TETRAHYDROPYRIDINES IN THE PRINS REACTION: A NOVEL 3-OXA-7-AZABICYCLO [3.3.1] NONANE DERIVATIVE

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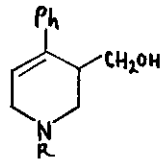
Abstract -Reaction of tetrahydropyridines obtained by the dehydration of a diastereoisomeric mixture of 1-benzyl-3,4-dimethyl-4-piperidinols with excess of aqueous formaldehyde and sulphuric acid(Prins reaction) gave 7-benzyl-1,9-dimethyl-9-hydroxy-3-oxa-7-azabicyclo [3.3.1] nonane. The stereochemistry of the bicyclic product(cis N/9-OH, piperidine boat-chair) and of the precursor 4-piperidinols is established from nmr(^{13}C and ^{1}H) and ir spectroscopic evidence.

Previous studies of 4-substituted 1,2,3,6-tetrahydropyridines in the Prins reaction have led to the isolation of 3-hydroxymethyl analogues(1) and, with a large excess of formaldehyde, cis-bicyclic 1,3-dioxanes(2).[1,2] Neither type of product



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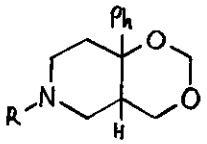

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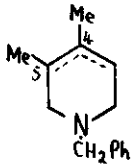
was isolated when a mixture of 1-benzyl-dimethyltetrahydropyridines(3)(from ^{1}H nmr evidence, chiefly the 4,5-dimethyl isomer) was used as the alkene substrate under conditions of excess of aldehyde;instead, the 3-oxa-7-azabicyclo [3.3.1] nonane (4) was isolated as major product.



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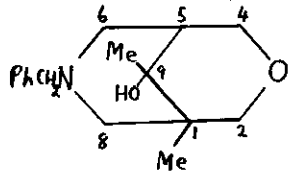

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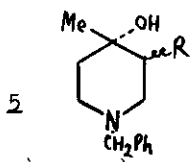
The tetrahydropyridines(3) were obtained by treating a diastereoisomeric mixture of 1-benzyl-3,4-dimethyl-4-piperidinols(5a) with thionyl chloride. The



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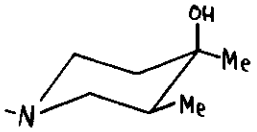
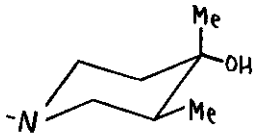
a)R=Me; b)R=H

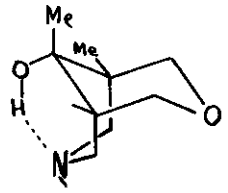


trans 3-Me/4-Me



cis 3-Me/4-Me

piperidinol mixture (from 1-benzyl-3-methyl-4-piperidone and methyllithium) was separated chromatographically and the major and minor isomers assigned trans and cis stereochemistry respectively on the basis of the higher field ^{13}C-chemical shift of 4-Me of the minor component (Table 2). The Prins reaction product of the tetrahydropyridines (3) was a solid base of molecular formula $C_{16}H_{23}NO_2$ that formed a monohydrobromide salt and a monoacetate. It cannot be a 1,3-dioxane since its ^1H nmr spectrum lacks a low field resonance near $\delta 5$ characteristic of methylene protons flanked by oxygen atoms[2] and the nmr (^1H and ^{13}C) features of the compound are consistent with its formulation as a 3-oxa-7-azabicyclo [3.3.1] nonane (Table 1).



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The stereochemistry (6) (cis N/9-OH, piperidine boat-chair) follows from the demonstration of intramolecular hydrogen bonding for a 0.003 molar solution in CCl_4, and magnitude of the couplings of the C-5 proton with those at C-6. ^3J Coupling constant values were obtained from the 220 MHz spectrum which was fully resolved; models reveal that a large value is only to be anticipated when the piperidine ring is in a boat conformation with the C-5 eclipsing one of the C-6 protons. The C_5-H resonance was reduced to a broad singlet ($W_{0.5}$ 6.5Hz, base width 16.5Hz) in the spectrum of the hydrochloride of (4) in DMSO-d_6, hence the salt (in which N-HO intramolecular bonding is not possible) has the all-chair conformation where the C_5-H proton is subject only to small couplings.

The conversion of the tetrahydropyridines (3) to a 3-oxa-7-azabicyclo [3.3.1] - nonane rather than a bicyclodioxane derivative is probably a result of excessive steric interactions in a compound of the latter type when it contains a pair of bridgehead substituents. The production of (4) represents a double Prins reaction concluded by formation of the tetrahydropyran ring through loss of water.

The nmr data (Table 1) presents several points of interest. Observation of the

N-benzylic methylene proton resonance as an AB quartet($\Delta\delta$0.06ppm) rather than a singlet illustrates the influence of axial substituents β to nitrogen on the magnetic non-equivalence of methylene protons of the type,[6] while the large downfield shift of the C-9 resonance on acylation(+11.1ppm) provides a further example of contrasting acylation shifts in secondary(about 3ppm) and tertiary cycloalkanols.[3] Finally, comparison of C-1 and C-5 chemical shifts of (4)(39.2 and 41.8ppm respectively) shows that the usual α-shielding effect of equatorial methyl(5-6ppm) is absent.[7] Chemical shift comparisons of C-3 and C-5 of the isomeric 4-piperidinols(5a) likewise show that the methylated carbon(C-3) has an unusually high field resonance(Table 2). The relief of gauche interactions between vicinal pairs of methyl substituents, a common feature of all these compounds, may induce ring deformations responsible for such chemical shift anomalies.

Table 1. Nmr characteristics of Prins product(4) in $CDCl_3$

	Chemical shifts (δ,ppm from TMS)	
C,H position(see 4)	^{13}C (22.5MHz)[a,b]	^{1}H (220MHz)
C-1	39.2_2 (39.0)	-
CH_2-2	75.0_9 (74.6_5)	3.33 d, 3.42 d, J 11Hz
CH_2-4	70.2_1 (69.2_3)	3.63 dd, 3.76 dd[e], J 11&2Hz
CH-5	41.8_2 (38.5_7)	1.88 m, J 9.5Hz plus three additional small couplings(base width 23Hz)
CH_2-6	53.8_5 (53.1_4)	2.54 dd[c], J 11&3Hz 3.18 dd[cd], J 11&9.5Hz
CH_2-8	61.3_2 (59.3_7)	2.67 d(br), 2.70 d(br), J 11Hz
C-9	71.2_4 (82.3_4)	-
C_1-Me	$17,7_2$ (17.6_8)	0.84 s
C_9-Me	20.1_5 (21.6_7)	1.26 s
N-CH_2(benzyl)	61.5_9 (62.4_6)	3.51 d, 3.57 d, J 13Hz[f]
Ph	137.9 (138.0)[g]	*m centred on 7.3*
	128.9 (128.9)	
	128.5 (128.1)	
	127.2 (126.7)	
C_9(OCOMe)	- (16.0_9)	-
(CO)	- (169.8)	-

Footnotes for Table 1. a) Assignments based on off-resonance spectra and chemical shift data of related compounds,[3-5] and application of well-known principles; b) Chemical shifts of corresponding acetate in parentheses; c) Collapsed to broad doublet when C_5-H irradiated; d) Each line showed additional small coupling; e) Collapsed to doublets(J 11Hz) when C_5-H irradiated; f) Assigned on the basis of chemical shift and ^2J value;[6] **g**) C-quaternary.

Experimental

Proton noise and off-resonance decoupled ^{13}C nmr spectra were recorded on a Jeol FX90Q spectrometer operating at 22.5MHz. Samples were prepared and instrumental parameters chosen as in ref. 6. Reaction products were purified by distillation in a Büchi GKR-50 glass tube(oven temperature setting 110-130°, 0.2mm pr). 1-Benzyl-3,4-dimethyl-4-piperidinols(5a) and dehydration products(3)-Methyllithium in ether(300ml, 1.5m) was added to ice-cooled 1-benzyl-3-methyl-4-piperidone(30g) in ether(100ml), the mixture stirred for 1h and then poured on ice-water. The base(25.6g) isolated from the ether solidified after distillation and was chromatographed on silica gel. Elution with ethyl acetate(3):chloroform(1) gave trans-(5a),mp 48-49°, hydrobromide, mp 154.5-155.5°, from ethanol-ether(Found:C,56.05; H,7.44;N,4.55. $C_{14}H_{21}NO.HBr$ requires 56.00;H,7.38;N,4.66%). Base isolated from methanol eluates consisted chiefly of the cis isomer, as apparent from ^{13}C nmr data. 1-Benzyl-4-methyl-4-piperidinol was similarly prepared from the corresponding 4-piperidone. It gave a hydrochloride, mp 130-133°, from ethanol-ether(Found:C,62.48;H,8.54;N,5.51. $C_{13}H_{19}NO.HCl\ 0.5H_2O$ requires C,62.24;H,8.37;N,5.58%). ^{13}C nmr data on the 4-piperidinols are given in Table 2. A mixture of the alcohols(5a)(18.6g) and $CHCl_3$(100ml) was heated under reflux for 4h with thionyl chloride(18.6g). Solvent and volatile reactants were removed by distillation and the residue made alkaline with aqueous NaOH; the free base, recovered as usual, was distilled to give a mixture of 3,4- and 4,5-dimethyl-1-benzyl-1,2,3,6-tetrahydropyridines(3) in which the latter isomer preponderated as judged from relative integrals of the 3-H(m,δ5.3), 3-Me(d,δ1.0) and 4,5-diMe(broad s, δ 1.56,1.62) ^1H nmr resonances(mixture in $CDCl_3$).

7-Benzyl-1,9-dimethyl-9-hydroxy-3-oxa-7-azabicyclo[3.3.1]nonane(4) and derivatives- A mixture of the tetrahydropyridines(3)(10g), aqueous formaldehyde(84ml, 37%), concentrated H_2SO_4(41.6ml) and water(42ml) was heated under reflux for 5h. The cooled product was made alkaline with NH_3-H_2O and extracted with ether which

was then dried and evaporated. The residue was distilled to give (4)(8.75g) which formed a hydrobromide, mp 255-256°,from isopropanol(Found:C,56.22;H,7.10;N 4.02. $C_{16}H_{23}NO_2$.HBr requires C,56.14;H,7.10;N,4.10%). The base derived from the HBr salt, had mp 98.5-99° from petroleum ether-acetone(Found:C,73.62;H,8.98;N,5.39. $C_{16}H_{23}NO_2$ requires C,73.52;H,8.87;N,5.36%),$\tilde{\nu}_{max}$(cm^{-1}, $3x10^{-3}$m in CCl_4, 5mm cell) 3600w(free OH), 3240s(bonded OH), and m/e 261(M^+). The base(4)(1g) after treatment with acetic anhydride(1g) in boiling toluene(10ml), gave the acetate of (4), isolated as a hydrochloride, mp 205.5-206°, from ethanol-ether(Found:C,63.33;H,7.78 ;N,3.82. $C_{18}H_{25}NO_3$.HCl requires C,63.61;H,7.71;N,4.12%),$\tilde{\nu}_{C=O}$1730cm^{-1}(mull).

Table 2. ^{13}C chemical shifts of some 1-benzyl-4-methyl-4-piperidinols in $CDCl_3$(δ,ppm from TMS)[a]

	C-2	C-3	C-4	C-5	C-6	C_3-Me	C_4-Me	N-CH_2
(5b)	49.7_9	38.8_4	67.7_2	38.8_4	49.7_9	-	29.7_4	63.1_1
(5a) major	56.7_2	39.2_7	69.0_7	39.4_9	49.4_1	12.1_3	28.0_0	63.1_1
(5a) minor	57.6_4	41.0_6	71.1_3	39.7_6	51.0_8	13.1_1	21.4_2[b]	62.4_6

Footnotes: a) Footnote (a) of Table 1 applies; Ph carbon resonances were near 138.6, 129.1, 128.1 and 126.9 in all cases; b) The higher field resonance of this carbon compared with corresponding shifts of 5b and 5a(major) is evidence that C_4-Me of 5a(minor) has a preferred axial orientation(ref.8).

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