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STEREOCHEMISTRY OF HYDROBORATION OF 3(or 5)-METHYL-4-PHENYL-1,2,5,6-TETRAHYDROPYRIDINES

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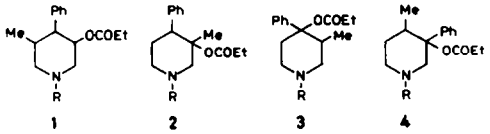
Abstract—Hydroboration of N-substituted 5 - methyl - 4 - phenyl - 1,2,5,6 - tetrahydropyridines gave, as a sole product, the 5-methyl-4-phenyl-3-piperidinols, while the 3 - methyl - 4 - phenyl - 1,2,5,6 - tetrahydropyridines gave the 3-methyl-4-phenyl-3-piperidinols together with the 4-boryl-3-methyl-4-phenylpiperidine amine boranes. Structural and configurational assignments were made through the analysis of spectral data (IR, ^{1}H NMR and MS).

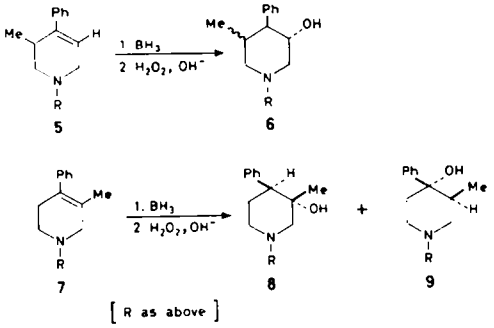
In the course of studies on structure-activity relationships of narcotic piperidine derivatives we were interested in the synthesis of some new esters of 4-phenyl-3-piperidinols of structure **1** and **2**, which can be viewed either as analogues of **3**, potent analgesics related to the reversed ester of pethidine (prodine-type compounds)[1,2] or **4** which are devoid of analgesic properties up to a dose of 100 mg/kg (hot-plate test in mice).[3]

The present paper describes the synthesis of these compounds through hydroboration of the tetrahydropyridines **5** and **7**. The latter were prepared by dehydration of 3 - methyl - 4 - phenyl - 4 - piperidinols with a mixture of acetic and hydrochloric acids.[4] The hydroboration of **5**, followed by oxidation of the intermediate organoborane with alkaline hydrogen peroxide, gave the piperidinol **6** by a *cis*-hydration mechanism.[5] From the hydroboration of the olefin **7** both piperidinols **8** and **9** could be expected as a result either of a *cis*-hydration mechanism or of electronic factors (the +M effect of 4-Ph and +I effect of 3-Me favouring **8** and **9** respectively and the two directions of attack were verified experimentally. Nevertheless while the piperidinol **8** was isolated as free base after alkaline oxidation of the intermediate organoborane, the organoborane **10**, was the final product of the reaction (R=CH_2Ph or CH_2CH_2Ph).

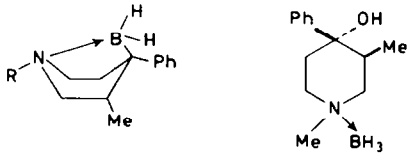


These carboboranes were particularly stable to further oxidation because the structure **10** was stabilized through boron-piperidine N-bonding (formation of an internal salt with a cyclic boat conformation). This cyclization occurred when the nitrogen lone pair occupied an axial position in the transition state, and attainment of this active conformation was facilitated since the N-benzyl and N-phenethyl groups were in equatorial positions.[6]

The absence of an analogous carboborane derivative as a final product of the hydroboration of **7a** could not be due to a strong decrease in the population of the conformer with an axially oriented lone pair; the axial-equatorial free energy difference between the lone pair and the N–Me group was about 0·65 kcal/mol, in favour of the Me group equatorial, as reported by Jones *et al.*[7] The isolation of the



amine borane **11** together with the piperidinol **9a** accounted for the absence of the carboborane **10a** in this hydroboration. The tetrahydropyridine **7a**, being more basic than the corresponding **7b** and **7c** by the +I contribution of the Me group, formed a stable amine borane salt before borane addition to the double bond. The cleavage of the C–B bond, no more stabilized through the N–B bonding as in **10**, occurred easily in the subsequent alkaline oxidation treatment. The amine borane **11**, once formed, was partially converted to the free piperidinol base **9a** in the alkaline medium of the oxidation step or by further alkaline treatment at reflux temperature after isolation.

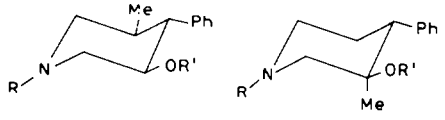


The intermediate carboboranes leading to piperidinols **6** and **8** could not be stabilized through N–B bonding, the C-3-BH_2 group being far from nitrogen (see conformations **12** and **13** with C-3-BH_2 instead of C-3-OR') and a cyclic internal salt obtained through inversion of chair conformation was highly unfavoured on thermodynamic grounds.

The new synthesized compounds were identified on the basis of elemental analyses, IR, ^{1}H NMR and mass spectroscopy. Acylation of these piperidinols with acid anhydride gave the corresponding esters.

Structural assignments. The piperidinols **6** were assigned a *c* - 5 - methyl - *t* - 4 - phenyl - *r* - 3 - hydroxy

configuration (12) on the basis of ^{1}H NMR and IR evidences. The C-3-H signal, a distinct multiplet in all spectra examined (Table 1) moved to lower field by acylation of the OH group as a result of acylation shift,[8] $\Delta\delta$ being 1·40 ppm as expected for secondary alcohols. The band width of *ca.* 30 Hz (separation of the external peaks) ($W_H \sim 20$ Hz) is typical of an axial proton receiving two $^3J_{a/a}$ and one $^3J_{a/e}$ coupling contributions and consequently of an equatorial C-3-OH.[9] The equatorial orientation of the OH group was also confirmed by the presence of a sharp band at 3610 cm^{-1} in the IR spectrum of **6a** in CCl_4 ($4·4 \times 10^{-3}$ M), typical of free OH form.[10] The C-5-Me signal was an unsymmetric doublet (Table 1) which did not suffer any downfield shift when the base was protonated, confirming its equatorial orientation. Downfield shifts seen in the signal of C-Me groups in 1-3 relation with the N atom, after protonation, was used as a criterion to differentiate between axial and equatorial Me groups.[11] With the C-3-OH group equatorial also the C-4-Ph equatorial orientation was anticipated, the hydroboration-oxidation reaction being a *cis*-hydration mechanism with retention of configuration.



12 13

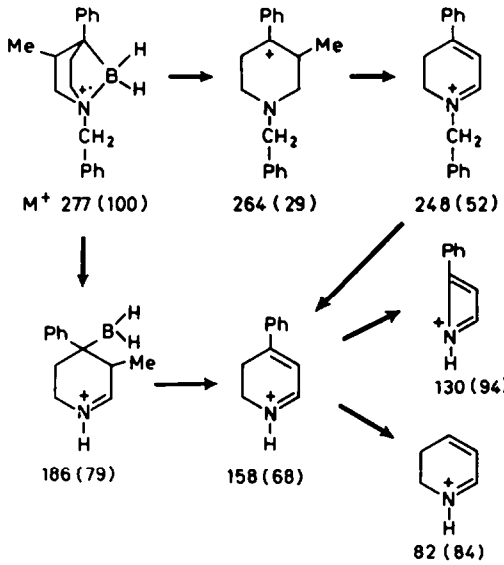
The piperidinols **8** were assigned a *t* - 4 - phenyl - *r* - 3 - hydroxy configuration (**13**) on the basis of an analysis of their ^{1}H NMR and IR data as described below. (a) Conversion of the bases to the hydrochloride salts caused a δ 0·18 deshielding of the C-3-Me signal in DMSO-d_6 and δ 0·27 in $CDCl_3$; this effect was indicative of a 1,3-diaxial interaction between the C-3-Me and the N–H group.[11,12] (b) The presence of a sharp band at 3600 cm^{-1} in the IR spectrum of **8a** in CCl_4 ($8·28 \times 10^{-3}$ M), characteristic of a free OH (equatorial), confirmed this evidence. (c) The N-benzyl methylene protons of **8b** (Table 1) gave a closely spaced AB quartet and the magnetic non-equivalence of these protons was reported as evidence of the presence of an axially oriented 3-methyl substituent.[13,14]

Borane derivatives. The structure of **10** as an internal salt was corroborated by the comparison of the ^{1}H NMR chemical shifts of the N-benzyl and N-phenethyl protons with those of the corresponding piperidinol bases. The N-benzyl methylene protons of **10b** resonated at δ 4·00 (in corresponding piperidinol bases the same protons resonated in the range δ 3·40–3·60[3,15]). The ethylene protons of the phenethyl group of **10c** gave a main peak at δ 3·03 (in corresponding piperidinol bases the same protons resonate around δ 2·70–2·75[3,15]). This downfield shift reflected the decrease of electron density and consequently the reduced contribution to shielding of the N atom when its lone pair of electrons was shared with the B atom. This effect is similar to that seen when piperidines are converted to hydrochloride salts. In these, the chemical shifts of the N-substituents were downfield with respect to those in the corresponding bases as a result of increased deshielding by positively charged nitrogen.[15,16]

The amine borane **11** showed a singlet at δ 2·53 for the N–Me protons, while the same protons gave a singlet at δ 2·25 in the corresponding piperidinol base **9a**; again this downfield shift reflected the transfer of electrons away from the N atom and toward the B atom.

The mass spectra of **10b** and **10c** displayed a molecular ion peak of very high relative intensity (M^+ 277, 100% for **10b**, M^+ 291, 61% for **10c**). This, together with the fact that the piperidinol **9b** displayed a small peak for the parent ion (M^+ 281, 21%), even absent in the spectrum of **9c**, further supported the stabilization attained by the molecular ion through the cyclic bridge structure.

Compound **10b** underwent two main fragmentations upon electron impact (Scheme 1): (a) hydrogen transfer and elimination of the N-benzyl group (*m/e* 186); (b) loss of BH_2 to *m/e* 264, which further fragmented to *m/e* 248 by loss of CH_3 and H. The mass 186 ion further fragmented to *m/e* 158 by loss of BH_2 and CH_3 and the latter ion decomposed by loss of C_2H_4 to the mass 130 ion, or by loss of C_6H_5 and H migration to *m/e* 82, 5,6-dihydropyridine ion. Other major fragments are at *m/e* 91, tropylium ion (100%); 77, phenyl ion (26%) and 42, $CH_2{=}\overset{+}{N}{=}CH_2$ (28%). Difference in the fragmentation of **10c** compared to that of **10b** appeared to be related particularly to the N-phenethyl substituent; the initial fragmentation pattern being characterized by the loss of a tropylium ion, *m/e* 200 (M^+–C_7H_7, 21%). The latter decomposed further by loss of BH_2 and H to mass 186 ion (67%). Other major fragments are at *m/e* 158, 4 - phenyl - 5,6 - dihydropyridine ion (100%); 144, 1 - methyl - 4 - phenylazacyclobutadiene ion (56%); 130, 2-phenylazacyclobutadiene ion (100%); 105, phenethyl ion (58%); 91, tropylium ion (43%); 77, phenyl ion (21%) 42, $CH_2{=}\overset{+}{N}{=}CH_2$ (42%).



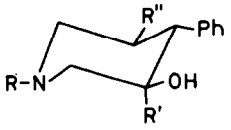
Scheme 1. Fragmentation pattern of **10b** (% relative intensities in parenthesis)

Biological results. The analgesic activity of the propionyl ester of **6a** and **8a** was examined by the hot-plate test in mice using subcutaneous injection.[17] Both the esters did not exhibit any analgesic activity up to a dose level of 100 mg/kg.

EXPERIMENTAL

M.ps (uncorrected) were taken in a Büchi-Tottoli capillary m.p. apparatus. The OH absorption region of IR spectra was measured on a Perkin-Elmer 225 spectrometer, using IR silica cells (path-length 1-2 cm). ^{1}H NMR spectra were recorded with a Varian T-60 spectrometer. Mass spectra were determined on a Perkin-Elmer 271 spectrometer, ionizing energy 70 eV.

Table 1. ^{1}H NMR chemical shifts (δ)[a] of N - substituted - 3(or 5) - methyl - 4 - phenylpiperidin - 3 - ols and related esters



Compound	R	R'	R''	3-H	3-Me	5-Me	N-R
6a	Me	H	Me	3·80sx W_H 20	—	0·62d[b]	2·25s
Acetyl-**6a**	Me	H	Me	5·20sx W_H 20	—	0·66d[b]	2·33s
Propionyl-**6a**	Me	H	Me	5·16sx W_H 24	—	0·68d[b]	2·33s
6b	CH_2Ph	H	Me	3·86sx W_H 18	—	0·63d	3·58s (CH_2Ph)
6c	CH_2CH_2Ph	H	Me	3·90sx W_H 20	—	0·66d	2·76m[c] (CH_2CH_2Ph)
8a	Me	Me	H	—	1·12s	—	2·33s
8a (DMSO-d_6)	Me	Me	H	—	0·96s	—	2·18s
8a-HCl (DMSO-d_6)	Me	Me	H	—	1·14s	—	2·76d (Me-$\overset{+}{N}$-H), J3
Propionyl-**8a**	Me	Me	H	—	1·46s	—	2·33s
Propionyl-**8a** -HCl	Me	Me	H	—	1·73s	—	2·94d (Me-$\overset{+}{N}$-H), J5
8b	CH_2Ph	Me	H	—	1·12s	—	3·65, 3·53, Abq (CH_2Ph)
8c	CH_2CH_2Ph	Me	H	—	1·12s	—	2·75 m[c] (CH_2CH_2Ph)

[a] From internal TMS in $CDCl_3$, unless otherwise stated (s: singlet, d: doublet, q: quartet, sx: sextet, m: multiplet.

[b] Unsymmetrical doublet.

[c] Main peak of multiplet.

[d] **8a**-HCl was little soluble in $CDCl_3$ and $\Delta\delta$(HCl-base) of C-3-Me was determined in DMSO-d_6.

Table 2. Substituted 3-piperidinols and piperidine amine boranes

Compound	Form	M.p.	Mol. formula	Found % C	Found % H	Found % N	Required % C	Required % H	Required % N
6a	HCl	236–238°[a]	$C_{13}H_{20}ClNO$	64·33	8·32	5·70	64·57	8·33	5·78
6b	HCl	260–261°[b]	$C_{19}H_{24}ClNO$	71·64	7·57	4·30	71·78	7·60	4·40
6c	HCl	258–259°[b]	$C_{20}H_{26}ClNO$	72·63	7·74	4·28	72·40	7·89	4·22
Acetyl-**6a**	Picrate	151–152°[b]	$C_{21}H_{24}N_4O_9$	52·94	5·08	11·76	52·69	4·94	11·65
Propionyl-**6a**	Picrate	164–166°[b]	$C_{22}H_{26}N_4O_9$	53·73	5·30	11·42	53·87	5·34	11·42
8a	HCl	235–236°[b]	$C_{13}H_{20}ClNO$	64·50	8·52	5·78	64·57	8·33	5·78
8b	HCl	247–248°[a]	$C_{19}H_{24}ClNO$	72·03	7·67	4·31	71·78	7·60	4·40
8c	HCl	258–259°[b]	$C_{20}H_{26}ClNO$	72·29	7·84	4·35	72·40	7·89	4·22
Propionyl-**8a**	HCl	231–232°[a]	$C_{16}H_{24}ClNO_2$	64·79	8·22	4·81	64·52	8·12	4·70
10b	—	113–114°[a]	$C_{19}H_{24}BN$[c]	81·97	8·69	4·95	82·32	8·72	5·05
10c	—	137–138°[d]	$C_{20}H_{26}BN$[e]	88·44	8·99	4·85	82·48	9·01	4·88
11	—	147–147°[b]	$C_{13}H_{22}BNO$[f]	71·48	10·40	6·10	71·25	10·11	6·38

[a] From EtOH–Et_2O. [b] From EtOH. [c] B%: Found 3·82: reqd. 3·90. [d] From EtOH–$CHCl_3$. [e] B%: found 3·94; reqd. 3·71. [f] B%: Found 4·93; reqd. 4·93.

N - *Substituted* - 5 - *methyl* - 4 - *phenyl* - (**5**) *and* 3 - *methyl* - 4 - *phenyl* - 1,2,5,6 - *tetrahydropyridines* (**7**). A mixture of N-substituted 3 - methyl - 4 - phenyl - 4 - piperidinol[16] (0·04 mole), conc. HCl (33 ml) and glacial AcOH (62 ml) was heated under reflux for 12 or 70 hr. The soln was concentrated to half volume, made alkaline with aqueous ammonia and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give a crude mixture of **5** and **7** (the olefin **5** prevailing after shorter heating period, while **7** was the major component of the mixture after prolonged heating periods[4]). The mixture was chromatographed: the N–Me derivatives on alumina (neutral, activity 3) with light petroleum (b.p. 30–50°)–ether 1:1 as eluant; the N-benzyl- and N-phenethyl derivatives on silica gel with light petroleum-ether 2:1 as eluant. The purity of the fractions was checked by TLC (same systems as for columns), spots detected by Dragendorff's reagent. In every case the tetrahydropyridines **5** were the more readily eluted isomers. New compound was **7c**, hydrochloride m.p. 228–229° from EtOH–Me_2CO. (Found: C, 76·82; H, 7·70; N, 4·48. $C_{20}H_{24}ClN$ requires: C, 76·54; H, 7·70; N, 4·46%).

N - *Substituted* - c - 5 - *methyl* - t - 4 - *phenylpiperidin* - r - 3 - *ols* (**6**). A 1 M soln of diborane in THF[5b] (20 ml) was added dropwise to an ice-cooled and stirred soln of **5** (20 mmole) in 20 ml THF.

After addition, the mixture was stirred 2 hr at 0°, then 2 hr at room temp. Under ice-cooling excess diborane was decomposed carefully with water (2 ml) and the intermediate organoborane oxidized by addition of 5 ml 6 N NaOH followed by addition of 5 ml 30% H_2O_2 while the temp. was allowed to rise to 50–60°. Stirring was continued for 2 hr. The THF was removed under reduced pressure, and the aqueous soln extracted with ether. The extract was dried (Na_2SO_4), evaporated to leave a light yellow oil which was converted to the hydrochloride salt; yield 70–80%.

Acyl derivatives of **6a**. These were prepared by refluxing for 3 hr the piperidinol **6a** (0·5 g) with Ac_2O (1 ml), pyridine (0·5 ml) and toluene (10 ml); or propionic anhydride, pyridine and xylene in the same proportions. The mixture was evaporated under reduced pressure, made alkaline with aqueous ammonia and extracted with ether. The extract was dried (Na_2SO_4), evaporated to leave a residue which was distilled in a ball tube oven (80–90°/0·05 mm Hg). These esters were characterized as picrates. They gave the corresponding parent piperidinol hydrochlorides rather than stable ester hydrochlorides on treatment with ethereal hydrochloric acid.

1 - *Benzyl(or* 1 - *phenethyl)* - 3 - *methyl* - t - 4 - *phenylpiperidin* - r - 3 - *ols* (**8**) *and* 1 - *benzyl(or* 1 - *phenethyl)* - 4 - *boryl* - 3 - *methyl* - 4 - *phenylpiperidine amine boranes* (**10**). A 1 M soln of diborane in THF (68 ml) was added dropwise to an ice-cooled, stirred soln of **7b** (9 g, 34 mmole). After addition, the mixture was stirred 2 hr at 0°, then 2 hr at room temp. Under ice-cooling excess diborane was decomposed with water (4 ml) followed by addition of 6 N NaOH (10 ml) and 30% H_2O_2 (10 ml). Temp. was allowed to rise to 50°, then the soln was stirred for an additional hr at this temp. The THF was evaporated under reduced pressure and the aqueous soln extracted with chloroform. The dried extract was evaporated to leave a residue which was extracted with cold ether. On evaporation the ether extract yielded mainly **8b**, which was purified through a column of alumina (neutral, activity 3) with light petroleum (b.p. 30–50°)-ether 1:1 as eluant, and characterized as hydrochloride, yield 30–40%. The residue left after extraction with ether was refluxed with ether-acetone, on cooling, crystals (1·8 g) were obtained. Recristallization from Et_2O–EtOH or sublimation under vacuum (130–140°/0·05 mm Hg) afforded pure **10b**, m.p. 113–114°.

The piperidinol **8c** and the derivative **10c** were obtained in the same way from **7c**.

1,3 - *Dimethyl* - t - 4 - *phenylpiperidin* - r - 3 - *ol* (**8a**), 1,t - 3 - *dimethyl* - 4 - *phenylpiperidin* - r - 4 - *ol* (**9a**) *and its amine borane* **11**. The above procedure was employed for the hydroboration-oxidation of **7a**. The THF was evaporated under reduced pressure from the mixture and the aqueous soln extracted with several portions of chloroform. Evaporation of the solvent, after drying, left a thick oil, which gave pure crystals (yield 45%), m.p. 147–148° after crystallization from EtOH. The residue from the mother liquors was chromatographed on alumina (neutral, activity 3) and eluted with light petroleum (b.p. 30–50°)-ether 1:1. The first eluted isomer was **9a**, m.p. 117–118°. The product was identical (m.p., m. m.p., TLC, NMR spectral comparison) with a sample prepared otherwise.[18] The second fraction was **8a**, hydrochloride m.p. 234–235° from EtOH.

Propionyl derivative of **8a**. Compound **8a** (1 g), propionic anhydride (2 ml), pyridine (1 ml) and xylene were refluxed for 3 hr, and worked up in the usual way (see acyl derivatives of **6a**). The ester, after distillation in a ball tube oven (80–90°/0·1 mm Hg), was characterized as hydrochloride, m.p. 230–232°.

1,t - 3 - *Dimethyl* - 4 - *phenylpiperidin* - r - 4 - *ol* (**9a**) *from* **11**. A mixture of **11** (200 mg), 50% KOH (2 ml) and THF (5 ml) was heated under reflux for 1 hr. After removal of the solvent, the residue was diluted with water and extracted with ether. Evaporation of the solvent, after drying, gave **9a**, m.p. 117–118° (lit.[18] 118–119°).

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