for 16 h and the mixture poured onto ice (20 g), neutralized with ammonium hydroxide, extracted with chloroform, and dried with magnesium sulfate. After evaporation of solvent III was obtained as white crystals, 1.0 g (41.7%) with mp 168-169°C and R_f 0.57.

Monocrystalline II and III suitable for x-ray analysis were grown from a mixture of water-ethanol. It was found that II is a hemihydrate of 1-phenethyl-4-methyl-4-hydroxypiperidine.

X-Ray experiments were carried out on a four circle automatic Hilger–Watts diffractometer (λ MoKα, graphite monochromator).

Crystals of II are monoclinic: a = 10.222(1), b = 10.959(1), c = 12.731(1) A, β = 107.2°, V = 1362.3(2) $Å^3$, M = 228.4, Z = 4 ($[C_{14}H_{21}NO)½H_2O]$, d_{calc} = 1.120 g/cm^3, space group Pc.

Crystals of III are monoclinic: a = 6.795(1), b = 12.392(1), c = 9.679(1) A, β = 109.59(1)°, V = 767.8(1) $Å^3$, M = 260.4, Z = 2, d_{calc} = 1.132 g/cm^3, space group Pn.

Using $\theta/2\theta$ scanning, the intensities of 1926 independent reflections for II ($\theta < 27°$) and 1479 for III ($\theta < 28°$) were measured. The structures were solved by a direct method and refined in a full matrix least squares anisotropic approximation for nonhydrogen atoms. In both structures the positions of the H atoms were localized in difference electron density synthesis and their contributions with fixed positions and thermal parameters included in the computation of F_{calc}. The final difference factors were: R = 0.046 and R_w = 0.054 for II and R = 0.039 and R_w = 0.044 for III. Coordinates of nonhydrogen atoms for II and III are given in Tables 3 and 4. All calculations were carried out using the INEXTEL program [3] on an Eclipse S/200 computer.

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