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CONFORMATIONAL EQUILIBRIA IN 3-HYDROXYPIPERIDINE AND IN SOME OF ITS METHYL DERIVATIVES

S. VAŠÍČKOVÁ, A. VÍTEK and M. TICHÝ

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague 6

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Conformational equilibria in the epimeric 2-methyl, 5-methyl, and 6-methyl 3-hydroxypiperidines as well as in their N-methyl derivatives, have been estimated from the integrated intensities of the bonded hydroxyl vibrational bands in their infrared spectra, using as "biased" standards the epimeric 2,6-dimethyl-3-hydroxypiperidines. In 3-hydroxypiperidine and its N-methyl derivative the OH-axial conformer has been found to be more stable by 0·3 kcal mol^{-1} and 0·6 kcal mol^{-1}, respectively. In this conformer the hydrogen-bonded rotamer is prefered to the non-bonded rotamers by 1·0 kcal mol^{-1} whereas in the N-methyl series this preference is about 2·5 kcal mol^{-1}.

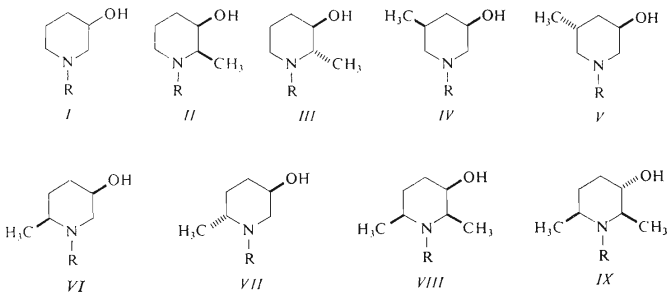
A long time ago we demonstrated[1] that the conformational equilibria in piperidines, substituted in the position 3 with hydroxyl group can be studied by the IR-spectroscopic determination of intramolecular hydrogen bond between the axial hydroxyl and the ring nitrogen.

We have found that the spectrum of the 3-hydroxypiperidine shows comparable amounts of free and bonded hydroxyl bands[1]. Later we used the IR-determination of hydrogen bonding in the elucidation of configuration of alkaloids ψ-conhydrine[1], veratramine[2] and carpaine[3]. Since that time, several authors[4-6] have tackled the question of 3-hydroxypiperidine conformation in qualitative as well as quantitative way.** Lyle and coworkers[4] used the NMR spectroscopy to evaluate the conformer population in 3-hydroxypiperidine and in some of its derivatives. Their measurements, however, were performed on relatively concentrated solutions. Intermolecular association which undoubtedly occurs at these concentrations may well affect the conformational equilibrium making thus the results misleading. Therefore we considered it to be worth reexamining the situation under conditions of high dilution using the infrared technique. Recent progress in the quantitative separation of overlapping bands by means of computer[8-10] has made it possible to evaluate

* Part LXXII: This Journal *38*, 1537 (1973).

** After this work was finished, two Dissertations[7,8] dealing with this subject were announced.

the spectra with such degree of accuracy which would allow a reliable conformational analysis[11]. The aim of our present study was to determine the conformational equilibria in 3-hydroxypiperidine and in some of its methyl-substituted derivatives (NH-series), as well as in their N-methyl derivatives (NMe-series) (Scheme 1).



I *II* *III* *IV* *V*

VI *VII* *VIII* *IX*

a, R = H
b, R = CH_3

SCHEME 1

Synthesis and Configurational Assignment

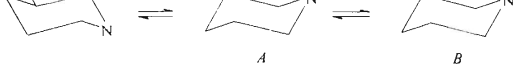
All compounds were prepared by catalytic reduction of the corresponding hydroxy pyridines in acetic acid. Crude separation of the epimers was achieved by fractional distillation (the hydrogen-bonded isomer being much more volatile) or by vapour phase chromatography, and the compounds were purified by crystallisation or *via* picrates. Compound *Vb* was obtained by equilibration of the epimer *IVb* on Raney nickel followed by separation by vapour phase chromatography. Unfortunately, similar attempt to prepare *Va* from *IVa* failed.

The configuration of the compounds follows unequivocally from their spectra in the 3 μ region. In the case of 2,6-dimethyl-3-hydroxypiperidines four epimers are in principle possible. Since the reduction of 2,6-dimethylpyridine system should afford products with *cis*-relationship of the methyls, our two isomers arising in the hydrogenation should be *VIIIa* and *IXa*, and these can easily be distinguished by absence of hydrogen bonding in *IXa*. Even without the assumption of the *cis*-relationship of the methyl groups the spectrum alone would be sufficient for decision between *VIIIa*, *IXa* and the other two epimers since the first should exhibit no hydrogen bonding, the second should be almost exclusively in the hydrogen-bonded form whereas the spectra of the remaining two isomers should be similar to that of 3-hydroxypiperidine (*cf.* discussion ref.[3]).

Selection of Standards and Calculation of the Energy of the Hydrogen Bond

In the 3-hydroxypiperidine system only one of the possible chair conformations is capable of intramolecular hydrogen bonding (Scheme 2). Thus, any bonded hydroxyl band found in the spectrum of a 3-hydroxypiperidine must be ascribed to this conformer.

For the conversion of spectral data (apparent integrated intensities) into concentration of the "bonded" or "non-bonded" conformers it was necessary to have spectra of conformationally biased compounds. As the respective standards for the species with axial and equatorial hydroxyl it is possible to use compounds *VIII* and *IX* which evidently are conformationally homogeneous. The use of these standards is of course justified only if the "intrinsic" integrated intensities of the bands in the spectra of the standards and of the bands of corresponding conformations of the mobile compounds are identical (*cf.* Appendix). Although this assumption cannot be proved directly, it is very probably justified as suggested by very similar intensities for a series of similar conformationally homogeneous compounds[12]. Another support of this assumption comes from a comparison of the values of integrated intensity of the conformationally homogeneous compounds *VIII* and *IX* with the mean values of the "intrinsic" integrated intensities of the bonded and free hydroxyl bands, B_f and B_b, obtained from the spectra of all compounds of the series by the least squares method (see Appendix).* This treatment yields in the NH-series (compounds *Ia*–*IXa*) the values $B_f = 1870$ and $B_b = 3430$. The first value (B_f) is in excellent agreement with the value of the observed intensity of the equatorial standard *IXa*, $B'_{f,E} = 1840$. Before comparing the B_b value with the value for the axial standard *VIIIa*, denoted as $B'_{b,A}$, we must make a correction** for the non-bonded rotamers of the axial hydroxyl group, and therefore $B'_{b,A} = x_{b,A} \cdot B_b = (1 - x_{f,A}) B_b = (1 - B'_{f,A}/B_f) \cdot B_b = (1 - 300/1870) \cdot 3430 = 2880$, where $x_{b,A}$



A *B*

N = NH or NCH_3

SCHEME 2

* The indexes denote: *f* and *b* free and bonded hydroxyl, respectively, *A* and *E* the axial and equatorial standard, respectively.

** Under the reasonable assumption that the "intrinsic" integrated intensity of the free axial and free equatorial hydroxyl is approximately the same[12].

and $x_{f,A}$ are the respective mole fractions of the bonded and free hydroxyl in the axial standard (*VIIIa*). This value again agrees with the experimental value $B'_{b,A} = 2960$ found for *VIIIa*. In the NMe-series practically all the axial hydroxyl is bonded (B'_f (*VIIIb*) = 30) and therefore $B'_b \approx B_b$. In this series, $B'_{f,E}$ (*IXb*) = 2010 and $B'_{b,A}$ (*VIIIb*) = 3150, as compared with 2060 and 3270, respectively, computed by the least squares method.

It is possible to evaluate the energy difference between the rotamers with bonded and non-bonded axial hydroxyl group (Scheme 2, *A* and *B*, respectively) in the NH-series. The equilibrium constant $K_{HB} = x_{f,A}/x_{b,A} = x_{f,A}/(x_{f,E} - x_{f,A}) = B'_{f,A}/(B'_{f,E} - B'_{f,A}) = 300/(1840 - 300) = 0{\cdot}19$ (from compounds *VIIIa* and *IXa*) corresponds to the Gibbs free energy difference $\Delta G^0 \sim 1{\cdot}0$ kcal mol^{-1} in favour of the rotamer with bonded hydroxyl group. Similar energy difference for the NMe-series cannot be evaluated since the equilibrium is shifted too far to the bonded hydroxyl side (we esti-

TABLE I

Apparent Integrated Intensities, B (l cm^{-2} mol^{-1}), and Wavenumbers, ν (cm^{-1}), for the Free and Bonded Hydroxyl Bands in Compounds *I*—*IX* at 40°C in Tetrachloroethylene

Compound	R = H				R = CH_3			
	ν_f	B'_f	ν_b	B'_b	ν_f	B'_f	ν_b	B'_b
I	3 616 3 627	930[a]	3 534	1 820	3 611 3 626	730[a]	3 543	2 370
II	3 632	240	3 527	2 860	3 619 3 629	80[a]	3 532 3 561	2 960[a]
III	3 611 3 630	1 890[a]	3 523	100	3 610 3 635	1 390[a]	3 522	980
IV	3 611 3 625	1 840[a]	—	—	3 619 3 627	2 240	—	—
V	not measured				3 625	40	3 546	3 590
VI	3 626	370	3 535	2 870	3 626	110	3 537 3 562	3 020[a]
VII	3 614 3 627	1 830[a]	3 523	100	3 610 3 626	1 640[a]	3 534	310
VIII	3 633	300	3 524 3 548	2 960[a]	3 630	30	3 530 3 562	3 150[a]
IX	3 613 3 633	1 840[a]	—	—	3 610 3 634	2 010[a]	—	—

[a] Sum of integrated intensities of both hydroxyl bands.

mate the value to be about 2·5 kcal mol^{-1}), although the frequency of the bonded hydroxyl band is practically the same as for the NH series (3543 cm^{-1} *vs* 3534 cm^{-1}).

Conformational Equilibrium in 3-*Hydroxypiperidine and its* N-*Methyl Derivative*

The equilibrium constant K_i for a mobile compound is defined as the ratio of the molar fractions of the conformers with axial hydroxyl (x_a) and of the OH-equatorial conformers (x_e), $K_i = x_{a,i}/x_{e,i}$, where index *i* refers to the mobile compound. For its evaluation we may use the following equations:*

$$K_i = B'_{b,i}/(B'_{b,A} - B'_{b,i}) \qquad (1)$$

TABLE II

Percentage of the OH-Axial Conformer and Free Energy Values, ΔG^0_{exp} (kcal mol^{-1}), for the Conformational Equilibria in Compounds *I*–*IX* at 40°C in Tetrachloroethylene[a]

Compound	R = H		R = CH_3	
	%	ΔG^0_{exp}	%	ΔG^0_{exp}
I	63·0 (61·7)	−0·3 (−0·3)	72·5 (75·2)	−0·6 (−0·7)
II	99·0 (97·0)	−2·9 (−2·2)	90·5 (94·0)	−1·4 (−1·7)
III	3·5 (3·4)	2·1 (2·1)	30·0 (31·1)	0·5 (0·5)
IV	[b]		[b]	
V	not measured		[c]	
VI	99·3 (97·3)	−3·1 (−2·2)	92·4 (95·9)	−1·6 (−2·0)
VII	3·5 (3·4)	2·1 (2·1)	9·5 (9·8)	1·4 (1·4)

[a] The ΔG^0_{exp} values are calculated using the values B_b obtained by the method of least squares ($B'_{b,A}$ = 2 880 for the NH-series, $B'_{b,A}$ = 3 270 for the NMe-series); the values in parentheses are calculated using the data for *VIII* and *IX* as standards. The corresponding equilibria are depicted in Scheme 4. [b] Only free hydroxyl band present. [c] The *B* value is higher than that of standard, *cf.* Table I.

* The meaning of the indexes is the same as in the footnote on p. 1793. As already mentioned, in the NH-series the mole fraction of the OH-axial conformers, $x_{a,i}$, includes the rotamers with bonded as well as the with free hydroxyl.

or $$K_i = (B'_{f,E} - B'_{f,i})/(B'_{f,i} - B'_{f,A}) . \quad (2)$$

Since the bands of the free hydroxyl are usually composite and since the Eq. (*2*) uses two different standards we prefer the values K_i obtained from the bonded hydroxyl bands (Eq. (*1*)); nevertheless the values calculated from B'_f agree in most cases reasonably well with that obtained from B'_b.

The free energy differences, ΔG^0, for the conformational equilibria computed from B'_b in the compounds *Ia* – *VIIa* and *Ib* – *VIIb* are listed in Table II. As is evident from the Table, the ΔG^0 value for 3-hydroxypiperidine and for its N-methyl derivative is about 0·3 kcal mol^{-1} and 0·6 kcal mol^{-1}, respectively, the conformer with the axial hydroxyl being favoured in both substances. This result is in marked contrast with the findings of Lyle and coworkers[4] who report 0·37 kcal mol^{-1} for the first and 0·25 kcal mol^{-1} for the second compound, both in favour of the equatorial conformer. This great discrepancy may be caused by different experimental conditions, *i.e.* by the different concentration used (~5M *vs* 5 . 10^{-3}M solution): in higher concentrations the equatorial conformer may be preferred as a result of intermolecular association.

The stabilisation of the conformer with axial hydroxyl due to hydrogen bonding in *Ia* and *Ib* is thus about 0·8 kcal mol^{-1} and 1·1 kcal mol^{-1}, respectively. At first glance, the small (0·3 kcal mol^{-1}) difference in the stabilisation energy in *Ia* and *Ib* contradicts the great energy difference found for the equilibrium between rotamers of the axial hydroxyl group (1·0 kcal mol^{-1} in the NH series and about 2·5 kcal mol^{-1} in the NMe-series). The explanation may rest in the competition of the OH..N and NH..OH bonding in the axial form in the NH-series (Scheme 3, forms *A* and *B*,

A *B* *C* *D*

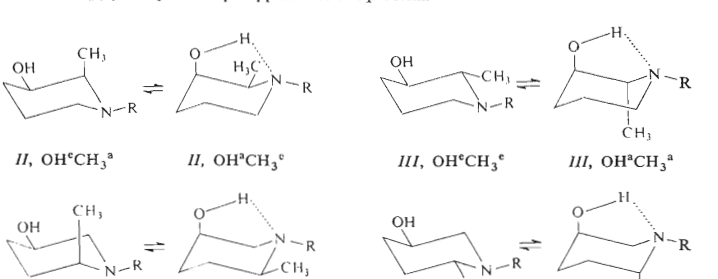
SCHEME 3

respectively). In the NMe-series the molecule undoubtedly exists almost exclusively in the conformation with axial lone pair (the OH-axial non-bonded species, such as *D* being very rich in energy) whereas in the NH-series a significant portion of conformers with axial hydrogen may be present, and one of them (*B*) may be stabilised by NH..OH hydrogen bonding.

Conformational Equilibria in Substituted 3-Hydroxypiperidines

3-Hydroxypiperidines which are substituted with methyl group in a vicinal position to the hydroxyl may in principle provide information about the magnitude of the interactions between vicinal substituents on the piperidine ring. Although these interactions were studied and evaluated

in the cyclohexane system[13–15], almost no data exist as yet in the piperidine series. We tried therefore to apply the spectroscopic approach to this problem.



II, $OH^eCH_3^a$ *II*, $OH^aCH_3^e$ *III*, $OH^eCH_3^e$ *III*, $OH^aCH_3^a$

VI $OH^eCH_3^a$ *VI* $OH^aCH_3^e$ *VII* $OH^eCH_3^e$ *VII* $OH^aCH_3^a$

a, R = H
b, R = CH_3

SCHEME 4

In the *cis*-isomers *IIa* and *VIa*, as well as in *IIb* and *VIb* the equilibrium is shifted very far (more than 90%) to the side of the OH-axial conformer, making thus an exact evaluation of the energy difference very difficult. In the first approximation, ΔG^0 is roughly 2·5 kcal mol^{-1} for both *IIa* and *VIa* whereas for the N-methyl compounds *IIb* and *VIb* it ranges in the $-1{\cdot}6$ to $-1{\cdot}8$ kcal mol^{-1} region. For the *trans*-isomers, the ΔG^0 values are 2·1, 2·1, 0·5 and 1·4 kcal mol^{-1} for *IIIa*, *VIIa*, *IIIb*, and *VIIb*, respectively, with the OH-equatorial conformer predominating in all cases.

Knowing the energy difference between conformers with axial and equatorial hydroxyl in *Ia* and *Ib* we may try to estimate the conformational equilibrium under assumption of the same OH/CH_3 and CH_3/CH_3 interactions as found[13,16–19] in cyclohexane derivatives and to compare these values with that actually found. Thus, *e.g.* for the equilibrium in *IIb*, $OH^eCH_3^a \rightleftarrows OH^aCH_3^e$, the ΔG^0 increments will be the following: in $OH^aCH_3^e$ for the hydroxyl group (including the hydrogen bond) $\Delta G^0 = -0{\cdot}6$ kcal mol^{-1} (taken from *Ib*), for OH^a/CH_3^e interaction $\Delta G^0 = 0{\cdot}7$ kcal mol^{-1}, for CH_3^e/CH_3^e $\Delta G^0 = 0{\cdot}9$ kcal mol^{-1}; in $OH^eCH_3^a$ for OH^e/CH_3^a interaction $\Delta G^0 = 0{\cdot}8$ kcal mol^{-1}, for CH_3^a/CH_3^e $\Delta G^0 = 0{\cdot}9$ kcal mol^{-1} and for the axial methyl $\Delta G^0 = 1{\cdot}7$ kcal mol^{-1}. The calculated energy difference is thus $\Delta G^0 = 0{\cdot}8 + 0{\cdot}9 + 1{\cdot}7 - (-0{\cdot}5 + 0{\cdot}7 + 0{\cdot}9) = 2{\cdot}3$ kcal mol^{-1}. The energy values for other equilibria were calculated similarly and the pertinent data are given in Table III.*

* This way of calculation is of course only very crude. We know very little *e.g.* about the interaction between the N-methyl group and a neighbouring methyl; this interaction is taken in our calculation to be 0·9 kcal mol^{-1}, the same as in the 1,2-dimethylcyclohexane[16–19].

The calculated energy values (ΔG^0_{calc}) agree for some compounds with the found values (ΔG^0_{exp}) when the latter are derived using *VIII* and *IX* as standards; however, in the case of *IIb*, *IIIa*, *VIIa* there is a serious discrepancy, showing that the calculation of the conformational equilibria in these systems by simple addition of interactions taken from the cyclohexane system is not reliable and further study of this problem is required.

APPENDIX

The apparent molar integrated intensity B_φ for a spectral band corresponding to a form φ of a given compound (which we call the "intrinsic" integrated intensity) is defined as*

$$B_\varphi = 1/(a_\varphi d) \int A_\varphi(\nu)\, \mathrm{d}\nu = 1/(\gamma_\varphi x_\varphi c d) \int A_\varphi(\nu)\, \mathrm{d}(\nu)\,, \qquad (1)$$

where a_φ is the activity of the form φ, d is the cell path length, γ_φ is the activity coefficient, x_φ is the mole fraction of the form φ, c is the (analytical) concentration of the given compound and

TABLE III

Comparison of the Experimental (ΔG^0_{exp}) and Calculated (ΔG^0_{calc}) Free Energy Values (kcal . . mol)$^{-1}$ for the Conformational Equilibria in Compounds *II*, *III*, *VI* and *VII*

Equilibrium[a]	R = H		R = CH_3	
	ΔG^0_{exp}	ΔG^0_{calc}	ΔG^0_{exp}	ΔG^0_{calc}
II, (OH^e, $CH_3^a \rightleftarrows OH^a$, CH_3^e)	−2·9 (−2·2)	−2·1	−1·4 (−1·7)	−2·3
III, (OH^e, $CH_3^e \rightleftarrows OH^a$, CH_3^a)	2·1 (2·1)	1·0	0·5 (0·5)	0·8
VI, (OH^e, $CH_3^a \rightleftarrows OH^a$, CH_3^e)	−3·1 (−2·2)	−2·0	−1·8 (−2·0)	−2·2
VII, (OH^e, $CH_3^e \rightleftarrows OH^a$, CH_3^a)	2·1 (2·1)	1·4	1·4 (1·4)	1·2

[a] The corresponding equilibria are depicted in Scheme 4. The calculation is based on the following values: $OH^e \rightleftarrows OH^a$ $\Delta G^0 = -0{\cdot}3$ kcal mol^{-1} and 0·6 kcal mol^{-1} for the NH- and NMe-series (taken from *Ia* and *Ib*), respectively; values of the vicinal interactions OH^e/CH_3^a, OH^a/CH_3^e, OH^e/CH_3^e, CH_3^e/CH_3^e, and CH_3^a/CH_3^e are taken[13,16–19] as 0·83, 0·66, 0·38, 0·9 and 0·9 kcal mol^{-1}, respectively; see also note [a] in Table II.

* Many authors relate incorrectly this molar quantity to concentration; this is justified if and only if $a = c$. We are indebted to Dr M. Horák, J. Heyrovský Institute of Physical Chemistry and Electrochemistry, ČSAV, for a valuable discussion on this point.

$A\varphi(\nu)$ is the function describing the apparent profile of the spectral line absorbance. In our study we may suppose that the activity coefficient is approximately equal to unity and therefore the activity of the form φ is equal to $a_\varphi = x_\varphi c$. For the sum of mole fractions over all possible forms φ we may write

$$\sum_\varphi x_\varphi = 1 . \qquad (2)$$

We may now relate the "intrinsic" integrated intensity, B_φ, to the *observed* integrated intensity of the corresponding spectral band, B'_φ, using the equation

$$B'_\varphi = x_\varphi B_\varphi . \qquad (3)$$

The observed integrated intensity, B'_φ, is the only quantity directly available from the spectrum.

Furthermore we assume, that the "intrinsic" integrated intensity $B_{\varphi,i}$ for the i-th studied compound may be substituted by a mean value, B_φ, valid for the whole set of compounds, *i.e.* that

$$B_{\varphi,1} = B_{\varphi,2} = \ldots = B_{\varphi,n} = B_\varphi . \qquad (4)$$

Now, for the equilibrium between hydrogen bonded (*b*) and non-bonded (*f*) forms we obtain from Eqs (*2*) and (*3*) an overdetermined set of equations

$$B'_{b,i}/B_b + B'_{f,i}/B_f = 1 , \qquad (5)$$

which can be solved for B_b and B_f by the method of least squares. The values of mole fractions x_b and x_f are then obtained by backsubstitution into Eq. (*3*).

EXPERIMENTAL

Spectroscopic Measurements

The measurements were made in Infrasil cells of 20 mm thickness on $4{\cdot}0-5{\cdot}0 \cdot 10^{-3}$ mol l^{-1} solutions* in tetrachloroethylene at 40°C. A linear relationship between absorbance and concentration in the range of concentrations of $2-15 \cdot 10^{-3}$ mol l^{-1} has been found. At least two independent measurements were made for each compound. The compounds were uniform according to vapour phase chromatography and were distilled or sublimed immediately before measurement. The bands were separated numerically on an Elliott 503 computer under assumption of Lorentzian (Cauchy) type of the bands, using the damped least squares method[9,10].

Preparation of Compounds

Compounds *Ia* and *Ib* were prepared according to the literature[20,21]. The compounds *VIIb* and *IXb* were already described, the first was prepared by reduction of 3-hydroxy-6-methyl-2-piperidone[22] whereas the latter was obtained by biological oxidation of *cis*-2,6-dimethylpiperidine[23].

* Due to a typographical error the concentration of the measured compounds in Part LVII of this series[15] is erroneously given as $3{\cdot}5-5{\cdot}0 \cdot 10^{-1}$ mol l^{-1}, the correct value being $3{\cdot}5-5{\cdot}0 \cdot 10^{-3}$ mol l^{-1}. This concentration was used in all our hydrogen bonding studies.

cis- and *trans*-3-Hydroxy-2-methylpiperidine (*IIa* and *IIIa*)

A solution of 3-hydroxy-2-methylpyridine[24,25] (6·20 g) in acetic acid (50 ml) was hydrogenated in the presence of Adams catalyst (2·0 g) at 40°C (5·05 l of hydrogen consumed), the catalyst was filtered off, conc. hydrochloric acid was added and the solvent evaporated. The residue was dissolved in methanol (25 ml) and passed through a Zerolit FF column (70 ml, in OH cycle), pre-washed with methanol. The solvent was evaporated and the semi-solid residue distilled. Two fractions were collected: b.p. 90—92°C/14 Torr and b.p. 95—115°C/14 Torr. The first fraction (2·5 g) containing mainly the *cis*-isomer was treated with picric acid in ether and the resulting picrate on two crystallizations from water melted at 183·5—184°C. For $C_{12}H_{16}N_4O_8$ (344·3) calculated: 41·86% C, 4·68% H, 16·28% N; found: 41·74% C, 5·07% H, 16·41% N. The base *IIa*, m.p. 94·5—95·5°C (ethyl acetate), was obtained by passing the methanolic solution of the pure picrate through a Zerolit FF column (pre-washed with methanol), evaporation of the solvent and sublimation; yield 1·5 g. For $C_6H_{13}NO$ (115·2) calculated: 62·57% C, 11·38% H, 12·16% N; found: 63·01% C, 11·60% H, 12·26% N. Crystallization of the second fraction from ethyl acetate gave 0·5 g of the *trans*-isomer *IIIa*, m.p. 139—140°C. For $C_6H_{13}NO$ (115·2) calculated: 62·57% C, 11·38% H, 12·16% N; found: 62·79% C, 11·41% H, 12·21% N. *Picrate*, m.p. 146—146·5°C (ethyl acetate). For $C_{12}H_{16}N_4O_8$ (344·3) calculated: 41·86% C, 4·68% H, 16·28% N; found: 42·30% C, 5·07% H, 16·43% N.

cis-3-Hydroxy-5-methylpiperidine (*IVa*)

Hydrogenation of 3-hydroxy-5-methylpypiridine[26] (3·0 g) in acetic acid (40 ml) on platinum oxide (2·5 g) at 60°C proceeded very slowly (20 h) and afforded the *cis*-isomer *IVa*, m.p. 95—96°C, practically as the sole product. For $C_6H_{13}NO$ (115·2) calculated: 62·57% C, 11·38% H, 12·16% N; found: 62·59% C, 11·52% H, 12·10% N. Attempts to equilibrate this compound on Raney nickel in 2-propanol resulted in formation of three compounds (according to vapour phase chromatography) which we were unable to separate.

cis- and *trans*-3-Hydroxy-6-methylpiperidine (*VIa* and *VIIa*)

A solution of 3-hydroxy-6-methylpyridine[27] (15·0 g) in acetic acid (150 ml) was hydrogenated in the presence of Adams catalyst (6·0 g) at 40—50°C. The catalyst was filtered off, conc. hydrochloric acid (30 ml) was added to the filtrate and the solvent distilled off. The residue was treated with powdered potassium hydroxide and extracted many times with ether, the ethereal layer was evaporated and the residue, containing according to vapour phase chromatographic analysis about 25% of the *cis*-isomer *VIa*, was distilled. Two fractions were collected: the first, b.p. 95—98°C/11 Torr, was strongly enriched in the *cis*-isomer, whereas the second, b.p. 104—106°C/11 Torr, was principally the *trans*-isomer.

Preparative gas–liquid chromatography of the first fraction followed by purification *via* picrate yielded 1·4 g of the *cis*-isomer *VIa*, m.p. 48·5—49·5°C (pentane). For $C_6H_{13}NO$ (115·2) calculated: 62·57% C, 11·38% H, 12·16% N; found: 62·40% C, 11·39% H, 12·23% N. *Picrate*,* m.p. 181·5—182·5°C (ethyl acetate); for $C_{12}H_{16}N_4O_8$ (344·3) calculated: 41·86% C, 4·68% H, 16·28% N; found: 41·74% C, 5·07% H, 16·41% N.

* Nicodemus and Wulff[28] obtained by the reduction of 3-hydroxy-6-methylpyridine a product, m.p. 96—97°C. This is in good agreement with the melting point of our *trans*-isomer, however, the melting point of their picrate (183°C), prepared from the product of reduction on nickel, corresponds undoubtedly to the *cis*-isomer.

Crystallisation of the second fraction from ethyl acetate afforded 4·4 g of the *trans*-isomer *VIIa*, m.p. 97—97·5°C (lit.[22] m.p. 96—97°C). For $C_6H_{13}NO$ (115·2) calculated: 62·57% C, 11·38% H, 12·16% N; found: 62·49% C, 11·51% H, 11·89% N. *N-Benzoyl derivative*, m.p. 128·5—129·5°C (ligroin–benzene). For $C_{13}H_{17}NO_2$ (219·3) calculated: 71·20% C, 7·82% H, 6·39% N; found: 70·96% C, 7·86% H, 6·37% N. *Picrate*,* m.p. 155—156°C: For $C_{12}H_{16}N_4O_8$ (344·3) calculated: 41·86% C, 4·68% H, 16·28% N; found: 41·54% C, 4·62% H, 16·54% N.

3-Amino-2,6-dimethylpyridine

Heating of ethyl 2,6-dimethylnicotinate[29] (51 g) with 100% hydrazine hydrate (25 ml) for 5 hours to 110°C in a sealed tube afforded 42·7 g of the hydrazide, m.p. 146·5—147·5°C (ethanol). For $C_8H_{11}N_3O$ (165·2) calculated: 58·16% C, 6·71% H, 25·44% N; found: 58·24% C, 6·69% H, 25·99% N. A stirred solution of the hydrazide (41·5 g; 0·25 mol) in 1·17M-HCl (234 ml; 0·274 mol) was treated with an aqueous solution (100 ml) of sodium nitrite (21·0 g; 0·305 mol) at −5—0°C during 15 min. After another 30 min the liberated azide was extracted with ether, the organic layer dried and taken down *in vacuo*. The crystalline residue was dissolved in anhydrous ethanol (150 ml) and the solution was refluxed for 3 h. The solvent was distilled off and the residue was refluxed with a solution of KOH (50 g) in ethanol (150 ml) and water (60 ml) for 8 h. The upper ethanolic layer was separated, taken to dryness and the remaining solid was extracted in a Soxhlet extractor with ether, giving 21·2 g (69%) of the pure amine, m.p. 122·5—123°C (lit.[30] m.p. 124°C.)

The amine was transformed into 2,6-dimethyl-3-hydroxypyridine, m.p. 211—212°C, essentially as described by Batkowski and Plazek[31] who give m.p. 207°C.

TABLE IV

Physical Constants and Analytical Data for the N-Methyl Derivatives *IIb*—*IXb*

Compound	B.p., °C/Torr	Found		
		% C	% H	% N
IIb[a]	55—57[b]	65·00	11·89	10·68
IIIb[a]	110/15	64·59	11·80	10·85
IVb[a]	104/10	65·38	11·94	10·41
Vb[a]	41—43[b]	65·44	11·54	10·63
VIb[a,c]	120/11	65·39	11·95	10·87
VIIb[a,c]	102—103/15	64·93	11·76	10·92
VIIIb[d,e]	62—63[b]	67·45	11·98	9·66
IXb[d]	120/10	67·12	11·92	9·36

[a] For $C_7H_{15}NO$ (129·2) calculated: 65·07% C, 11·70% H, 10·84% N. [b] Melting point, uncorrected. [c] Lit.[23] states for 1,6-dimethyl-3-hydroxypiperidine of unspecified stereoisomeric purity b.p. 65—67°C/8 Torr. [d] For $C_8H_{17}NO$ (143·2) calculated: 67·09% C, 11·96% H, 9·78% N. [e] Lit.[23] gives m.p. 57—57·5°C.

cis- and *trans*-2,6-Dimethyl-3-hydroxypiperidine (*VIIIa* and *IXa*)

2,6-Dimethyl-3-hydroxypyridine[31] (8·2 g) was hydrogenated over platinum oxide (4·0 g) in acetic acid (100 ml), the catalyst was filtered off, the filtrate mixed with hydrochloric acid and taken down *in vacuo*. The residue was crystallized twice from ethanol to give 3·0 g of the hydrochloride of the all-*cis* isomer *VIIIa*, m.p. 262—263°C. Passing the methanolic solution of the hydrochloride through an Amberlite IRA-400 column liberated *VIIIa* (1·9 g), m.p. 107—108°C (ligroin). For $C_7H_{15}NO$ (129·2) calculated: 65·07% C, 11·70% H, 10·84% N; found: 65·33% C, 11·75% H, 10·67% N. The mother liquors from the crystallisation of the hydrochloride were passed through an Amberlite column, the solution taken to dryness and the remaining bases carefully distilled. When about one half of the material was distilled over, the distillation was interrupted and the crystalline residue crystallized twice from dioxane affording thus 0·4 g of pure *IXa*, m.p. 141·5 to 142°C. For $C_7H_{15}NO$ (129·2) calculated: 65·07% C, 11·70% H, 10·84% N; found: 65·43% C, 12·00% H, 10·74% N. Brown and collaborators[32] give for a 2,6-dimethyl-3-hydroxypiperidine prepared by another route m.p. 144—152°C.

N-Methyl Derivatives

All the N-methyl derivatives, except for *Vb*, were prepared by Clarke-Eschweiler methylation of the corresponding secondary piperidinols, and their constants together with the analytical data are given in Table IV.

trans-3-Hydroxy-1,5-dimethylpiperidine (*Vb*)

A solution of *IVb* (0·7 g) in 2-propanol (10 ml) was refluxed with about 1 g of Raney nickel for 5 h. The catalyst was filtered off, washed with 2-propanol, the filtrate was acidified with dilute hydrochloric acid and taken down *in vacuo*. The mixture of the residue with powdered potassium hydroxide was shaken with moist ether, and the solvent was distilled off leaving a mixture of *IVb* and *Vb* in the ratio 88 : 12. Preparative vapour phase chromatography on Carbowax afforded 47 mg of *Vb*, m.p. 41—43°C (pentane). For analytical data see Table IV.

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