

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

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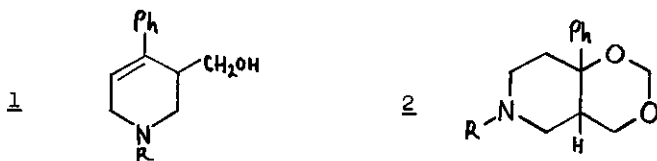
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Abstract -Reaction of tetrahydropyridines obtained by the dehydration of a diastereoisomeric mixture of 1-benzyl-3,4-dimethyl-4-piperidinols with excess of aqueous formaldehyde and sulphuric acid (Prins reaction) gave 7-benzyl-1,9-dimethyl-9-hydroxy-3-oxa-7-azabicyclo [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 ^1H) and ir spectroscopic evidence.

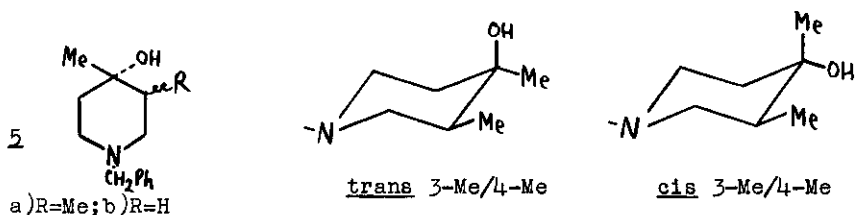
Previous studies of 4-substituted 1,2,3,6-tetrahydropyridines in the Prins reaction have led to the isolation of 3-hydroxymethyl analogues (1) and, with a large excess of formaldehyde, *cis*-bicyclic 1,3-dioxanes (2).^{1,2} Neither type of product



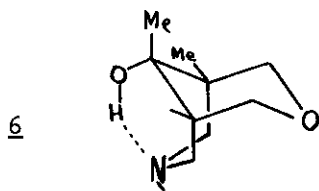
was isolated when a mixture of 1-benzyl-dimethyltetrahydropyridines (3) (from ^1H nmr evidence, chiefly the 4,5-dimethyl isomer) was used as the alkene substrate under conditions of excess of aldehyde; instead, the 3-oxa-7-azabicyclo [3.3.1]nonane (4) was isolated as major product.



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



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 $\text{C}_{16}\text{H}_{23}\text{NO}_2$ 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 atoms² 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).



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 $\text{C}_5\text{-H}$ 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 $\text{C}_5\text{-H}$ 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 ($\Delta\delta 0.06\text{ppm}$) 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 ($+11.1\text{ppm}$) 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 ($5-6\text{ppm}$) is absent.⁷ Chemical shift comparisons of C-3 and C-5 of the isomeric 4-piperidins (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

C,H position (see <u>4</u>)	Chemical shifts (δ , ppm from TMS)	
	^{13}C (22.5MHz) ^{a,b}	^1H (220MHz)
C-1	39.2 ₂ (39.0)	-
CH ₂ -2	75.0 ₈ (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 ₆ (53.1 ₄)	2.54 dd ^c , J 11&3Hz 3.18 ad ^{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 C₅-H irradiated; d) Each line showed additional small coupling; e) Collapsed to doublets (J 11Hz) when C₅-H irradiated; f) Assigned on the basis of chemical shift and ²J value;⁶ g) C-quaternary.

Experimental

Proton noise and off-resonance decoupled ¹³C 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)-Methyl lithium 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. C₁₄H₂₁NO.HBr requires C, 56.00; H, 7.38; N, 4.66%). Base isolated from methanol eluates consisted chiefly of the cis isomer, as apparent from ¹³C 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. C₁₃H₁₉NO.HCl 0.5H₂O requires C, 62.24; H, 8.37; N, 5.58%). ¹³C nmr data on the 4-piperidinols are given in Table 2. A mixture of the alcohols (5a) (18.6g) and CHCl₃ (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, δ 5.3), 3-Me (d, δ 1.0) and 4,5-diMe (broad s, δ 1.56, 1.62) ¹H nmr resonances (mixture in CDCl₃).

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 H₂SO₄ (41.6ml) and water (42ml) was heated under reflux for 5h. The cooled product was made alkaline with NH₃-H₂O 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. $C_{16}H_{23}NO_2 \cdot HBr$ 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%), $\bar{\nu}_{max}$ (cm^{-1} , $3 \times 10^{-3}m$ 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. $C_{18}H_{25}NO_3 \cdot HCl$ requires C, 63.61; H, 7.71; N, 4.12%), $\bar{\nu}_{C=O} 1730 cm^{-1}$ (null).

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
(<u>5b</u>)	49.7 ₉	38.8 ₄	67.7 ₂	38.8 ₄	49.7 ₉	-	29.7 ₄	63.1 ₁
(<u>5a</u>) 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
(<u>5a</u>) 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 C₄-Me of 5a (minor) has a preferred axial orientation (ref.8).

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