Stereochemical Studies on Isomeric 1,2,5-Trimethyl-4-phenylpiperidin-4-ols: Reactions with Acyl Chlorides and Thionyl Chloride

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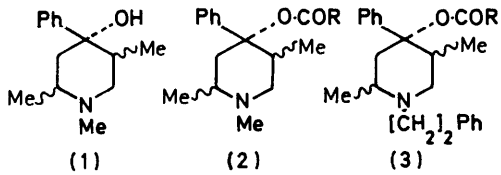
The acylation of some isomeric 2,5-dimethyl-4-phenylpiperidin-4-ols is described and ^{1}H n.m.r. features of the resultant esters are interpreted in terms of configuration and preferred conformation. Evidence of stereochemistry is also provided by the differing behaviour of 1,*t*-2,*t*-5- and 1,*t*-2,*c*-5-trimethyl-4-phenylpiperidin-*r*-4-ol towards thionyl chloride; both are dehydrated but the former gives a single product whereas the latter gives a binary mixture of alkenes. The analgesic activities of alcohols and esters related to trimeperidine in mice, as assessed by the hot-plate test, are reported.

We report the esterification and other reactions of isomeric 1,2,5-trimethyl-4-phenylpiperidin-4-ols (1) as part



(1) (2) (3)

a; R = Me b; R = Et

of a stereochemical study of the narcotic analgesic promedol [γ-(2b), trimeperidine] and its diastereoisomers.[1] Reaction of γ-, β-, and α- (1) (see preceding paper for explanation of terminology) with acetyl or propionyl chloride in boiling benzene for 12 h or more gave the ester (2) hydrochlorides; in some cases isolation of a pure product required the initial separation of unchanged alcohol by crystallization or chromatography. The m.p.s of α- and γ-(2a) hydrochloride differed from literature values (wide variations in melting behaviour

Table 1

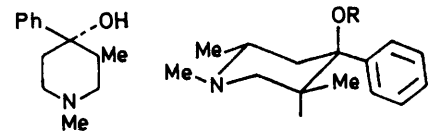
^{1}H N.m.r. characteristics of some isomeric acetates and propionates of 1,3-dimethyl-4-phenylpiperidin-4-ol (4)[3] and 1,2,5-trimethyl-4-phenylpiperidin-4-ol (1), as hydrochlorides in deuteriochloroform

Structure of parent alcohol	Isomer	N.m.r. signals of esters [a] 3- or 5-Me [b]	OAc [c]	O·CO·CH$_2$ [d]	O·CO·CH$_2$*Me* [e]
(4)	α	0·73 (0·73)	2·27	2·59	1·23
(1)	γ	0·71 (0·72)	2·25	2·58	1·23
(4)	β	1·02 (1·03)	2·09	2·38	1·07
(1)	β	0·97, 1·04 [f] (0·97, 1·02)	2·03	2·34	1·08
(1)	α	0·75 (0·77)	2·23	2·52	1·25

[a] δ in p.p.m. from internal tetramethylsilane. [b] d, *J* 6—7 Hz; propionate value in parentheses. [c] s. [d] q, *J* 6—7 Hz. [e] t, *J* 6—7 Hz. [f] Epimer signals, solvent $CDCl_3$ plus CF_3·CO_2H (1 drop).

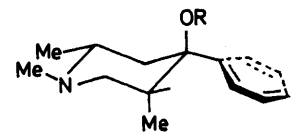
are reported, particularly for α-promedol hydrochloride),[2] but the compounds were spectroscopically pure, each isomer having a characteristic ^{1}H n.m.r. spectrum.

The *N*-phenethyl derivatives (3), obtained by treating the lithium salt of 2,5-dimethyl-1-phenethyl-4-piperidone with the appropriate acid anhydride, were the steric analogues of promedol (γ-) as judged from their ^{1}H n.m.r. features. Certain proton chemical shifts of γ- and β-esters (2) were closer to corresponding ones of the previously studied esters of α- and β-prodinol (4), respectively (Table 1), a fact which supports the prior assignments of (5a) (γ-) and (6a) (β-) as preferred conformations of the parent alcohols.[1] The higher field positions of the β-OAc and β-O·COEt resonances are of particular significance; in conformation (6b) the R proton groups



(4) (5)

α; *c*-3-Me, *r*-4-OH a; R = H
β; *t*-3-Me, *r*-4-OH b; R = COMe or COEt



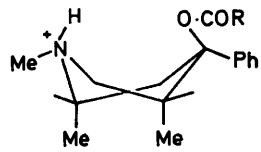
(6)

will spend some of their time above the plane of the phenyl ring (*i.e.* within the aromatic shielding zone) while those of (5b) will lie closer to the aromatic plane and tend to be deshielded by the phenyl group.[3-5]

As in the case of spectra of hydrochlorides of the promedol alcohols,[1] only those of the β-esters (2) showed evidence of epimeric conjugate acids in the duplication of 1-, 2-, and 5-methyl resonances. In deuteriochloroform containing a trace of trifluoroacetic acid, epimer populations were almost equal (as judged by signal intensities), but in deuterium oxide similarly acidified the isomer with the higher field 5-methyl chemical shift slightly preponderated. On the basis of previous arguments,[1,3] the major epimer is assigned the skew-boat conformation (7), and the epimer with the lower field 5-methyl resonance, conformation (8) (5-Me is

[1] A. F. Casy and K. M. J. McErlane, preceding paper.
[2] N. S. Prostakov and N. N. Mikheeva, *Russ. Chem. Rev.*, 1962, **31**, 556.
[3] A. F. Casy, *J. Medicin. Chem.*, 1968, **11**, 188.
[4] A. F. Casy, *Tetrahedron*, 1966, **22**, 2711.
[5] A. F. Casy, L. G. Chatten, and K. K. Khullar, *J. Chem. Soc.* (*C*), 1969, 2491.

closer to the deshielding influence of ^{+}NH in this form). The fact of the ester resonances being the same in spectra of the two epimers supports these conclusions since the environments of the ester substituents differ little in conformers (7) and (8).



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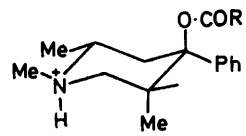
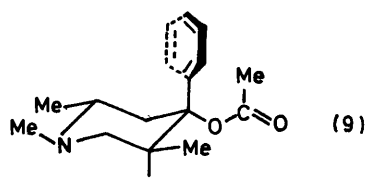


(8)

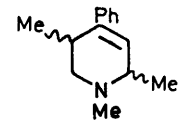
The OAc resonance of the α-base (2a) (δ 1·95 p.p.m.) was at significantly higher field than those of the β- and γ-esters (δ 2·02 and 2·17, respectively), a result which indicates the α-ester substituent to be substantially shielded by the aromatic group. In the spectrum of α-(2a) hydrochloride the OAc signal had moved to δ 2·23 p.p.m. This large downfield shift following protonation of the basic centre was not seen in spectra of other isomers and indicates that the α-ester suffers a major conformational change when the salt is formed. Another unusual feature, providing further evidence in the last respect, is the fact that the 5-methyl signal (δ 1·06 p.p.m.) of α-(2a) moved *upfield* to δ 0·75 when the base was protonated. In all other cases the 5-methyl shift (base ⟶ hydrochloride) was to lower field. This effect was also apparent in spectra of α-promedol alcohol (1), although smaller in extent [5-methyl chemical shifts: δ 0·75 (base in $CDCl_3$) and 0·68 (base in $CDCl_3$–$CF_3{\cdot}CO_2H$); 0·65 (base) and 0·53 p.p.m. (hydrochloride) in $(CD_3)_2SO$]. α-Promedol alcohol (1) has the configuration *c*-2-Me, *t*-5-Me, *r*-4-OH,[1,6] and the unusual chemical shift of the corresponding acetate is accounted for if the base has a significant population of the axial phenyl conformer (9). In this arrangement, the aromatic ring



(9)

should adopt a preferred orientation at right angles (or nearly so) to the mean plane of the piperidine ring so as to avoid interactions with the 2,6-diaxial hydrogen atoms;[7] the equatorial 5-methyl group is then close to the aromatic plane and should be deshielded in consequence while the OAc group will be shielded as it rotates above the plane of the aromatic ring. The chemical shift data show that (9) is not favoured for α-esters after protonation.

Since the differing reactions of thionyl chloride with the diastereoisomeric prodinols (4) provide evidence of configuration,[8] reactions of γ- and β-(1) with this reagent were investigated. The γ-alcohol, like α-prodinol, gave a mixture of tri- and tetra-substituted alkenes, (10) and (11), whereas β-(1) gave a single isomeric form of (10) as sole product. The alkene (10) was partially converted into (11) after equilibration in acid, hence the former derivative must be the initial dehydration product of β-(1). These results corroborate the assigned configurations if the alkene formations are assumed to proceed *via* formation of a chlorosulphite followed by



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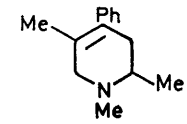
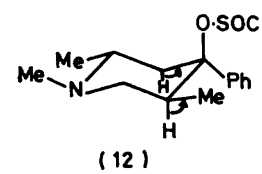


(11)

trans-diaxial elimination of SO_2 and HCl. Thus, in the γ-alcohol (12), two *trans*-diaxial pathways are open to the elimination process, whereas only one is available in the case of the β-isomer (13). Acid-catalysed dehydration of β-(4) under mild conditions similarly led to the exclusive formation of a trisubstituted alkene.[9] Differences in the reaction products derived from β-(1) and β-(4) after thionyl chloride treatment (the latter is not



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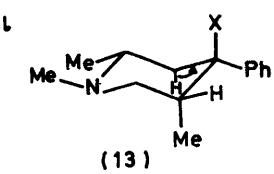
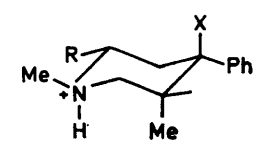


(13)

X = O·SOCl or Cl

dehydrated but yields a 4-chloro-derivative with retention of configuration)[8,10] must be due to stability differences between (14a) and (14b); these may arise because conformational isomers of (14a) which relieve non-bonded interactions of the axial 4-X and 3-methyl



(14)

a; R = H X = O·SOCl or Cl
b; R = Me

groups are less liable to arise in the case of (14b) because these place methyl adjacent to nitrogen in less favourable orientations. The alkene obtained from β-(1) should have the stereochemistry (15) if the configurational assignment of the precursor is correct. The ^1H n.m.r. spectrum of (15) hydrochloride gave evidence of the separate existence of epimeric conjugate acids, duplicate 1-, 2-, and 5-methyl resonances being seen; each pair of

[6] W. H. DeCamp, personal communication.
[7] N. L. Allinger, J. Allinger, M. A. DaRooge, and S. Greenburg, *J. Org. Chem.*, 1962, **27**, 4603; N. L. Allinger and M. T. Tribble, *Tetrahedron Letters*, 1971, 3259.
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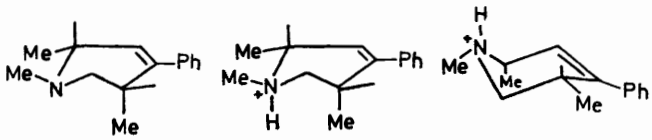
[9] A. F. Casy, A. H. Beckett, and M. A. Iorio, *Tetrahedron*, 1967, **23**, 1405.
[10] A. F. Casy, M. M. A. Hassan, and A. P. Parulkar, *Canad. J. Chem.*, 1969, **47**, 3133.

these coalesced to a broad ill-resolved band when the temperature was raised or in the presence of deuterium oxide. Preferred conformations of the *trans*- and *cis*-1,5-dimethyl epimers are assigned as (16) and (17) respectively on the basis of previous studies of analogues



(15) (16) (17)

lacking a 2-methyl substituent,[11] with the lower field 5-methyl resonance (δ 1·12 p.p.m.) attributed to the *trans*- and the higher field signal (δ 0·93) to the *cis*-isomer.

TABLE 2

Hot-plate ED_{50} values in mice of piperidin-4-ols (1) and related esters after subcutaneous injection

Compound	ED_{50} (mg per kg)
γ-(1)	56·3
γ-(2a)	6·2
γ-(3a)	2·8
β-(1)	35·4
β-(2a)	0·8
α-(2a)	2·6
Pethidine	4·7

The hot-plate ED_{50} values in mice for the propionates (2b) and (3b) have been reported;[12] data for isomeric alcohols (1) and acetates (2a) and (3a) are given in Table 2. Relative potencies of alcohols, acetates, and propionates in the series and the potency-raising influence of replacing *N*-methyl by *N*-phenethyl are typical of the 4-phenylpiperidine class of narcotic analgesic.[13,14] In both acetates and propionates of (1), the isomeric potency order in mice was β > α > γ; the significance of these data will be discussed elsewhere.

EXPERIMENTAL

The ^1H n.m.r. spectra were recorded with a Varian A-60D spectrometer.

Esters of Isomeric 1,2,5-*Trimethyl*-4-*phenylpiperidin*-4-*ols*.—Acetyl chloride (3·5 g) was added to γ-(1) (5 g) in benzene (50 ml); the mixture was heated under reflux for 12 h and then evaporated. The free base was recovered from the residual salt and treated with light petroleum (b.p. 40—60°). Crystals of γ-(1) (0·3 g) which separated were removed; the residue was acidified with ethanolic hydrogen chloride and diluted with ether to give γ-(2a) hydrochloride (1·3 g), m.p. 223—226° (lit.,[15] 223—224°) (Found: C, 64·7; H, 8·4. Calc. for $C_{16}H_{24}ClNO_2$: C, 64·5; H, 8·1%). The γ-propionate (2b) hydrochloride was similarly prepared, by use of propionyl chloride, except that the salt from the benzene solution was fractionally crystallized directly to give a product (3·8 g), m.p. 202—203° (lit.,[2] 198—199°; lit.,[16] 222—223°) (Found: C, 65·1; H, 8·7. Calc. for $C_{17}H_{26}ClNO_2$: C, 65·5; H, 8·4%). A mixture of β-(1) (0·5 g), acetyl chloride (1·6 g), and benzene (100 ml) was stirred for 4 h and then heated under reflux for 12 h. The product was evaporated and the residue was dissolved in methanol–ether; β-(2a) *hydrochloride* (0·4 g), m.p. 181—183°, then separated (Found: C, 64·5; H, 8·1; N, 4·6. $C_{16}H_{24}ClNO_2$ requires C, 64·5; H, 8·1; N, 4·7%). The following esters were similarly obtained: β-(2b) hydrochloride, m.p. 180—183° (lit.,[15] 181—182°) (Found: C, 65·5; H, 8·4%) (6 h room and 48 h reflux temperature); α-(2a) *hydrochloride*, m.p. 197—198° (Found: C, 64·25; H, 8·2; N, 4·5%), and α-(2b) hydrochloride, m.p. 184—185° (lit. ranges[2,15] vary from 98—102° to 227—229°) (Found: C, 65·4; H, 8·1; N, 4·2. Calc. for $C_{17}H_{26}ClNO_2$: C, 65·5; H, 8·4; N, 4·5%). In the last case the reaction product (as free base) was chromatographed on neutral alumina and eluted with 3 : 1 chloroform–ether. The ester salt was derived from initial fractions which were free from α-(1) (i.r. evidence).

2,5-*Dimethyl*-1-*phenethyl*-4-*phenylpiperidin*-4-*ol and Esters*.—The reaction between 2,5-dimethyl-1-phenethyl-4-piperidone (10 g)[16] and phenyl-lithium [from lithium (0·7 g) and bromobenzene (9·4 g)[1]] gave 2,5-*dimethyl*-1-*phenethyl*-4-*phenylpiperidin*-4-*ol* (15 g), m.p. 98—100° [from chloroform–light petroleum (b.p. 40—60°)] (Found: C, 81·5; H, 8·6. $C_{21}H_{27}NO$ requires C, 81·5; H, 8·8%), δ($CDCl_3$) 0·64 and 1·03 p.p.m. (d, *J* 6—7 Hz, 5- and 2-Me). It gave a *hydrochloride*, m.p. 198—199° (from ethanol–ether) (Found: C, 72·9; H, 8·1. $C_{21}H_{28}ClNO$ requires C, 72·9; H, 8·2%), δ($CDCl_3$) 0·63 and 1·1 p.p.m. (d, *J* 6—7 Hz, 5- and 2-Me).

The reaction between the 4-piperidone and phenyl-lithium was repeated on the same scale. Half the product was poured on to propionic anhydride (20 g) and the mixture was stirred for 2 h. Water was added, followed by aqueous ammonia (to pH 8), and the free base was extracted with chloroform (2 × 75 ml) and recovered as usual. The product (5 g) was chromatographed on neutral alumina and eluted with chloroform. The initial 100 ml of eluate, free from the piperidin-4-ol (i.r. evidence), was evaporated and the residue was dissolved in ethanolic hydrogen chloride and ether to give the *propionate* (3b) *hydrochloride* (1·5 g), m.p. 173—176° (Found: C, 71·7; H, 8·0. $C_{24}H_{32}ClNO_2$ requires C, 71·7; H, 8·0%), δ($CDCl_3$) 1·58 and 0·73 (d, *J* 6—7 Hz, 2- and 5-Me), 1·23 (t, *J* 7 Hz, O·CH_2*Me*), and 2·57 p.p.m. (q, *J* 7 Hz, OCH_2Me). Acetic anhydride (20 g) was added to the remaining half of the lithium complex and the product was stirred for 2 h. The solid which separated was collected and treated with aqueous ammonia, and the free base was isolated as usual. This base (3 g), with ethanolic hydrogen chloride and ether, gave the *acetate* (3a) *hydrochloride* (0·5 g), m.p. 221—223° (Found: C, 70·9; H, 8·0. $C_{23}H_{30}ClNO_2$ requires C, 71·2; H, 7·8%), δ($CDCl_3$) 1·55 and 0·73 (d, *J* 6—7 Hz, 2- and 5-Me) and 2·26 p.p.m. (s, OMe).

Action of Thionyl Chloride upon the Piperidinols β-(1) *and* γ-(1).—Freshly distilled thionyl chloride (0·6 g) was added to β-(1) (0·44 g) in chloroform (50 ml); the mixture was heated under reflux for 4 h and evaporated. The residue was crystallized from ethanol–ether to give (10) *hydrochloride* (0·4 g), m.p. 178—179° (Found: C, 70·7; H, 8·4; N, 5·9. $C_{14}H_{20}ClN$ requires C, 70·7; H, 8·5; N, 5·9%), $\lambda_{max.}$ (EtOH)

[11] A. F. Casy, A. H. Beckett, M. A. Iorio, and H. Z. Youssef, *Tetrahedron*, 1965, **21**, 3387.
[12] A. F. Casy and K. McErlane, *J. Pharm. Pharmacol.*, 1971, **23**, 68.
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[14] A. F. Casy, *Progr. Medicin. Chem.*, 1970, **7**, part 2, 229.
[15] I. N. Nazarov, N. S. Prostakov, and N. I. Shvetsov, *Zhur. obshchei Khim.*, 1956, **26**, 2798.
[16] M. M. A. Hassan and A. F. Casy, *Org. Magn. Resonance*, 1970, **2**, 197.

242 nm (log ε 3·92), δ(base in $CDCl_3$) 5·53 (m, vinylic proton) and 1·07 and 0·83 p.p.m. (d, *J* 6—7 Hz, 2- and 5-Me) (base from total hydrochloride had an identical ^1H n.m.r. spectrum). The base (10) gave a *methiodide*, m.p. 119—121° (from acetone) (Found: C, 52·7; H, 6·7; N, 3·75. $C_{15}H_{22}IN$ requires C, 52·5; H, 6·5; N, 4·1%), δ[$(CD_3)_2SO$] 3·24 and 3·64 (s, NMe) and 1·56 and 1·03 p.p.m. (d, *J* 6—7 Hz, 2- and 5-Me). The base derived from γ-(1) (2·2 g) after similar treatment with thionyl chloride (2·4 g) was a mixture of (10) and (11): δ($CDCl_3$) 1·55br p.p.m. (s, vinylic Me) plus signals due to (10). It gave a hydrochloride (isomer mixture), m.p. 174—179° (Found: C, 70·5; H, 8·3; N, 6·0%). The reaction between α-prodinol [α-(4)] and thionyl chloride as above also led to a mixture of tri- and tetra-substituted alkenes; δ(base in $CDCl_3$) 5·75 (m, vinylic proton) and 1·57br p.p.m. (s, vinylic Me).

This work was supported by the Medical Research Council of Canada. We thank Dr. E. L. May, National Institute of Health, Bethesda, for the biological assays.

[1/1105 *Received, June 30th,* 1971]