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SYNTHESIS AND CONFORMATIONAL STUDY OF SOME DIASTEREOISOMERIC 4-METHYL-3-PHENYL-3-PIPERIDINOLS AND RELATED ESTERS

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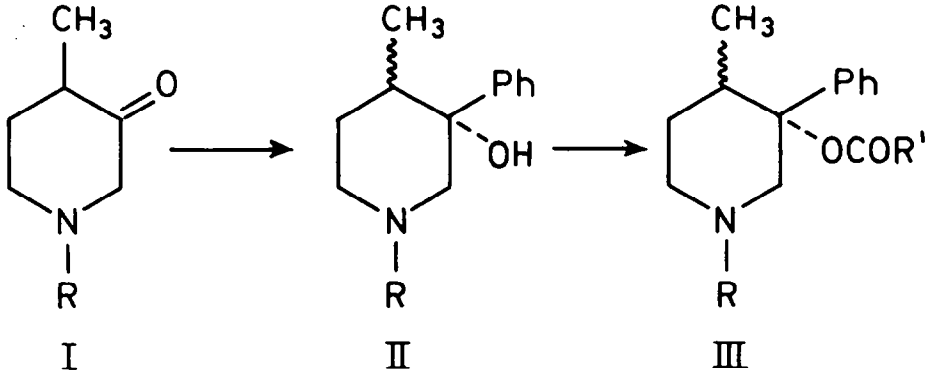
Abstract—Diastereoisomeric 4-methyl-3-phenyl-3-piperidinols and related esters have been prepared by phenylation of 4-methyl-3-piperidones and subsequent acylation. The synthesis of the intermediate piperidones is also described. Configurational and conformational assignments are based on the IR and NMR study of OH absorption bands of the diastereoisomeric pair II, of the desmethyl analogue X (R = H) and of VII. NMR spectroscopic differences found in the ester Me group, as affected by magnetic anisotropy of the C-3-Ph substituent, also provide useful guidance in the assignment of configurations and probable conformations.

IN ORDER to obtain further evidence of conformational requirements for analgesic activity,[1] we undertook the synthesis of α- and β-4-methyl-3-phenyl-3-propionyloxy-N-substituted-piperidines* (isoprodine type compounds) in which the substituents at C-3 and C-4 are reversed with regard to the substituents of α- and β-prodine type compounds.[2]

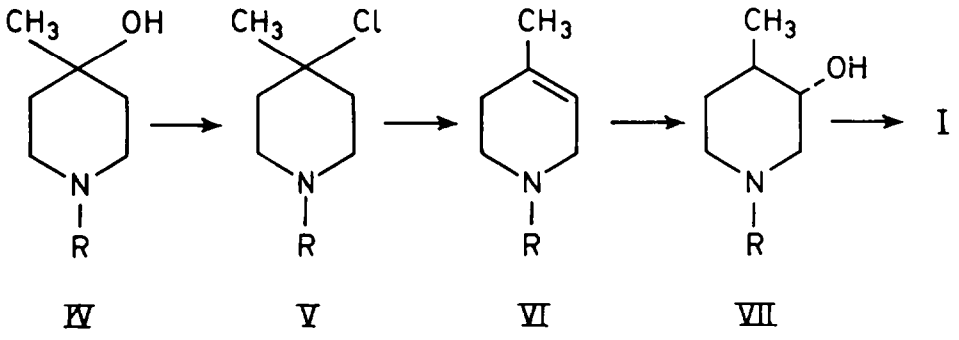
The key intermediates in this synthesis are the 4-methyl-3-piperidones (I) which by reacting with phenyl lithium gave the piperidinols (II) and by subsequent acylation the isoprodine type compounds (III).



a ; R = CH_2Ph b ; R = CH_2CH_2Ph

* In this paper α and β refer to the orientation of the C-3-Ph substituent with respect to the C-4-Me group respectively as *trans* and *cis*.

The synthetic sequence shown in Scheme I was utilized for the preparation of I.



a ; R = CH_2Ph b ; R = CH_2CH_2Ph

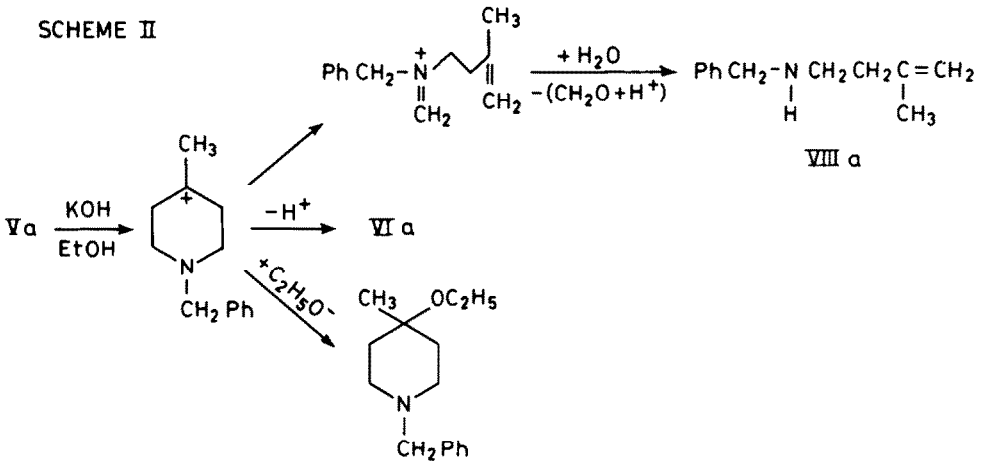
SCHEME I

Dehydration of IVa by treatment with a mixture of acetic and hydrochloric acids at the reflux temperature did not go to completion. Following the course of the reaction by TLC with solvent (B), we found that, after 19 hr reflux, a mixture of IVa, Va and VIa in the ratio 36:21:43 was obtained. This ratio was unaffected by further heating and was assumed to be the equilibrium value under these experimental conditions. The olefine VIa, after a 6 hr reflux period in hydrochloric acid (*d* 1·18), was recovered together with IVa and Va in the ratio of 29:27:44. Further heating did not affect this ratio. The fact that under the same acidic conditions the 4-arylpiperidinols were completely dehydrated[3] indicates that the resulting olefin attained an enhanced stability through conjugation of the aromatic ring with the double bond.

The dehydration of IVa, via the chloro derivative Va gave better results. Treatment of IVa with thionyl chloride gave a mixture of Va and VIa: the chloro derivative being partially dehydrochlorinated under these conditions. To complete the elimination, the crude mixture, isolated as base, was stirred overnight with aqueous potassium hydroxide in ethanol at room temperature. The reaction product contained the olefin VIa as the major component and a by-product which proved to be VIIIa. When the crude mixture was treated with the alkaline solution at reflux temperature then, besides the olefin, a by-product was isolated and identified as IXa. These results are consistent with the assumption that the reaction proceeds through a common carbonium ion intermediate (Scheme II). This carbonium ion, resulting from the heterolysis of the C—Cl bond, by losing a proton gave an olefin (E_1 mechanism), or by reacting with ethoxide ion gave IXa (S_Ni mechanism), or it may undergo fragmentation with the participation of the nitrogen electron pair to give a fragmentation product, VIIIa. In the solvolytic reaction of 1,4-dimethyl-4-chloropiperidine (0·001 M NaOH in 80% ethanol) Grob *et al.*[4] obtained a fragmentation product, 4-methylamino-2-methyl-but-1-ene in a yield of 85% with 1,4-dimethyl-4-piperidinol as a by-product, suggesting a synchronous fragmentation as a principal mechanism of the reaction.

Hydroboration and subsequent oxidation of VI, following a procedure adopted by Lyle *et al.*[5] for an analogous reaction, gave predominantly the 4-Me/3-OH *trans* compound VII together with 10% of IV. Attempts to oxidize the organoborane complex directly to the ketone I by chromic acid following the method adopted by Brown and Garg[6] for homocyclic compounds were unsuccessful. The oxidation of

SCHEME II



SCHEME II

VII with chromic trioxide proceeded well when the specific experimental conditions described in this paper were used. Any modification resulted in poor yields of a mixture of products.

Phenylation of I, using phenyl lithium, gave predominantly one isomer. TLC indicated that two components in the ratio of 9:1 were present in the crude mixture. Isolation of the compound in minor yield has been effected by column chromatography of the mother liquors after crystallization of the major component.

Conformational assignments

The assignment of the configuration 3-Ph/4-Me *trans* for the predominant isomer of the phenylation and *cis* for the minor component was made on the basis of their IR and NMR spectra compared with those of VII and of the desmethyl analogue X.

The 3-OH/4-Me *trans* configuration of VII is well established on the basis that hydroboration proceeds in a *cis* manner and that oxidation of the B—C bond occurs with retention of configuration. The IR spectrum of VIIa (Fig 1) shows a strong unsymmetric band at 3630 cm^{-1}, independent of concentration, indicating a free OH group, a small band at 3530 cm^{-1} due to intramolecular H- bonding and a broad band in the range 3300–3400 cm^{-1} which disappeared on high dilution. It thus appears likely that VII adopts predominantly the chair form with e-3-OH and e-4-Me (Fig 2); $-\Delta G^{\circ}_{X}$[1·7 (Me)[7] + 0·37 (OH)[5]] of about 2 Kcal/mole, between the conformer VII (Fig 2) and the corresponding inverted chair form, corresponds to a population of about 96% and this is in agreement with the IR spectral data which show only a small band for the intramolecularly H- bonded form.

The NMR spectrum of VIIa (Table 1, No. 1) shows an overlapped multiplet for the carbinol hydrogen which shifts downfield on acetylation, appearing as a sextet at τ 5·40 with a half band width of 24 Hz which is characteristic[5, 8, 9] of an axial carbinol proton and thus an equatorial alcohol.

The IR spectrum of α-IIa (Fig 1) shows a strong band at 3500 cm^{-1}, suggesting an intramolecular O—H . . . N bonding and consequently an axial OH. Piperidinol X (R = H) and β-IIa exhibit two bands: a strong absorption respectively at 3500 and

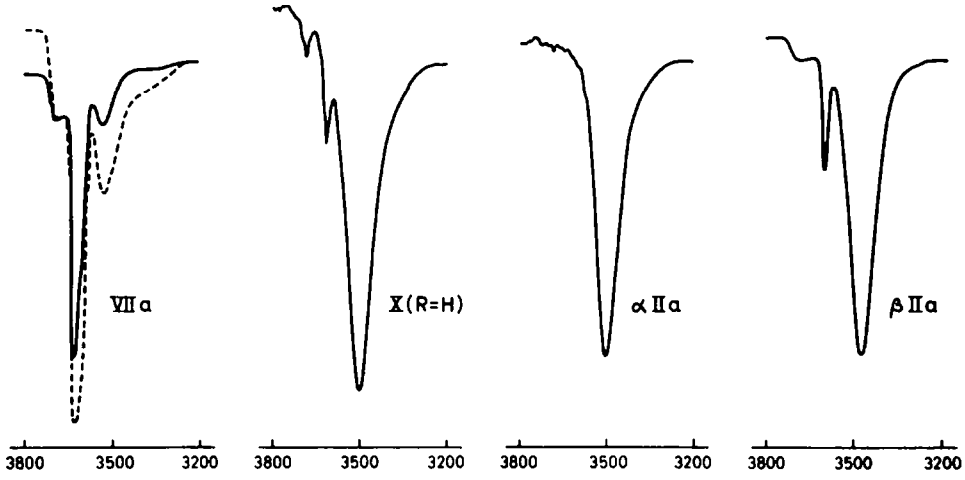


Fig 1. IR spectra of 3-piperidinols in CCl_4 solution: ——— 0·005M, ------ 0·03M.

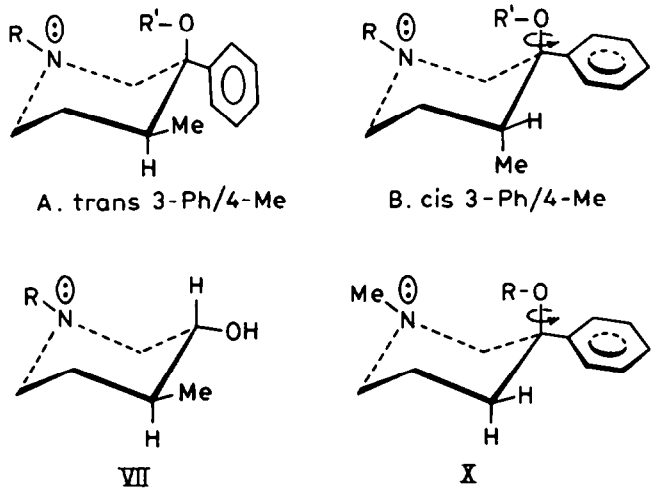


Fig 2. Probable conformations of some 3-piperidinols and related esters.

3480 cm^{-1} (O—H . . . N intramolecular bonding) and a sharp peak at 3618 and 3600 cm^{-1} (O—H . . . π intramolecular bonding) (Fig 1), indicating the presence of an axial OH. In X (R = H) and in β-II the lack of any equatorial substituent in C-2 and C-4 allows the aromatic ring to adopt an orientation perpendicular to the C—O bond (Fig 2, B), hence the O—H and π-system are in favourable geometrical juxtaposition for interaction.[10] In α-II the presence of an equatorial C-4-Me deffects the phenyl ring out of the plane parallel to the piperidine ring adversing the directional availability of π electrons for H- bonding (Fig 2, A).

The NMR signal of the OH proton in X (R = H) and α- and β-IIa (Table 1, No. 4, 7 and 9) which appears at unusually low field and does not suffer any shift at concentration changes in $CDCl_3$ (from 10 to 2·5% w/v), further suggests the presence of

strong H-bonding. The effect of dilution is far more remarkable on the chemical shift of the OH proton of VIIa which moves from τ 7·62 to τ 8·12 with the same concentration changes, rather suggesting intermolecular H-bonding.

Examination of NMR spectra of α- and β-IIIa (R′ = COMe and COEt) (Table 1, No. 11, 12, 15 and 16) reveals that the more significant difference resides in the chemical shift of the ester Me signal: in β-esters being of the same value as found for the desmethyl analogue X (R = COMe and COEt) (Table 1, No. 5 and 6), and in α-ester being about 10 Hz downfield. In the last case the presence of an e-C-4-Me prevents a parallel orientation of the phenyl ring to the piperidine ring and the

TABLE 1. NMR CHARACTERISTICS[a] OF SOME 3-PIPERIDINOLS AND RELATED ESTERS

No.	Structure	C-3-Substituent H	C-3-O-Function	C-4-Me	Others
1	VIIa	6·64 m[b]	7·62 s, (OH)	8·98 d *J* 3·5	6·48 s, (N-CH$_2$Ph) 2·67 s, (N-CH$_2$Ph)
2	Acetyl-VIIa	5·40 sx W_H 24	7·98 s, (COCH$_3$)	9·08 d *J* 6	6·49 s (N-CH$_2$Ph) 2·72 s (N-CH$_2$Ph)
3	VIIb	6·65 m[b] Ph	6·87 s, (OH)	8·96 d *J* 2·5	7·33, 7·29 m[c] (N-CH$_2$CH$_2$Ph) 2·78 s, (N-CH$_2$Ph)
4	X (R = H)	2·65 m[c] W_H 17	6·40 s, (OH)	—	7·70 s, (NCH$_3$)
5	X (R = COMe)	2·67 m[c]	7·95 s, (COCH$_3$)	—	7·69 s, (NCH$_3$)
6	X (R = COEt)	2·67 s	8·93 t, (COCH$_2$CH$_3$) *J* 7	—	7·69 s, (NCH$_3$)
7	α-IIa	2·70 m[c, d]	6·47 s[e] (OH)	9·35 d *J* 6	6·47 s, (N-CH$_2$Ph)
8	α-IIb	2·78 m[c, d]	6·55 s, (OH) W_H 9	9·35 d *J* 6	7·28 s, (N-CH$_2$CH$_2$Ph)
9	β-IIa	2·77, 2·67 m[c, d]	6·43 s[e] (OH)	9·39 d *J* 7	6·43 s, (N-CH$_2$Ph)
10	β-IIb	2·83 m[c, d]	6·50 s, (OH) W_H 9	9·33 d *J* 6	7·25 s, (N-CH$_2$CH$_2$Ph)
11	α-IIIa (R′ = COMe)	2·70 s[d]	7·78 s, (COCH$_3$)	9·29 d *J* 6	6·02, 5·82 AB-q, (N-CH$_2$Ph)
12	α-IIIa (R′ = COEt)	2·70 s[d]	8·77 t, (COCH$_2$CH$_3$) *J* 8	9·30 d *J* 6	6·02, 5·82 AB-q (N-CH$_2$Ph)
13	α-IIIb (R′ = COMe)	2·78 s[d]	7·90 s, (COCH$_3$)	9·30 d *J* 6	7·33 s, (N-CH$_2$CH$_2$Ph)
14	α-IIIb (R′ = COEt)	2·83 m[c, d]	8·83 t, (COCH$_2$CH$_3$) *J* 7·5	9·28 d *J* 6	7·33 s, (N-CH$_2$CH$_2$Ph)
15	β-IIIa (R′ = COMe)	2·73 m[c, d]	7·98 s, (COCH$_3$)	9·38 d *J* 6	6·47 s, (N-CH$_2$Ph)
16	β-IIIa (R′ = COEt)	2·73, 260 m[c, d]	8·93 t, (COCH$_2$CH$_3$)	9·36 d *J* 6	6·47 s, (N-CH$_2$Ph)

[a] Chemical shifts in τ units (ppm) from TMS as internal standard (s: singlet, d: doublet, t: triplet, q: quartet, sx: sextet, m: multiplet). Coupling constants (*J*) and half width (W_H) in Hz.

[b] Overlapped signal.

[c] Main peak(s).

[d] Include aromatic benzyl protons.

[e] Overlapped by the benzylic methylene protons; integral decreases of 1 proton with D_2O

screening contribution of the aromatic ring current towards the acyl methyl.[11] Casy[12] has demonstrated that chemical shift differences between acyloxy functions in α- and β-prodine type compounds can provide evidence of their conformation: differences of the same order between the ester Me singnals (in β-isomers being always at higher field) were reported.[13, 14]

An additional feature of different conformations appears in the benzylic methylene signal in α- and β-IIIa (R′ = COMe and COEt). In α-isomers these protons experience two different environments and show a typical AB quartet (Fig 3), while in β-isomers the same protons are equivalent and exhibit a single peak as found in α- and β-IIa. Asymmetry of the molecule together with the restricted rotation of the acyloxy group about the C-3-O bond may account for magnetic non-equivalence of these protons.

A further point of interest is that the C-6 equatorial proton absorbs at lower frequency than found for the remaining protons of the piperidine ring in all the esters examined as a consequence of long-range deshielding effect of the ester carbonyl group. This effect is greater in α-III (a and b) (R′ = COMe and COEt) where the e-6-H shows the downfield part of an ABC pattern centred at τ 5·93 in α-IIIa (Fig 3) and at τ 5·82 in α-IIIb. In β-IIIa (R′ = COMe and COEt) and in X (R = COMe and COEt) the same proton shows two broad bands (apparent multiplets) centred at τ 6·70 (J_{gem} 12 Hz).

On the basis of the above evidence it is concluded that addition of phenyl-lithium, as reported by Beckett *et al.*[2] for the prodine type compound, is prevalently from the less hindered side, i.e., equatorial to the piperidine ring which is assumed to exist in the chair form with the C-4-Me equatorial, with preferential formation of the more stable product: the α-piperidinol.

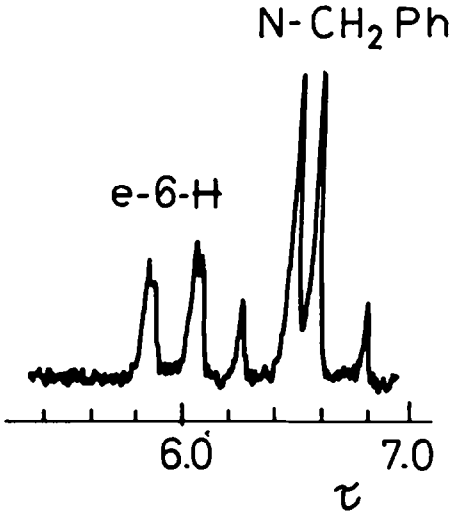


FIG 3. Part of the NMR spectrum of α-IIIa (R′ = COMe and COEt).

EXPERIMENTAL

Chromatography was carried out on a silica gel (0·08 mm) column and on glass plates coated with thin layers of silica gel G (Merck). The composition of the mixture and the purity of the isolated compounds were checked by TLC, usual solvents being mixtures of (A) chloroform-acetone, 2:1 v/v, (B) acetone-methanol, 9:1 v/v, and (C) light petroleum (b.p. 30–50°)-ether, 2:1v/v. The spots were detected by spraying with

Dragendorff's reagent. Relative proportions of the components in a mixture were estimated by duplicating the areas of the spots on paper, cutting out and weighing. IR spectra were run routinely with a Unicam SP 200 spectrometer; the OH absorption region of the reported spectra were measured with a Perkin Elmer Model 125 spectrometer, with infrared silica cells of path-lengths 1–2 cm. NMR spectra were determined with a Varian T-60 spectrometer in $CDCl_3$, with TMS as internal standard. M.ps are uncorrected. Microanalyses were performed by the Microanalytical department of our Institute under the direction of Prof. M. Marzadro.

1-*Phenethyl-4-methyl-4-piperidinol* was prepared from 1-phenethyl-4-piperidone[2b] and MeLi as reported:[15] m.p. 66°, from ether-light petroleum. (Found: C, 76·62; H, 9·52; N, 6·80. $C_{14}H_{21}NO$ requires: C, 76·66; H, 9·65; N, 6·39%).

Elimination of 1-*aralkyl-4-methyl-4-piperidinols.* Thionyl chloride (20 ml) was added dropwise to a stirred soln of IVa (41 g, 0·2 mole) in chloroform (150 ml) at 0°. The mixture was allowed to warm at room temp and gently refluxed for further 2 hr. The cooled soln was poured onto crushed ice, made basic with aqueous ammonia, the organic layer separated, washed with water, dried (Na_2SO_4) and the solvent removed. The crude product was dissolved in EtOH (150 ml), KOH (11 g, 0·2 mole) in 11 ml water was added and the whole stirred overnight at room temp, and gently refluxed for a further 2 hr to complete the reaction. The EtOH was removed and the residue, diluted with water, was extracted with either. The combined extracts were dried, concentrated and the remaining oil fractionally distilled. The fractions, which contained two spots, were purified by chromatography on a column of silica gel with solvent (A). The tetrahydropyridine was the more readily eluted compound.

1-*Benzyl-4-methyl*-1,2,5,6-*tetrahydropyridine* (VIa), b.p. 71–74°/0·5 mm, n_D^{20}: 1·5415; hydrochloride m.p. 204°, from EtOH. (Found: C, 69·69; H, 8·05; N, 6·13. $C_{13}H_{18}ClN$ requires: C, 69·79; H, 8·11; N, 6·26%); NMR τ (base) 8·33 (s, W_H 5 Hz, CH_3), 6·45 (s, $\underline{CH_2}Ph$), 4·63 (m, W_H 8 Hz, vynilic), 2·65 (apparent s, aromatic).

4-*Benzylamino-2-methylbut*-1-*ene* (VIIIa), b.p. 62°/0·3 mm, n_D^{20}: 1·5211; hydrochloride m.p. 248°, from EtOH. (Found: C, 68·07; H, 8·56; N, 6·67. $C_{12}H_{18}ClN$ requires: C, 68·08; H, 8·56; N, 6·61%); NMR τ (base) 8·62 (s, disappears with D_2O, NH), 8·30 (s, CH_3), 6·23 (s, $\underline{CH_2}Ph$), 5·23 (s, $=CH_2$), 2·67 (s, aromatic).

Compounds VIb and VIIIb were obtained in a similar manner.

1-*Phenethyl-4-methyl*-1,2,5,6-*tetrahydropyridine* (VIb), b.p. 75–80°/0·2 mm, n_D^{20}: 1·5403; hydrochloride m.p. 226°, from isopropanol. (Found: C, 70·60; H, 8·39; N, 5·99. $C_{14}H_{20}ClN$ requires: C, 70·72; H, 8·48; N, 5·89%); NMR τ (base) 8·30 (s, W_H 7 Hz, CH_3), 8·62, 8·60 ($\underline{CH_2}\underline{CH_2}Ph$), 4·57 (m, W_H 7 Hz, vynilic), 2·72 (s, aromatic).

4-*Phenethylamino-2-methylbut*-1-*ene* (VIII*b*), b.p. 58–60°/0·2 mm, n_D^{20}: 1·5221; hydrochloride m.p. 236°, from EtOH. (Found: C, 68·84; H, 8·90; N, 6·02. $C_{13}H_{20}ClN$ requires: C, 69·16; H, 8·92; N, 6·20%); NMR τ (hydrochloride) 8·28 (s, CH_3), 6·73 (s, $\underline{CH_2}\underline{CH_2}Ph$), 5·23, 5·17 (apparent d, $=CH_2$), 2·77 (s, aromatic) 0·17 (broad s, $^+NH_2$).

An alkaline ethanolic soln of crude Va on heating vigorously at reflux temp yielded besides VIa the ethoxy compound IXa as by-product and was purified by column chromatography as above.

1-*Benzyl-4-methyl-4-ethoxypiperidine* (IXa), b.p. 96–98°/0·5 mm, n_D^{20}: 1·5149; hydrochloride m.p. 208°, from EtOH. (Found: C, 66·81; H, 9·05; N, 5·18. $C_{15}H_{24}ClNO$ requires: C, 66·77; H, 8·96; N, 5·18%); NMR τ (base) 8·86 (s, CH_3), 8·72 (t, *J* 7·5, $CH_2\underline{CH_3}$), 6·64 (q, *J* 7·5, $\underline{CH_2}CH_3$), 6·50 (s, $\underline{CH_2}Ph$), 2·70 (s, aromatic).

Preparation of 1-*benzyl-4-methyl-4-chloropiperidine* (Va). A mixture of IVa (5 g) and HCl (*d*, 1·18) was heated under reflux for 6 hr, concentrated under reduced pressure and the residue taken up in acetone. The solid which separated was recrystallised from EtOH to give 1·7 g of Va HCl, m.p. 189°. (Found: C, 59·97; H, 7·45; N, 5·66. $C_{13}H_{19}Cl_2N$ requires: C, 60·00; H, 7·35; N, 5·38%). Va HCl was prepared in a similar manner from VIa and was identical in m.p. and spectral properties with the sample prepared as above.

Preparation of 1-*aralkyl-4-methyl-3-piperidinols* (VII). To a mixture of VIa (15 g, 0·08 mole) and $NaBH_4$ (4·80 g, 0·115 mole) in 50 ml THF, BF_3-etherate (21·6 ml, 0·18 mole) in 40 ml THF was added during 2 hr at 0–5° under N_2 and stirred for a further 2 hr at room temp. After cooling in ice, the excess hydride was decomposed with water (6·5 ml), 2N NaOH (20 ml) was added followed by dropwise addition of 30% H_2O_2 (20 ml) while the temp was allowed to rise to 45–55°. HCl (*d*, 1·18; 20 ml) was added dropwise to the stirred and cooled mixture and then the soln was partially evaporated under vacuum, made basic with 6N NaOH and extracted with ether. Distillation gave 13·4 g of a liquid boiling at 98–100°/0·07 mm. TLC revealed a two-component mixture. The minor product was proved to be IVa. The major component was assigned the structure of 4-Me/3-OH *trans* 1-benzyl-4-methyl-3-piperidinol (VIIa), which was isolated and purified as hydrochloride m.p. 168°, from EtOH. (Found: C, 64·55; H, 8·37; N, 5·68. $C_{13}H_{20}ClNO$ requires: C, 64·60;

H, 8·34; N, 5·79%). The *acetyl* derivative melts at 184°, from EtOH. (Found: C, 63·43; H, 7·79; N, 4·84. $C_{15}H_{22}ClNO_2$ requires: C, 63·47; H, 7·81; N, 4·93%).

The 1-phenethyl derivative (VIIb) was obtained in a similar manner. Fractional distillation was sufficient to afford a pure compound: b.p. 90–92/0·05 mm; m.p. 67°, from light petroleum; hydrochloride m.p. 212°, from EtOH. (Found: C, 65·65; H, 8·68; N, 5·52. $C_{14}H_{22}ClNO$ requires: C, 65·76; H, 8·66; N, 5·47%), NMR data are given in Table 1.

Preparation of 1-aralkyl-4-methyl-3-piperidones (I). To a soln of VIIa (10 g, 0·05 mole) in 100 ml acetone, and CrO_3 (6 g, 0·06 mole) in 15 ml water and 20 ml AcOH, H_2SO_4 (*d*, 1·84; 20 ml) was added dropwise at 5° with constant stirring. The mixture was stirred for further 5 hr and the temp was kept below 18°. After neutralization with aqueous ammonia (at pH higher than 8·5 emulsion becomes a very serious problem), ether was added, the layer separated, and the water layer was again extracted with ether. The combined extracts were dried, concentrated and the resulting oil was distilled to give pure Ia (5 g) as a pale oil which must be kept in a freezer as it darkened rapidly at room temp: b.p. 97–99°/0·4 mm, n_D^{18}: 1·5390; ν_{max}^{film} 1710 cm^{-1} (C=O), 1670 cm^{-1} (=C—OH); picrate m.p. 145°, from acetone-EtOH. (Found: C, 53·05; H, 4·69; N, 12·50. $C_{19}H_{20}N_4O_8$ requires: C, 52·78; H, 4·66; N, 12·96%).

In a similar manner the ketone Ib was obtained: b.p. 99–100°/0·5 mm, n_D^{20}: 1·5314; ν_{max}^{film} 1710 cm^{-1} (C=O), 1670 cm^{-1} (=C—OH); picrate m.p. 148°, from EtOH. (Found: C, 53·47; H, 5·03; N, 12·73. $C_{20}H_{22}N_4O_8$ requires: C, 53·81; H, 4·97; N, 12·55%).

Preparation of the diastereoisomeric 4-methyl-3-phenyl-3-piperidinols (II). Diastereoisomeric piperidinols were prepared by the previously described general method[3a] from 1-benzyl-4-methyl- and 1-phenythyl-4-methyl-3-piperidones and phenyl-lithium. The total product was treated with ethanolic HCl and diluted with dry ether. The hydrochloride which separated, after crystallization from EtOH, gave the pure hydrochloride of α-II. Evaporation of the mother liquors after the initial acid treatment, and chromatography of the residue, as a base, on silica gel with solvent (C), gave more α-II as the first eluted isomer, followed by β-II which was converted into the hydrochloride and further purified by crystallization from EtOH.

The desmethyl analogue X (R=H) was obtained from 1-methyl-3-piperidone[16] and phenyl-lithium. Results are listed in Table 2; the NMR spectra are reported in Table 1.

TABLE 2. 3-PHENYL-3-PIPERIDINOL HYDROCHLORIDES

Compound	M.p.	Formula	% Found (Required) C	H	N
α-IIa	251°	$C_{19}H_{24}ClNO$	71·95 (71·80)	7·60 (7·61)	4·33 (4·40)
β-IIa	233°	$C_{19}H_{24}ClNO$	71·70 (71·80)	7·65 (7·61)	4·40 (4·40)
α-IIb	236°	$C_{20}H_{26}ClNO$	72·33 (72·39)	7·90 (7·90)	4·18 (4·22)
β-IIb	233°	$C_{20}H_{26}ClNO$	72·47 (72·39)	7·82 (7·90)	4·40 (4·22)
X (R = H)	180°[a]	$C_{12}H_{18}ClNO$	63·20 (63·29)	7·92 (7·98)	6·15 (6·04)

[a] Hygroscopic, loses water at 98–105°

TABLE 3. 3-PHENYL-3-ACYLOXYPIPERIDINE HYDROCHLORIDES

Compound	Acyl	M.p.	Formula	% Found (Required) C	H	N
IIIa	COMe	222°	$C_{21}H_{26}ClNO_2 \cdot \frac{1}{2}H_2O$	68·42 (68·38)	7·66 (7·37)	3·80 (3·79)
IIIa	COEt	208°	$C_{22}H_{28}ClNO_2$	70·52 (70·67)	7·73 (7·55)	3·86 (3·75)
IIIa	COMe	206°	$C_{21}H_{26}ClNO_2$	70·17 (70·08)	6·99 (7·28)	3·79 (3·89)
IIIa	COEt	196°	$C_{22}H_{28}ClNO_2$	70·60 (70·67)	7·51 (7·55)	3·85 (3·75)
IIIb	COMe	201°	$C_{22}H_{28}ClNO_2$	70·68 (70·67)	7·51 (7·55)	3·73 (3·75)
IIIb	COEt	197°	$C_{23}H_{30}ClNO_2$	71·07 (71·21)	7·83 (7·79)	3·44 (3·60)
X	COMe	201°	$C_{14}H_{20}ClNO_2$	62·27 (62·37)	7·55 (7·47)	5·10 (5·19)
X	COEt	214°	$C_{15}H_{22}ClNO_2$	63·48 (63·49)	7·80 (7·82)	4·98 (4·93)

Esterification of 3-phenyl-3-piperidinols. A mixture of the piperidinol (0·5 g), Ac_2O (or propionic anhydride) (3 ml) and pyridine (0·5 ml) was heated under reflux for 3 hr. The mixture was cooled, diluted with water and aqueous ammonia and extracted with ether. The ether extracts were dried, evaporated under vacuum and the residue was acidified with ethereal HCl. The solid, which separated, was crystallized from EtOH or EtOH-ether. Alternatively α-IIIa (R = COMe and COEt) were prepared in good yield by heating under reflux the piperidinol (0·5 g) with Ac_2O (or propionic anhydride) (3 ml) and AcOH (or propionic acid) (1 ml) for 3 hr. Results are listed in Table 3; the NMR spectra are reported in Table 1.

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REFERENCES

1 [a] A. H. Beckett and A. F. Casy, *Progress in Medicinal Chemistry* (Edited by G. P. Ellis and G. B. West) Vol. 4. Butterworths, London (1965);
[b] R. A. Hardy Jr. and M. G. Howell, *Analgesics* (Edited by G. DeStevens) Vol. 5. Academic Press, New York (1965)

2 [a] A. H. Beckett, A. F. Casy, G. Kirk and J. Walker, *J. Pharm. Pharmacol.* **9**, 939 (1957);
[b] A. H. Beckett, A. F. Casy and G. Kirk, *J. Med. Pharm. Chem.* **1**, 37 (1959)

3 [a] A. F. Casy, A. H. Beckett, M. A. Iorio and H. Z. Youssef, *Tetrahedron* **21**, 3387 (1965);
[b] A. F. Casy, A. H. Beckett and M. A. Iorio, *Ibid.* **23**, 1405 (1967)

4 [a] C. A. Grob, *Fragmentation in solvolysis reaction, Theoretical Organic Chemistry*, Report on the Kekulè Symposium, London (1958);
[b] R. D'Archy, C. A. Grob, T. Kaffenberger and V. Krasnobajew, *Helv. Chim. Acta* **49**, 185 (1966)

5 R. E. Lyle, D. H. McMahon, W. E. Krueger and C. K. Spicer, *J. Org. Chem.* **31**, 4164 (1966)

6 H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.* **83**, 2951 (1961)

7 E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, Wiley, New York (1965)

8 B. P. Thill and H. S. Aaron, *J. Org. Chem.* **33**, 4376 (1968)

9 E. E. Smissman and G. S. Chappell, *J. Med. Chem.* **12**, 432 (1969)

10 M. Oki and H. Iwamura, *Bull. Chem. Soc. Japan* **32**, 955 (1959)

11 C. E. Johnson Jr. and F. A. Bovey, *J. Chem. Phys.* **29**, 1012 (1958)

12 A. F. Casy, *Tetrahedron* **22**, 2711 (1966)

13 A. F. Casy, M. A. Iorio and P. Rocha, *J. Chem. Soc.* (C) 942 (1967)

14 A. F. Casy, *J. Med. Chem.* **11**, 188 (1968)

15 J. M. McManus, J. W. McFarland, C. F. Gerber, W. M. McLamore and G. D. Laubach, *Ibid.* **8**, 766 (1965)

16 R. E. Lyle, S. A. Leone, H. J. Troscianiec and G. H. Warner, *J. Org. Chem.* **24**, 342 (1959)