Stereochemical Studies with Methyl Substituted Piperidyl-2-carbinols

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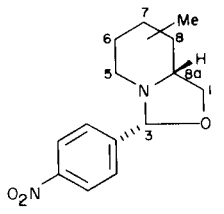
Configurations have been assigned to some methyl substituted 3-*p*-nitrophenylhexahydro-3*H*-oxazolo[3,4-*a*]pyridines (**1**) and to the methyl piperidyl-2-carbinols (**2**) derived from these on the basis of nmr and ir spectral data.

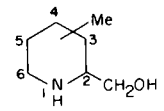
Many substituted derivatives of piperidyl-2-carbinol exhibit marked biological activity but with the notable exception of the α-ethyl- (1) and α-phenylpiperidyl-2-carbinols (2) very few simply substituted derivatives have been subjected to stereochemical studies. This paper describes the preparation of all but three of the methyl substituted piperidyl-2-carbinols (**2**) and provides spectral evidence leading to the assignment of their configurations.

In order to isolate the individual diastereoisomeric methylpiperidyl carbinols the mixture of carbinols obtained by catalytic hydrogenation or sodium-ethanol reduction of the appropriate methylpyridyl-2-carbinol (3) was converted to a mixture of methyl 3-*p*-nitrophenylhexahydro-3*H*-oxazolo[3,4-*a*]pyridines (**1**) by reaction with *p*-nitrobenzaldehyde. These bicyclic compounds, having been obtained pure by repeated fractional crystallization, were converted to the individual methylpiperidyl carbinols (**2**) by treatment with dilute hydrochloric acid. The α-methylpiperidyl-2-carbinols were prepared in a similar way from the mixture of carbinols obtained by catalytic reduction of 2-acetyl pyridine (4).

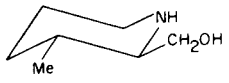
All the methyl substituted 3-*p*-nitrophenylhexahydro-3*H*-oxazolo[3,4-*a*]pyridines (**1**) showed Bohlmann bands (5) in the 2800-2600 cm^{-1} region of their ir spectra indicative of the presence of the *trans*-fused conformation, and a singlet between δ 4.53 and 4.83 in their nmr spectra assigned to the C3 proton. Comparison with the chemical shifts of H3ax and H3eq (δ 3.66 and 4.45 respectively) in *trans*-fused hexahydro-3*H*-oxazolo[3,4-*a*]pyridines (3) and allowing for the deshielding influence of the aryl substituent on the C3 proton shows that this singlet must arise from the pseudoaxial H3 proton. Thus all the methyl substituted 3-*p*-nitrophenylhexahydro-3*H*-oxazolo-[3,4-*a*]pyridines (**1**) must be adopting predominantly the *trans* fused ring conformation with a pseudoequatorial *p*-nitrophenyl group and either an axial or equatorial methyl group. In the case of the two 6-methyl- (**1b** and **1c**), the one 7-methyl- (**1d**), and the two 8-methyl-3-*p*-nitrophenylhexahydro-3*H*-oxazolo[3,4-*a*]pyridines (**1e** and



1a *cis*-5,8a-H-5-Me
b *cis*-6,8a-H-6-Me
c *trans*-6,8a-H-6-Me
d *cis*-7,8a-H-7-Me
e *cis*-8,8a-H-8-Me
f *trans*-8,8a-H-8-Me
g *cis*-1,8a-H-8-Me
h *trans*-1,8a-H-1-Me



2a *cis*-2,6-H-6-Me
b *cis*-2,5-H-5-Me
c *trans*-2,5-H-5-Me
d *cis*-2,4-H-4-Me
e *cis*-2,3-H-3-Me
f *trans*-2,3-H-3-Me
g *erythro*-α-Me
h *threo*-α-Me



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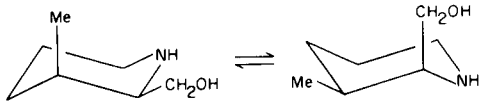

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1f) a decision regarding the configuration of the methyl group was readily made from the position of the centre of the methyl group "doublet" and the apparent $J_{CH\text{-}Me}$ in the respective nmr spectra since in such systems it has been established (6) that axial methyl group protons absorb at lower field and with a larger apparent coupling constant than equatorial methyl group protons. The methyl group protons in the only 5-methyl compound (**1a**) obtained absorb at higher field due to the proximity of the methyl and the *p*-nitrophenyl groups. This nmr criterion could not be used in the case of the pair of 1-methyl isomers (**1g** and **1h**) because of the pseudoaxial

and equatorial nature of the Cl substituents. However, the 100 MHz spectrum (carbon tetrachloride solution) of the isomer obtained in major yield showed a one-proton quintet assigned to Hl at δ 4.27 with J = 6.5 and 6.5 Hz, whereas the spectrum of the minor isomer had a sextet at δ 3.90 with J = 6.0 and 8.8 Hz. The higher field signal is suggestive of an axial (or pseudoaxial) proton, and the large vicinal coupling (8.8 Hz) between the Cl and angular protons is in accord with an axial-axial coupling (J1ax9a), whereas the lower field signal is indicative of an equatorial Cl proton, and the smaller value of J1eq9a (6.5 Hz) confirms this. These stereochemical requirements are satisfied by *trans*-fused conformations with *cis*-1,8a-H configuration for the major and *trans*-1,8a-H configuration for the minor isomer. On these grounds the assignment of configuration to the hexahydro-3*H*-oxazolo[3,4-*a*]pyridines were made as shown in Table I.

These bicyclic compounds and the alcohols obtained by treatment of these with dilute hydrochloric acid were expected to possess the same configuration of the methyl group with respect to the bridgehead hydrogen (in the case of the bicyclic system) and to the C2 hydrogen (in the case of the alcohol), since the configurations of some piperidyl ethanols have been established by a similar method assuming retention of configuration during the ring opening reaction (7). In fact the nmr spectral data obtained on the alcohols (Table II) confirmed the validity of the assumption. For example, *trans*-2,3-H-3-methylpiperidyl-2-carbinol (**2f**) is expected to exist predominantly in that chair conformation with both substituents equatorial and its nmr spectrum clearly shows the large chemical shift difference (Δae) between the C6 methylene protons (δ H6eq 3.12; δ H6ax 2.59) highly characteristic (8) of this conformation (**3**). In contrast the spectrum of its epimer showed a three proton absorption between δ 2.5 and δ 3.16 for the three protons α to nitrogen indicating the expected rapid chair-chair interconversion (**4** ⇌ **5**) responsible for the averaging of the relationship between the C2 methylene protons and the nitrogen lone pair.

Differences between the nmr spectra of the diastereoisomeric 5-methylpiperidyl-2-carbinols (**2b** and **2c**) were similar to those between the spectra of the 3-methyl carbinols (**2e** and **2f**) and similar conformational equilibria must exist for these. A similar spectrum to that of *trans*-2,3-H-3-methylpiperidyl-2-carbinol was obtained for the only 4-methyl isomer obtained indicating the *cis*-2,4-H-configuration (**2d**). The minor *trans* isomer could not be obtained in a pure state since the 4-methylpiperidyl carbinol used in the reaction with *p*-nitrobenzaldehyde contained some 2-methylpiperidyl-4-carbinol and the product only crystallized with difficulty. The chemical shift difference criterion cannot be used for the 6-methyl isomer (**2a**) but since this was the only product obtained by catalytic (9) or sodium ethanol reduction (3) of 6-methylpyridyl-2-carbinol it must be the thermodynamically more stable *cis*-2,6-H-epimer (**2a**).

In the above discussion inversion at the nitrogen atom has not been considered and (**3**) must exist as an equilibrium mixture of **3**(ax NH) ⇌ **3**(eq NH) and there will be two NH conformations corresponding to both **4** and **5**. From the large value of Δae (C6 methylene) in **3** the predominant conformation must be that with the NH equatorial but the small Δae in **4** ⇌ **5** does not provide evidence for the orientation of the NH. However, there is very little difference in the intensity of Bohlmann bands (5) in the ir spectra of these two isomers indicating a similar percentage NH equatorial conformation for both. In fact all the carbinols described in this paper show very similar absorption in the Bohlmann region.

The two isomers of α-methylpiperidyl-2-carbinol (**2g** and **2h**) obtained were assigned configurations utilizing a similar technique to that employed by Sicher and Tichy (1) for the epimeric α-ethylpiperidyl-2-carbinols for which it was shown that $\Delta\nu$, the difference in the ir stretching frequency of the bands due to the associated and free hydroxyl group, is greater in the *threo*- than in the *erythro*-isomer. Accordingly, the α-methylpiperidyl carbinol obtained from *trans*-1,8a-H-1-methyl-3-*p*-nitrophenylhexahydro[3,4-*a*]pyridine (**1h**), which showed the greater $\Delta\nu$ value (0.0005 *M* solutions in carbon tetrachloride) was assigned the *threo* configuration (**2h**) (*threo* 140 cm^{-1}; *erythro* 100 cm^{-1}).

EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Microanalytical Laboratory, Germany. Melting points are uncorrected. The nmr spectra were recorded on Perkin-Elmer R.10 60 MHz and Varian HA-100 MHz spectrometers as 10% solutions in carbon tetrachloride, using tetramethylsilane as internal reference.

Synthesis of Methyl Substituted 3-*p*-Nitrophenylhexahydro-3*H*-oxazolo[3,4-*a*]pyridines (**1**)

General Procedure.

A mixture of the *cis*- and *trans*- methyl substituted piperidyl-2-carbinols (0.125 *M*), obtained by either catalytic or sodium and ethanol reduction of the appropriate methyl substituted pyridyl-2-carbinol, and *p*-nitrobenzaldehyde (19 g., 0.13 mole) was dissolved in dry benzene (200 ml.) and refluxed until the theoretical amount of water (2.2 ml.) had been removed in a Dean and Stark water separator. After removal of solvent, the residual dark brown syrup was dissolved in ethanol, and allowed to stand at -40°, when crystallization occurred. The individual epimers were obtained by fractional recrystallization from ethanol and are described in the table.

TABLE II

Nmr Spectra (CCl_4 solution) of Methyl Substituted Piperidyl-2-carbinols (**2**)

Compound	NH, OH	Chemical Shifts (δ ppm) α-CH_AH_B	6eq	6ax	2ax	Me (a)	Coupling Constants (J Hz) JAB	JA2ax	JB2ax	J6eq6ax	JCH-Me (b)	Other
2a	3.88 [s]	←3.1 to 3.6 [m]→	----	←2.6 [m]→		1.1 [d]	----	----	----	----	6.5	----
2b	3.80 [s]	←3.4 [d]→	←2.3 to 2.8 [m]→			1.03 [d]	----	----	----	----	6.5	----
2c	4.03 [s]	3.42 (d) 3.26 (d)	3.02 [d]	2.19 [t]	2.49 [m]	0.85 [d]	-10.5	4.2 (d)	7.3 (d)	-11.5	6.5	3.5 (J6eq5ax) 2.0 (J6eq4eq) 10.5 (J6ax5ax)
2d	3.87 [s]	←3.07 to 3.6 [m]→	3.07 [d]	←2.60 [t]→		1.95 [d]	----	----	----	----	5.0	----
2e	3.8 [s]	←3.40 [m]→	←2.5 to 3.16 [m]→			0.93 [d]	----	----	----	----	6.7	----
2f	4.19 [s]	3.66 (d) 3.37 (d)	3.21 [d]	2.59 [m]	2.23 (t of d)	0.87 [d]	-10.5	3.3 (d)	7.3 (d)	-11.5	6.0	9.5 (J2ax3ax) (c) 7.0 (J2axB) (c) 3.0 (J2axA) (c)
2g	3.17 [s]	---- 3.2 (e)	3.07 [d]	←2.2 to 2.8 [m]→		1.08 [d]	----	3.5	----	-11.5	6.5	----
2h	3.88 [s]	3.40 (e) ----	3.1 [d]	2.60 [m]	2.2 [t]	1.15 [d]	----	----	8.0	-11.3	6.0	11.3 (J6ax6ax)

(a) Centre of Me doublet. (b) Apparent coupling constant. (c) Values obtained by first order analysis of H2ax signal. (d) Values obtained by analysis of 8 lines arising from α-CH_2 protons as the AB part of an ABX system. (e) 8 lines. [s], [d], [t], [m] signify singlet, doublet, triplet, multiplet respectively. With the exception of the spectra of **2c** and **2e**, which were recorded at 100 MHz, all other spectra were recorded at 60 MHz.

TABLE I

Physical Constants and Nmr Spectra of Methyl Substituted 3-*p*-Nitrophenylhexahydro-3*H*-oxazolo[3,4-*a*]pyridines (**1**)

Compound	Melting point	Analysis (a)	NMR (CCl_4) δ 3ax	δ Me (j) (b)
1a	75-76°	C, 64.21; H, 7.04; N, 10.78	4.83	0.54 (6.2)
1b	88-89°	C, 63.78; H, 6.82; N, 10.45	4.66	0.96 (6.7)
1c	89-90°	C, 63.93; H, 6.87; N, 10.72	4.56	0.84 (5.5)
1d	62-63°	C, 63.89; H, 6.90; N, 10.64	4.56	0.99 (4.2)
1e	69°	C, 64.22; H, 7.08; N, 10.75	4.62	1.04 (6.8)
1f	59°	C, 64.04; H, 7.03; N, 10.66	4.55	0.91 (5.8)
1g	59-60°	C, 64.26; H, 6.72; N, 10.68	4.53	1.22 (6.5)
1h	83°	C, 64.17; H, 7.00; N, 10.62	4.69	1.26 (6.0)

(a) *Anal.* Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. (b) Center of Me doublet and apparent $J_{CH\text{-}Me}$.

Synthesis of Racemic Epimers of Methyl Substituted Piperidyl-2-carbinols (**2**).

General Procedure.

The epimerically pure 3-*p*-nitrophenylhexahydro-3*H*-oxazolo-[3,4-*a*]pyridine (0.02 mole) was stirred with dilute hydrochloric acid (20 ml.) for 1 hour at room temperature. The precipitated *p*-nitrobenzaldehyde was removed by filtration, and the filtrate basified with aqueous sodium hydroxide solution and ether extracted four times. The ethereal solution was dried (sodium sulfate), concentrated and the residue distilled *in vacuo* to give the required epimerically pure methyl substituted piperidyl-2-carbinol. The physical characteristics of each isomer are given below.

cis-2,6-*H*-Methylpiperidyl-2-carbinol (**2a**).

This compound had m.p. 75° (9).

cis-2,5-*H*-5-Methylpiperidyl-2-carbinol (**2b**).

This compound had b.p. 80°/0.9 mm.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.89; H, 11.96; N, 10.64.

Picrate m.p. 136-137°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.58; H, 5.03; N, 15.64. Found: C, 43.52; H, 4.96; N, 15.47.

trans-2,5-*H*-5-Methylpiperidyl-2-carbinol (**2c**).

This compound had b.p. 88°/0.9 mm.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.39; H, 12.01; N, 10.81.

Picrate m.p. 151-152°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.58; H, 5.03; N, 15.64. Found: C, 43.61; H, 4.94; H, 15.88.

cis-2,4-*H*-4-Methylpiperidyl-2-carbinol (**2d**).

This compound had b.p. 90°/1.0 mm.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.31; H, 11.80; N, 10.93.

cis-2,3-*H*-3-Methylpiperidyl-2-carbinol (**2e**).

This compound had b.p. 70°/0.15 mm.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.23; H, 11.91; N, 10.72.

Picrate m.p. 130-131°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.58; H, 5.03; N, 15.64. Found: C, 43.49; H, 5.09; N, 15.79.

trans-2,3-*H*-3-Methylpiperidyl-2-carbinol (**2f**).

This compound had b.p. 80°/0.15 mm.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.98; H, 11.86; N, 10.80.

Picrate m.p. 123-124°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.58; H, 5.03; N, 15.64. Found: C, 43.65; H, 5.06; N, 15.74.

erythro-α-Methylpiperidyl-2-carbinol (**2g**).

This compound had b.p. 68°/0.18 mm.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.40; H, 11.66; N, 10.59.

threo-α-Methylpiperidyl-2-carbinol (**2h**).

This compound had b.p. 60°/0.15 mm.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.17; H, 11.96; N, 10.61.

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