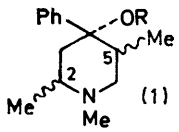
# Stereochemistry of Isomeric 1,2,5-Trimethyl-4-phenylpiperidin-4-ols: a $^1$H Nuclear Magnetic Resonance Study

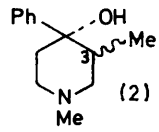
By A. F. Casy * and K. M. J. McErlane, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

Some $^1$H n.m.r. spectral features of three diastereoisomeric 1,2,5-trimethyl-4-phenylpiperidin-4-ols are reported and shown to provide evidence of the configurations *t*-2-Me,*c*-5-Me,*r*-4-OH (γ-isomer), *t*-2-Me,*t*-5-Me-*r*-4-OH (β-isomer), and *c*-2-Me,*t*-5-Me,*r*-4-OH (α-isomer). Evidence is given that significant skew-boat populations (with the 4-phenyl group pseudoequatorial) arise in the case of the α-alcohol as solute in deuteriochloroform, while preferred conformations of the γ- and β-isomers are piperidine chairs with the 4-phenyl group equatorial. Stable epimeric conjugate acids of the β-hydrochloride were detected in deuterium oxide. Present findings are compared with those of previous studies.

CONFLICTING evidence about the stereochemistry of the narcotic analgesic trimeperidine (promedol) and its isomers (1b) [1-5] and our interest in the conformation of




(1)




(2)

a; R = H
b; R = COEt

a; *c*-3-Me,*r*-4-OH (α)
b; *t*-3-Me,*r*-4-OH (β)

analgesics based on 4-phenylpiperidine [6-8] has prompted this study of tertiary alcohols derived from 1,2,5-trimethyl-4-piperidone (a *cis–trans* mixture) [9] and phenyllithium. The most abundant diastereoisomer [γ-(1a)] readily crystallized as the free base from the reaction product; a second form (β) was isolated from the mother liquors as a hydrochloride salt. Column chromatography of the total product on alumina (monitored by $^1$H n.m.r. spectroscopy) led to the recovery of a third isomer, designated the α-form. The remaining possible isomer (δ) [4] could not be isolated, although spectroscopic evidence of its presence in certain fractions was obtained. The m.p.s of our γ- and β-bases and hydrochloride salts correspond closely with those reported in the Russian literature but differ in the case of the α-isomer, the same being true for the corresponding esters; reported m.p. ranges for α-(1a) base and hydrochloride are the same or close to those of the β-forms. The isomeric purity of our samples was established by their $^1$H n.m.r. spectra, each isomer displaying characteristic signals.

Evidence of configuration and solute conformation of the isomers (1a) is based chiefly * upon analyses of their $^1$H n.m.r. spectra (in deuteriochloroform unless otherwise stated) aided by data for the previously studied 3-methyl analogues (2) (α- and β-prodinol) of established stereochemistry.[6,7] Arguments rest initially on the assumption that the piperidine ring adopts a chair conformation with the largest ring substituent (4-phenyl) equatorial. Signals have been assigned by comparing spectra of the normal alcohols with those of corresponding isomers in which the 3-methylene and 5-methine protons were replaced by deuterium; the deuteriated forms were obtained from 3,3,5-trideuterio-1,2,5-trimethyl-4-piperidone.[9] Data for the 3-methylene protons derived in this manner are given in Table 1. The two $^3J$ values for the γ-isomer are typically those of an axial–axial and an axial–equatorial pair of coupled protons [10] and show that the arrangement shown (3) must occur in this isomer, with the 2-methyl group equatorial. The significance of the axial 3-H signal being at lower field is discussed later. The 5-methyl signal (identified as the signal at higher field of the two methyl doublets because this signal forms a singlet in the spectrum of the deuteriated isomer) has chemical shifts very close to those of the 3-methyl group of α-prodinol (2a) (Table 2) which is known to be equatorial; [6] also, like the 3-methyl signal of (2a),[6] it has an appearance typical of that due to virtual coupling (deformed doublet with extra peaks, separation of outer lines increases from 6 to 7·2 Hz when

TABLE 1

3-Methylene $^1$H n.m.r. characteristics of isomeric 1,2,5-trimethyl-4-phenylpiperidin-4-ols in $CDCl_3$ [a]

| Isomer (1a) | Signal form [b] | δ [c] | $^2J$/Hz | $^3J$/Hz |
|---|---|---|---|---|
| γ | dd | 1·51 | 14·0 | 3·5 |
| | dd | 1·78 | | 11·0 |
| β | dd | 1·69 | 13·5 | 10·0 |
| | | Low-field signal (>2·5) not resolved | | |
| α | dd | 1·67 | 14·5 | 4·5 |
| | dd [d] | Near 2 | | 6·0 |

[a] First-order treatment of 100 MHz spectra. [b] All signals absent in spectra of deuteriated forms. [c] In p.p.m. from internal tetramethylsilane. [d] Only high-field half resolvable.

* Chemical evidence and spectroscopic data upon corresponding esters are given in the following paper.

[1] N. S. Prostakov and N. N. Mikheeva, *Russ. Chem. Rev.*, 1962, **31**, 556.
[2] N. S. Prostakov, B. E. Zaitsev, N. M. Mikhailova, and N. N. Mikheeva, *Zhur. obshchei Khim.*, 1964, **34**, 463.
[3] N. S. Prostakov, T. V. Yagodovskaya, and N. N. Mikheeva, *Zhur. obshchei Khim.*, 1964, **34**, 234.
[4] N. I. Shvetsov and V. F. Kucherov, *Doklady Akad. Nauk S.S.S.R.*, 1959, **126**, 1017.
[5] T. F. Vlasova and Yu. N. Sheinker, *Zhur. strukt. Khim.*, 1970, **11**, 640.
[6] A. F. Casy, *Tetrahedron*, 1966, **22**, 2711.
[7] A. F. Casy, *J. Medicin. Chem.*, 1968, **11**, 188.
[8] A. F. Casy, L. G. Chatten, and K. K. Khullar, *J. Chem. Soc. (C)*, 1969, 2491.
[9] M. M. A. Hassan and A. F. Casy, *Org. Magn. Resonance*, 1970, **2**, 197.
[10] S. Sternhell, *Quart. Rev.*, 1969, **23**, 236.

frequency changed from 60 to 100 MHz).[11,12] Further, the shift of the 5-methyl resonance which follows protonation of the basic centre (Table 2) is small and typical

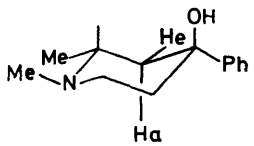
TABLE 2

5-Methyl (1a), 3-methyl (2), and OH chemical shifts [a] for isomeric promedol alcohols and prodinols

| Isomer | 5(3)-Me in solvent $(CD_3)_2SO$ | $CDCl_3$ | $C_5D_5N$ | OH in $(CD_3)_2SO$ |
|---|---|---|---|---|
| α-Prodinol (2a) | 0·48 (0·52) [b] | 0·63 (0·65) | 0·78 | 4·5 |
| γ-(1a) | 0·49 (0·53) | 0·63 (0·65) | 0·78 | 4·55 |
| β-Prodinol (2b) | 0·63 | 0·75 | 0·93 | 4·67 |
| β-(1a) | 0·68 | 0·75 | 0·96 | 4·78 |
| α-(1a) | 0·65 | 0·73 | 0·95 | 4·75 |

[a] In p.p.m. from internal tetramethylsilane. [b] Values in parentheses refer to hydrochloride salts.

of an equatorially orientated group in 3-substituted piperidines.[6,8] From this evidence it is concluded that γ-(1a) has the configuration *t*-2-Me, *c*-5-Me, *r*-4-OH and the preferred conformation (4) as solute in deuteriochloroform. The same has been shown to be true for γ-(1a) in the solid state.[13]

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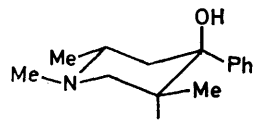
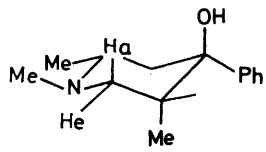


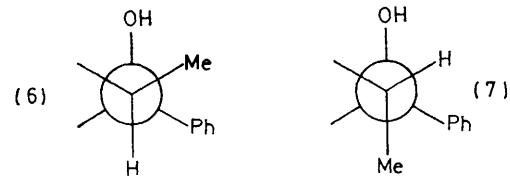

(4)

Only one of the 3-methylene signals could be resolved in the spectrum of β-(1a), but the magnitude of the measurable $^3J$ value shows axial–axial coupling to be involved, hence the 2-methyl group must be equatorially orientated (3) as in the γ-isomer. Thus, if the 4-phenyl is assumed to be equatorial and on the basis of know ledge of the configuration of γ-(1a), the β-5-methyl group




(5)

must be axial as in (5). Evidence in support is provided by chemical shift comparisons with the 3-methyl resonance of β-prodinol (2b), an analogue in which the methyl adjacent to the 4-phenyl group is known to be axial[6] (Table 2). In addition, the 5-methyl signal of β-(1a) like that of β-(2b) is almost free of virtual coupling effects, a clear doublet ($J$ 6·8 Hz) being observed at both 60 and 100 MHz. The OH signal of β-(1a) in [$^2H_6$]dimethyl sulphoxide is close to that of OH in β-prodinol, and at lower field than the OH signals of γ-(1a) and α-prodinol-(2a) (Table 2). In [$^2H_6$]dimethyl sulphoxide the predominant hydrogen-bound species are those formed between solute and solvent molecules and the OH resonance is essentially independent of concentration and small temperature variations;[14,15] its chemical shift, governed chiefly by the strength of the solute–solvent hydrogen bond, will therefore reflect the steric environment of the hydroxy-function. Since hydrogen bonding tends to deshield the OH proton,[16] then the higher field position of the γ- as compared with the β-OH signal indicates that hydrogen bonding is least effective in the γ-isomer. The 4-hydroxy-group is axial in both proposed conformations of these isomers but in the γ-form it will be hindered by a gauche 3-methyl group (6). In the β-isomer, the 3-methyl group (axial) is removed from the hydroxy-function (7) and should not impede hydrogen bonding with the solvent.



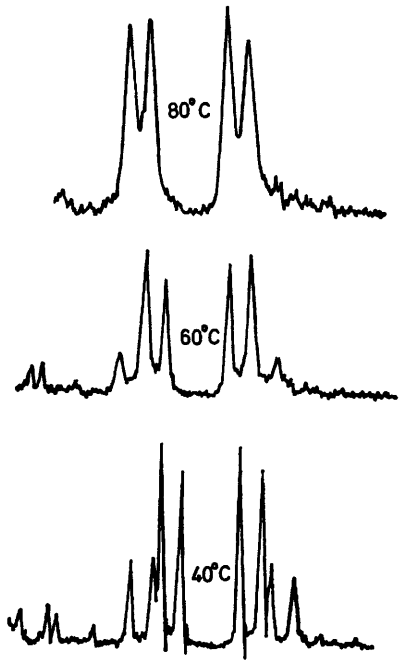

Newman projections of (1a) viewed down the C(5)–C(4) bond.

The 6-methylene signals in the spectrum of β-(1a) could not be resolved at 100 MHz but were identified as doublets ($^2J$ 12 Hz) at δ 2·68 and 2·08 p.p.m. in the spectrum of the deuteriated alcohol. Observation of a large chemical shift difference between the *ax*- and *eq*-6-H signals is consistent with the stereochemistry (5) since in this arrangement $H_a$ is deshielded by the axial 4-hydroxy-group[17] and by the axial 5-methyl group, whereas $H_e$ is shielded by the latter.[18] The multiplet adjacent to the *N*-methyl singlet remained complex in the 220 MHz spectrum of β-(1a) but the lower field 6-methylene and 2-methine signals moved apart, the former appearing as a doublet of doublets ($^2J$ 10·5, $^3J$ 3 Hz). The vicinal value is consistent with *ax–eq* coupling, as must occur if the 5-methyl group is axial (5). A well resolved one-proton doublet of doublets of similar situation (low field of all other ring proton signals) and with line separations as for the four-line signal already referred to was seen in the 100 MHz spectrum of (2b) in pyridine, and it is reasonable to assign both signals to axial protons flanked by nitrogen and *ax*-CMe as in (5).

The spectrum of β-(1a) hydrochloride in deuterium oxide, unlike that of the γ-salt, gave evidence of the presence of epimeric conjugate acids which arise as result of two modes (axial and equatorial) of proton uptake at the basic centre.[19] Both 2- and 5-methyl signals were duplicated as well as other signals, the higher

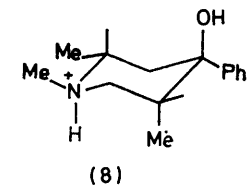
[11] E. D. Becker, *J. Chem. Educ.*, 1965, **42**, 591.
[12] R. U. Lemieux and J. D. Stevens, *Canad. J. Chem.*, 1965, **43**, 2059.
[13] W. H. De Camp, personal communication.
[14] R. J. Ouellette, *J. Amer. Chem. Soc.*, 1964, **86**, 3089.
[15] C. P. Rader, *J. Amer. Chem. Soc.*, 1969, **91**, 3248.
[16] J. A. Pople, W. B. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959.
[17] J. B. Carr and A. C. Huitric, *J. Org. Chem.*, 1964, **29**, 2506.
[18] H. Booth, *Tetrahedron*, 1966, **22**, 615.
[19] A. F. Casy, L. G. Chatten, and K. K. Khullar, *Canad. J. Chem.*, 1970, **48**, 2372.

field 2-methyl and the lower field 5-methyl doublets having the greater intensity. This interpretation is supported by the fact that a rise in the temperature (giving greater rates of proton exchange) causes the duplicate signals to merge and form single doublets of intermediate chemical shifts (Figure). Many salts of

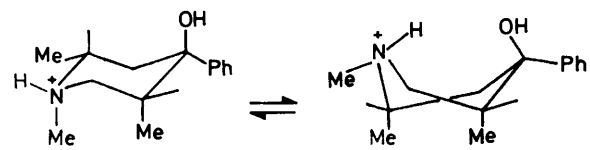



Part of the 60 MHz $^1$H n.m.r. spectrum of β-(1a) hydrochloride in deuterium oxide (plus a trace of hydrogen chloride) showing the effect of temperature on the 2- and 5-methyl resonances.

substituted piperidines fail to give n.m.r. evidence of epimeric $^+$NH isomers even in solutions of low pH, and in such cases one isomer (usually that produced by axial protonation) must be extensively favoured over the other. However, if the conjugate acid formed by equatorial protonation enables the relief of non-bonded interactions obtaining in the product of axial attack, then significant populations of the two species may be expected. Use of this principle provides corroboration of the configurational assignments made to γ- and β-(1a), as follows. Epimeric conjugate acids are not anticipated for the γ-isomer (4) because the product of equatorial protonation (*N*-methyl axial) merely introduces additional non-bonded interactions which may not be relieved by a conformational change, since any departure from (4) places the equatorial 2,5-dimethyl and 4-phenyl groups in less favourable orientations. In the β-isomer (5), the product of axial protonation (8) no doubt represents the major epimer, in spite of non-bonded interactions between N–H and 5-Me. The epimer (9), although clearly of higher energy in the chair form, may undergo a conformational change, *e.g.* to a skew-boat (as shown) or inverted chair, which reduces the non-bonded interactions of *two* axial methyl groups. On this basis the lower field 5-methyl signal (Figure) is assigned to the major isomer (8) and the higher field resonance to the minor form (9). The 5-methyl group in (8) is more subject to deshielding by the $^+$NH group than the same substituent in (9). There is evidence that β-prodinol



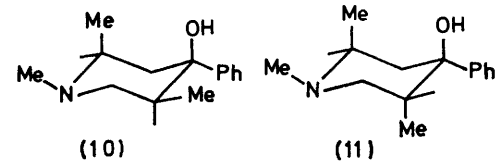

(8)




(9)

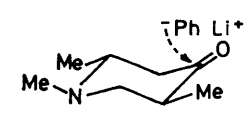
(2b) hydrochloride has a preferred skew-boat conformation in deuterium oxide,[7] and since its 3-methyl signal (δ 0·75 p.p.m.) is close to the higher field 5-methyl signal (δ 0·77) of β-(1a) hydrochloride in the same solvent it is likely that the minor epimer has a similar conformation. Adoption of the same type of conformation by (8) is improbable since it would place the *N*-methyl substituent in a less favourable orientation.

If assignments to γ- and β-(1a) are correct, the α-form must be either (10) or (11) or some conformer thereof.




(10) (11)

The smaller of the two $^3J$ values for couplings of the α-3-methylene protons (Table 1) agrees with both but the larger value of 6 Hz is too large for a gauche coupling yet too small for a diaxial interaction.[10] Structure (11) is the isomer expected from *trans*-1,2,5-trimethyl-4-piperidone (12) (the main component of the *cis–trans* mixture) because it is the inverted form of the product of axial attack by phenyl-lithium (equatorial attack gives the γ-isomer). Both α- and β-(1a) appear to have similar geometry about the C-3,C-4,C-5 half of the molecule, as judged by the near identity of 5-methyl chemical shifts in three solvents and OH resonances in [$^2H_6$]dimethyl sulphoxide (Table 2). The 6-methylene signals (unresolvable in the spectrum of the normal alcohol in [$^2$H]chloroform) were identified as doublets ($^2J$ 11 Hz) in the spectrum of deuteriated α-(1a) centred at δ 2·3 and 2·47 p.p.m. The higher field signal was resolved as a doublet of doublets ($^2J$ 11, $^3J$ 5·5 Hz) in the spectrum

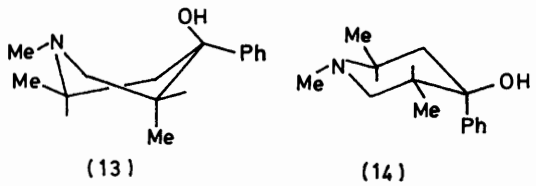



(12)

of α-(1a) run in [$^2H_5$]pyridine; the change in solvent apparently does not alter the conformation of the molecule significantly because the well defined doublet of doublets due to 3-H upfield of the *N*-methyl signal has the same separation in the two solvents. The 220 MHz spectrum of the α-alcohol showed a separation of the lower field 6-H signal and the 2-methine multiplet. The former, which appeared as an apparent narrow doublet in the 100 MHz spectrum, was a doublet of doublets with $^2J$ 11 and $^3J$ 8·5 Hz at 220 MHz. The 2-methine signal could not be resolved but its base width (30 Hz) was of the order anticipated from the 3-methylene and 2-methyl $^3J$ values, *viz.*, $3 \times 6{\cdot}5 + 4{\cdot}25 + 6{\cdot}0 = 29{\cdot}75$ Hz.

Coupling constant data for the methylene protons of α-(1a) are summarized below. The values 4·25 and 5·5 Hz fall in the range of $J_{ae}$ and (less probably) $J_{ee}$ coupling [10,20] but the higher values are typical of none of the vicinal couplings which arise in a single chair conformation. Instead they indicate that the molecule either has a preferred flexible conformation such as the

| | $^2J$ | $^3J$/Hz |
|---|---|---|
| 3-Methylene | 14·5 | 4·25, 6·0 |
| 6-Methylene | 11·0 | 5·5, 8·5 |



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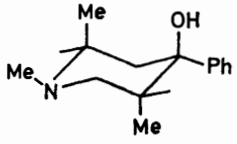
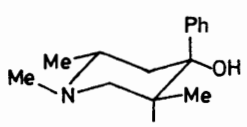
(14)



(15)

skew-boat (13), or displays a preference for more than one conformation, the $^3J$ values representing time-averaged values. On the basis of evidence for the similar geometry of the C-3, C-4, C-5 halves of the molecules of α-(1a) and β-(1a) (see before), the population of (14) in solution is likely to be small, since it places the 5-methyl and 4-hydroxy-groups in an environment markedly different from that of the same groups in β-promedol alcohol (5). A low population of the *eq*-phenyl chair (15) is also predicted because of the non-bonded interactions of the two axial methyl groups in this conformation. A flexible form such as (13) is a good candidate for the preferred conformation, however, since it provides the orientation of 4-phenyl, 4-hydroxy-, and 5-methyl substituents consistent with the chemical shift data (Table 2) and dihedral angles between vicinal C–H groups compatible with observed $^3J$ values. Preference for flexible forms is supported by the demonstration of intramolecular hydrogen bonding in α- (and β-) promedol alcohol.[5]

During this work a similar $^1H$ n.m.r. study at 100 MHz (no solvent stated) of the isomers (1a) was reported,[5] but no details of spectral analyses were given. Many of the chemical shift and coupling constant data correspond with our own provided allowance is made for the fact that the isomer designated ' α ' appears to correspond with our β-form and *vice versa*. Assignment of 2- and 5-methyl substituents as in (16) (' α ') and (17) (' β ') is made on the basis of $^3J$ couplings; some of these differ



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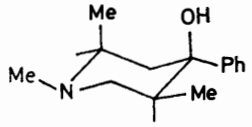
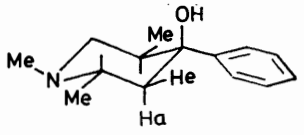


(17)

critically from our data while others could not be evaluated with certainty in the present work. The orientation of the 4-phenyl group is concluded to be axial in ' α ' (16) and equatorial in ' β ' (17) on the grounds of comparisons of observed and calculated chemical shift differences between the 3-methylene proton signals. Our conclusions about the stereochemistry of the isomers (1a) agree with the Russian report only in the case of the γ-isomer. We account for the fact that the axial 3-H signal is at lower field than the equatorial signal in the spectrum of γ-(1a) but at higher field in that of β-(1a) as follows. In the γ-isomer (18) the axial proton is deshielded by the 4-hydroxy-group [21] and the lone-pair on the nitrogen atom,[22] but its



(18)

lower field resonance (relative to the equatorial 3-H signal) is probably due to differential shielding of the two protons by the adjacent phenyl group. The aromatic and piperidine rings are probably almost perpendicular in the preferred conformation of the molecule as a result of the avoidance of non-bonded interactions between the 4-phenyl and equatorial 5-methyl substituents, support for this conclusion being provided by *X*-ray studies of α- and β-prodine.[23] In conformation (18), the axial 3-H falls within the deshielding zone and the equatorial 3-H within the shielding zone of the aromatic ring. Differential shielding in this respect should be less significant in isomers with an axial 5-methyl substituent [the orientation of the two

[20] W. A. Thomas in ' Annual Reports on NMR Spectroscopy,' ed. E. F. Mooney, vol. 1, Academic Press, London and New York, 1968, p. 44.
[21] R. U. Lemieux and J. D. Stevens, *Canad. J. Chem.*, 1966, **44**, 249.
[22] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.
[23] G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Cryst.*, 1960, **13**, 525; F. R. Ahmed, W. H. Barnes, and L. A. Masironi, *ibid.*, 1963, **16**, 237.

rings shown in (18) is no longer preferred] as is apparent from the higher field position of the axial 3-H signal in the spectrum of β-(1a), assigned the conformation (5).

Final confirmation of these interpretations of $^1$H n.m.r. data for α- and β-(1a) must await completion of the crystallographic study.

## EXPERIMENTAL

The $^1$H n.m.r. spectra were recorded with Varian A-60D or HA-100 spectrometers.

*Isomeric* 1,2,5-*Trimethyl-4-phenylpiperidin-4-ols*(1a).— 1,2,5-Trimethyl-4-piperidone (56·4 g) was added dropwise to a stirred solution of phenyl-lithium in ether (100 ml) [from lithium (6·7 g) and bromobenzene (75·4 g)] and the mixture was stirred overnight. Next day, the product was heated under reflux for 4 h, then cooled and poured on ice and glacial acetic acid (50 ml). The aqueous phase was separated, washed with ether (2 × 100 ml), and made alkaline with solid sodium hydroxide. The free base was extracted with chloroform (4 × 100 ml); the extract was dried ($Na_2SO_4$) and evaporated to give the isomeric mixture (1a) (57 g) as an oil (no ketone present as judged by i.r. spectrum). The oil was diluted with a small volume of light petroleum (b.p. 40—60°) and stored at 5°; crystals of γ-(1a) separated. These were collected and the mother liquors were diluted with more solvent. Four crops of the γ-isomer (33 g), m.p. 106—107°, were isolated in this way. It gave a hydrochloride, m.p. 159—160° (from ethanol–ether) (lit.,[24]) 107—108° for the base, 158—159° for the hydrochloride (Found: C, 65·5; H, 8·7; N, 5·3. Calc. for $C_{14}H_{22}ClNO$: C, 65·8; H, 8·7; N, 5·5%), and a *methiodide*, m.p. 223—225° (from acetone) (Found: C, 49·9; H, 6·7; N, 4·1. $C_{15}H_{24}INO$ requires: C, 49·9; H, 6·7; N, 3·9%). The residue from the light petroleum was dissolved in acetone and acidified with hydrogen chloride; β-(1a) hydrochloride (4·5 g), m.p. 233—235°, separated after storage at 5° (Found: C, 65·6; H, 8·7; N, 5·4%). The free base had m.p. 106—109° [from light petroleum (b.p. 40—60°)] [lit., 106—107° (ref. 24) and 102—103° (ref. 4) for the base, 233—236° for the hydrochloride [24]]. The β-base gave a *methiodide*, m.p. 232—234° (from acetone) (Found: C, 49·7; H, 6·7; N, 3·7%). α-(1a) Hydrochloride (6·8 g.), m.p. 125—129° [lit., 173—174° (ref. 24), 230—231° (ref. 25)] (Found: C, 65·5; H, 8·6; N, 5·4%), separated from the remaining mother liquors (acetone replaced by ethanol–ether) after storage for several weeks at 5°. Other crops of the α-hydrochloride, obtained in repetitions of the reaction, melted in the range 100—105°. The α-base, m.p. 101—102° [lit., 102—103° (ref. 24), 106—107° (ref. 25)] gave a methiodide, m.p. 278— 280° (from acetone) (Found: C, 50·0; H, 6·7; N, 4·0%).

*Chromatographic Separation.*—The crude isomeric mixture (1a) (15 g) was introduced on to a column (75 × 5 cm) of Woelm neutral alumina (750 g) prepared in chloroform. The column was eluted with the same solvent; each tenth fraction of the 200 20 ml fractions collected was examined by $^1$H n.m.r. spectroscopy and compositions (judged by 2- and 5-methyl resonances) were as follows:

| Fractions | Composition | Weight (g) |
|---|---|---|
| 31—83 | γ [a] | 5·8 |
| 84—110 | γ(δ?) [b] | 2·2 |
| 111—130 | α,[c] β [d] | 1·2 |
| 140—190 | α, β, γ | 5·0 |

[a] δ 1·09 (2-Me) and 0·62 p.p.m. (5-Me). [b] Minor doublets at δ 1·25 and 0·73 p.p.m. [c] δ 1·17 (2-Me) and 0·74 p.p.m. (5-Me). [d] δ 1·13 (2-Me) and 0·75 p.p.m. (5-Me).

Fractions flanked by samples having similar spectra were bulked. γ-(1a) was isolated from nos. 31—83 and 84—110 as free base. Fractional crystallization of the residue from nos. 111—130 (as hydrochloride) gave β-(1a) hydrochloride followed (after seeding) by the α-salt.

*Isomeric* 3,3,5-*Trideuterio*-1,2,5-*trimethyl-4-phenylpiperidin-4-ols.*— 3,3,5-Trideuterio-1,2,5-trimethyl-4-piperidone [9] (14 g) was treated with phenyl-lithium [from lithium (1·7 g) and bromobenzene (18 g)] as above. The total base in light petroleum yielded two crops of the γ-3,3,5-trideuterio-analogue of (1a) (8 g). It gave a *hydrochloride*, m.p. 152—154° [Found: C, 65·0; H(D), 9·7; N, 5·3. $C_{14}H_{19}D_3ClNO$ requires: C, 65·0; H(D), 9·4; N, 5·4%]. The residue from the mother liquors in acetone–hydrogen chloride gave β-*trideuterio*-(1a) *hydrochloride* (1·8 g), m.p. 228—229° [Found: C, 64·7; H(D), 9·4; N, 5·4%]. The α-deuteriated salt (0·3 g), m.p. 110—120° [Found: C, 64·9; H(D), 9·5; N, 5·6%] was deposited from the final residue (acetone replaced by ethanol–ether) after several weeks storage at 5°; the 5-methyl resonance of this salt at 100 MHz showed it to contain minor amounts of the β- and γ-isomers.

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[24] I. N. Nazarov, N. S. Prostakov, and N. I. Shvetsov, *Zhur. obshchei Khim.*, 1956, **26**, 2798.

[25] N. S. Prostakov and N. N. Mikheeva, *Zhur. obshchei Khim.*, 1961, **31**, 108.