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Improved Stereospecific Syntheses of Novel 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines

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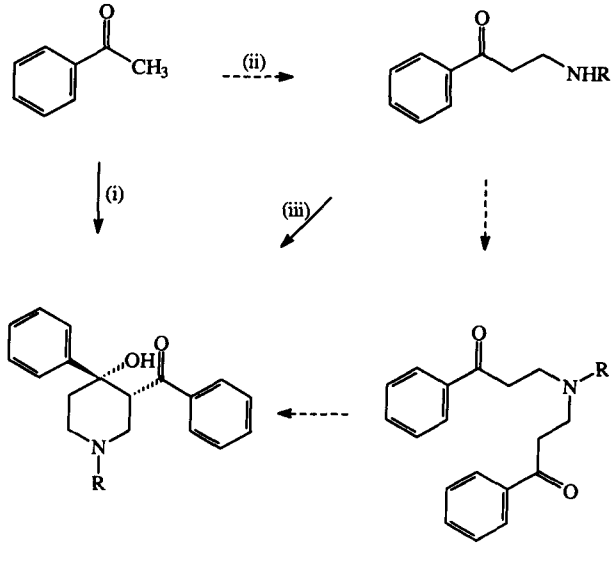
Abstract

The stereoselective synthesis of conformationally restricted 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidine hydrochlorides via the Mannich reaction followed by an intramolecular aldol condensation is reported. The compounds were evaluated by ^{1}H NMR and ^{13}C NMR techniques.

As part of an investigation into the design and synthesis of novel histamine-receptor antagonists, we required an efficient and unambiguous synthesis of the precursor 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines. These compounds are chemically versatile intermediates and some biological activity has been reported (Stenlake et al 1989). Previous synthesis of some of these analogues required two-or three-step syntheses (Plati & Wenner 1949; Plati et al 1949) with no NMR data to support the structure of the piperidines.

With the exception of 3-benzoyl-1-cyclopropyl-4-hydroxy-4-phenylpiperidine **4**, which was synthesized from the *mono*-Mannich product, the synthesis of 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidine hydrochlorides (**1–3** and **5–7**) was achieved when two mols of acetophenone and one of amine hydrochloride were heated in the presence of excess formaldehyde and 30% hydrochloric acid (analytical data, Table 1). This reaction proceeded via *mono*- and *bis*-Mannich products and an acid-catalysed aldol condensation (Plati & Wenner 1949) (scheme 1).



Scheme 1. Synthesis of 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines. **1** R = methyl; **2** R = ethyl; **3** R = 2-phenethyl; **4** = cyclopropyl; **5** R = isopropyl; **6** R = 1-ethylpropyl; **7** = cyclohexyl.
Reagents and conditions: i) RNH_2, XS CH_2O, 30% HCl, reflux 1h; ii) RNH_2, XS CH_2O, 10% HCl, reflux 1h; iii) NaO, MeOH, MeOH, RT, 2h

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To illustrate the structural analysis of the piperidines synthesized, a 400-MHz ^{1}H NMR (recorded on a Jeol GX400MHz Fourier Transform NMR spectrometer) spectrum of 3-benzoyl-1-methyl-4-hydroxy-4-phenylpiperidine **2** (Fig. 1) is used as an example. The aromatic protons resonated in the region of δ 7·90–7·10, in which two protons were deshielded and assigned to the two ortho hydrogens of the ring of the benzoyl substituent. The remaining eight protons were centred around δ 7·5(3H), δ 7·4 (2H). δ 7·2(2H) and δ 7·1(1H).

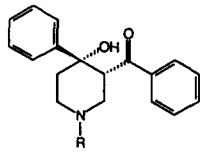
A doublet of doublets at δ 2·93 was assigned to the equatorial H-2 proton. This proton was assigned as such because it is in the equatorial plane and β-deshielded by the benzoyl group. The equatorial H-6 proton was a multiplet at δ 2·77. A multiplet at δ 2·72–2·65 which integrated to two protons was assigned to the axial H-2 and H-6 hydrogens. The *N*-methyl singlet resonated at δ 2·39. The position of this signal is comparable with literature values (Williams & Fleming 1989) (δ 2·3).

The two most shielded signals were assigned to the H-5 protons. The multiplet centred around δ 2·07 was assigned to the axial H-5 proton, whilst the doublet of triplets at δ 1·84 was given to the equatorial H-5 proton. The multiplicity of the former signal is due to one di-axial coupling with the axial H-6 proton, one axial-equatorial coupling with the H-6, one geminal coupling with the H-5 proton and long-range coupling with the 4-hydroxy proton. This signal simplified on the addition of deuterium oxide.

The doublet of doublets at δ 4·40 was assigned to the H-3 proton, as it is the most deshielded proton of the piperidine ring due to the presence of the electron-withdrawing α-carbonyl. The multiplicity of this signal can be justified by the coupling of one di-axial (11·3 Hz) and one axial-equatorial (3·2 Hz) interaction with the H-2 protons. On the basis of these coupling constants the H-3 proton must be situated in the axial position. Consequently, the benzoyl group must lie in the less sterically crowded equatorial plane. Lastly, the hydroxy proton (δ 5·16) showed a doublet of magnitude 2·6 Hz.

The piperidines synthesized have asymmetric centres in the ring at the 3- and 4-positions. This can give rise to two possible diastereomers, and hence four conformers (Fig. 2).

Table 1. Analytical data for 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines.



Compound Formula	R =	Yield (%)	Solvent	m.p. (°C)	Found C	(%) H	(Required) N
1 $C_{19}H_{21}NO_2 \cdot HCl$	Methyl	59	EtOH	183–184	68·8 (68·8	6·67 6·6	4·17 4·2)
2 $C_{20}H_{23}NO_2 \cdot HCl$	Ethyl	28	EtOH	132–133	69·1 (69·5	7·03 6·9	4·2 4·1)
3 $C_{26}H_{27}NO_2 \cdot HCl$	2-Phenethyl	38	EtOH	189–190	73·6 (74·0	6·62 6·64	3·27 3·32)
4[a] $C_{21}H_{23}NO_2$	Cyclopropyl	91	EtOH	153–154	78·3 (78·5	7·18 7·17	4·26 4·36)
5 $C_{21}H_{25}NO_2 \cdot HCl$	Isopropyl	39	EtOH	163–164	70·2 (70·1	7·25 7·23	3·92 3·89)
6 $C_{23}H_{29}NO_2 \cdot HCl$	1-Ethylpropyl	42	EtOH	180–181	71·4 (71·2	7·76 7·74	2·89 2·84)
7 $C_{24}H_{29}NO_2 \cdot HCl$	Cyclohexyl	49	EtOH	174–175	72·0 (72·1	7·47 7·51	3·45 3·50)

[a] Synthesized from the *mono*-Mannich product.

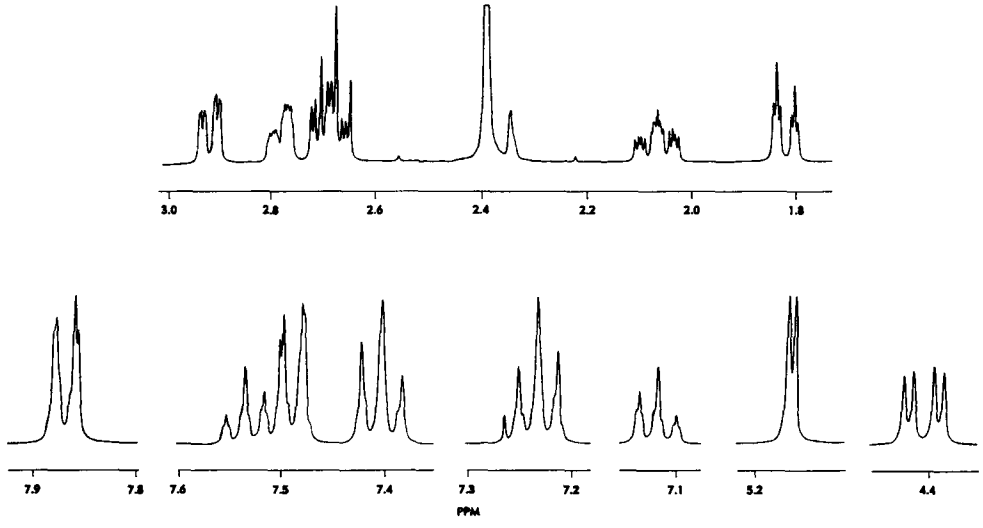


FIG. 1. 400 MHz. ^1H NMR spectrum of 3-benzoyl-4-hydroxy-1-methyl-4-phenylpiperidine hydrochloride.

The ^1H and ^{13}C NMR (recorded on a Jeol CX270MHz Fourier Transform NMR spectrometer) data for all the piperidines synthesized (Tables 2 and 3, respectively), confirmed that only one diastereomer was produced for each analogue. In all of the piperidines analogues, all of the H-3 proton signals were doublets of doublets with one large coupling (11·0–12·1 Hz.) and one small coupling (4·4–4·0 Hz.), indicating that it lies in the axial plane, and also a doublet for the OH proton signals was apparent.

Out of the possible four conformers illustrated in Fig. 2, it is clear that conformer **B** and **D** show that the 3-methine proton of the ring is situated in the equatorial plane, and as stated earlier, the piperidines formed had the 3-methine proton in the axial position.

Conformer **A** exhibits a W-pathway from the hydroxy proton to the axial H-5 proton (Newman diagram, Fig. 3). A W-pathway of this nature only exists if the molecule concerned is of a fixed orientation (Casy et al 1992), as is the case in this example (due to conformational restriction caused by the intramolecular H-bonding of the carbonyl of the 3-benzoyl substituent of the ring to the 4-hydroxy group).

Conformers **C** and **D** will not exhibit intramolecular hydrogen bonding between the 3-benzoyl and the 4-hydroxy groups as both groups are either equatorial (conformer **C**) or axial (conformer **D**) to one another and hence too far apart for any interaction. Taken together, these spectral features confirm that, in all cases, the relative stereochemistry of the piperidines is consistent with the conformation shown in Fig. 2A.

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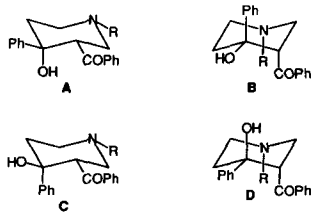

FIG. 2. Conformational analysis of 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidine hydrochlorides.

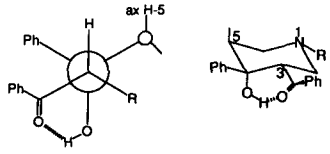

FIG. 3. Newman diagram illustrating W-pathway of 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidine hydrochlorides.

Table 2. 270 MHz. ^{1}HNMR characteristics of 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidine hydrochlorides.

Compound No.	R =	H-2/H-6	H-3	H-5	0H	Ar-H	N-R
1	Methyl	3·48, m	5·57, dd[a]	eq: 2·16[a], dt ax: 2·83, m	5·07, d, 2·6 Hz	8·07, m	2·90, s, CH_3
2	Ethyl	3·50, m	5·63, dd 4·0, 11·7 Hz	eq: 2·01[a], dt ax: 2·93, m	5·08, d, 2·9 Hz	8·13, m	1·55[a], t, CH_3 3·19[a], q, CH_2CH_3
3	2-Phenethyl	3·60, m	5·60, dd[a]	eq: 2·01[a], d ax: 2·90, m	5·18, d, 1·8 Hz	8·04, m	3·60, m, CH_2CH_2Ph
4[b]	Cyclopropyl	3·14, m	4·43, dd 3·7, 11·4 Hz	eq: 1·83, m ax: 1·83, m	5·18, d, 2·7 Hz	7·98, m	0·59, m, 2 × CH_2 2·03, m, NC*H*
5	Isopropyl	2·93, m	4·38, dd 4·0, 11·0 Hz	eq: 1·86[a], dt ax: 2·03, m	5·17, d, 2·4 Hz	7·89, m	1·11, d, 6·6 Hz., $CH(CH_3)_2$; 2·93, m, NC*H*
6	1-Ethylpropyl	3·62, m	5·91, dd 3·7, 11·7 Hz	eq: 1·99, m ax: 2·99, m	5·09, d, 2·6 Hz	8·16, m	1·17, 2xt, 7·7, 7·3 Hz., $CH(CH_2CH_3)_2$ 2·14, m, $CH(CH_2CH_3)_2$
7	Cyclohexyl	3·58, m	5·85, dd 3·7, 11·4 Hz	eq: 2·05, m ax: 3·17, m	5·09, d, 2·6 Hz	8·15, m	2·05, m; 2·45, m; 3·58[a],tt

[a] Unresolved signals, [b] as the free base.

Table 3. ^{13}C NMR chemical shifts of 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidine hydrochlorides.

Compound No.	R =	C-2	C-3	C-4	C-5	C-6	C = O	Ar-C	N-R
1	Methyl	51·57	46·19	71·19	36·59	50·66	201·16	124·28–134·70 (6 × *C*H) 143·65 (*C*q)	43·14, *C*H$_3$
2	Ethyl	51·57	45·99	71·79	36·39	50·09	201·52	127·66–133·34 (4 × *C*H)	47·84, *C*H$_2$ 9·11, *C*H$_3$
3	2-Phenethyl	50·27	45·99	71·06	35·95	48·23	200·35	123·97–137·89 (7 × *C*H) 135·35, 143·56 (*C*q)	57·54, *C*H$_2$CH$_2$Ph 29·68, CH$_2$*C*H$_2$Ph
4[a]	Cyclopropyl	52·87	50·40	73·27	39·70	49·40	204·41	124·52–133·79 (5×*C*H) 128·21, 147·32 (*C*q)	38·24, *C*H 6·32, 6·16 2 × *C*H$_2$
5	Isopropyl	48·52	50·96	73·27	40·12	44·20	204·57	124·51–133·73 (5 × *C*H)	54·62, *C*H 18·49, 18·26, 2 × *C*H$_3$
6	1-Ethylpropyl	48·36	45·99	71·97	36·26	44·68	202·0	124·42–134·83 (5 × *C*H) 134·64, 143·85 (*C*q)	69·70, *C*H 23·00, 2 × *C*H$_2$ 21·50, 2 × *C*H$_3$
7	Cyclohexyl	47·91	45·99	72·04	36·36	44·43	201·97	124·42–134·86 (5 × *C*H) 134·67, 143·88 (*C*q)	63·96, NCH 27·21–24·91 (3 × *C*H$_2$)

[a] As the free base.

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