STEREOCHEMISTRY OF NITROGEN HETEROCYCLES.

68.* STEREOCHEMISTRY OF 2,5-DIMETHYL-4-PIPERIDONE, 2,5-DIMETHYL-4-PIPERIDOL, AND THEIR N-BENZOYL DERIVATIVES

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The isomers of 1-benzoyl-2,5-dimethyl-4-piperidone were obtained and equilibrated (89.8% cis ⇄ 10.2% trans isomer, preferred conformations 2a, 5e, and 2a, 5a). The position of the equilibrium between the isomers of 2,5-dimethyl-4-piperidone was determined by two independent methods (89.5% trans ⇄ 10.5% cis isomer). The differences in the free energies of the isomers, the conformational energy of the β-CH_3 group, and the energy of syn-axial 1,3-interaction between the CH and the unshared electron pair were calculated; the decrease in the conformational energy of the β-methyl group in the series of piperidine (1.6), 4-piperidone (1.47), and N-acyl-4-piperidone (1.28 kcal/mole) was explained by the successive weakening of the repulsive interaction between the β-CH_3 group and the n-pair of the nitrogen as a result of the flattening of the ring and of the conjugation between the free electron pair of the nitrogen and the π electrons of the acyl carbonyl group. The last previously unknown fourth isomer of 2,5-dimethyl-4-piperidol, which exists in the 2e,4a,5a conformation, was obtained by the reduction of cis-1-benzoyl-2,5-dimethyl-4-piperidone followed by debenzoylation. In contrast to the secondary amine, its N-benzoyl- and N-benzyl-substituted derivatives exist in the alternative 2a,4e,5e conformation. The configurations and conformations of the isomers were determined by means of the IR and NMR spectra.

Derivatives of piperidine are of great importance as physiologically active substances and as models for the conformational analysis of six-membered saturated azacyclic compounds. In connection with the proposed use of the isomers of 2,5-dimethyl-4-piperidol as model compounds in stereochemical investigations we required all four isomers of this amino alcohol. Up to the present time three isomers of 2,5-dimethyl-4-piperidol have been known [2, 3], i.e., 2r,4c,5t (I), 2r,4t,5t (II), and 2r,4c,5c (III). The configurations of the isomers were determined on the basis of the methods of production in [2, 3], the IR spectra [4] [(I) and (II)], the dissociation constants [5], and the PMR spectra [6] [(I-III)].

The present article is devoted to the synthesis of the fourth isomer of 2,5-dimethyl-4-piperidol. The two isomers of 1-benzoyl-2,5-dimethyl-4-piperidone were obtained at the same time, the ratio of the isomers of 2,5-dimethyl-4-piperidone and 1-benzoyl-2,5-4-piperidone in the equilibrium mixtures was determined, and the differences in the free energies of the trans and cis isomers and the conformational energies of the β-methyl groups were calculated.

Earlier [7, 8] we showed that the benzoylation of 2t-methyl-4-oxo-9r-H-trans-decahydroquinoline in an alkaline medium or the isomerization of 1-benzoyl-2t-methyl-4-oxo-9r-H-trans-decahydroquinoline makes it possible to obtain 2t-methyl-4-oxo-9r-H-cis-decahydroquinoline (which is unstable in the free state) in the form of the stable 1-benzoyl derivative. It was shown by x-ray crystallographic analysis [9] that in spite of the strong steric stain in the decahydroquinoline fragment this ketone exists in the conformation with the 1,3-diaxial orientation of the α,α' substituents of the piperidone ring. On the basis of this ketone it was possible to obtain the last most difficultly obtainable isomer of 2-methyl-4-hydroxy-decahydroquinoline [10]. For the synthesis of 2r,5c-dimethyl-4t-piperidol we used a similar

*For Communication 67, see [1].

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TABLE 1. The Preferred Conformations and the Spectral Characteristics of the Stereoisomers of 2,5-Dimethyl-4-piperidol (I-IV), 1-Benzoyl-2,5-dimethyl-4-piperidone (VII, VIII), and 1-Benzoyl and 1-Benzyl-4-piperidols (IX, X) and (XI, XII)

Compound*	Conformation	PMR spectrum, δ, ppm													IR spectrum, ν, cm^{-1}	
		2e	2a	3e	3a	4e	4a	5e	5a	6e	6a	2-CH_3	5-CH_3	C_6H_5	OH*[4]	(N)C–H
I	2e4e5e	—	2,66	1,92	1,05	—	3,11	—	1,38*[4]	2,97	2,26	1,03	0,96	—	3627 sh, 3608 (1,4)	2800
II	2e4a5e	—	3,00	1,77	1,31	3,84	—	—	1,66	2,67	2,75	1,03	0,89	—	3636 (1,0)	2833
III	2e4e5a	—	2,62	1,65	1,20	—	3,76	1,91	—	2,89	2,74	1,12	0,98	—	3622 (1,0)	2895
IV	2e4a5a	—	3,15	1,55	1,55	3,63	—	1,54*[4]	—	2,56	3,07	1,09	1,01	—	3624 (1,0)	2838
VII	2a5a	4,72	—	2,16	2,82	—	—	2,43	—	3,86	3,56	1,21	1,14	7,37	—	
VIII	2a5e	4,81	—	2,15	2,67	—	—	—	2,57	4,36	2,93	1,19	0,97	7,21	—	
IX	2a4a5e	4,32	—	1,72	1,72	3,83	—	—	1,70*[4]	3,74	3,03	1,37	0,89	7,28	3635 (1,0)*[5]	
X	2a4e5e	4,53	—	1,5 ... 1,8		—	3,47	—	1,3 ... 1,8	3,96	2,59	1,17	0,94	7,31	3628, sh. 3609 (1,6)	
XI	2e4e5a	—	2,39	1,5 ... 1,8		—	3,75	1,92*[4]		2,06	2,61	1,19	0,97	7,21	3625, sh. 3613 (0,8)	2792
XII	2a4e5e	3,04	—	1,6 ... 1,8		—	3,45	—	1,6*[4]	2,51	2,27	1,03	0,94	7,27	3626, sh 3610, sh. 3643 (1,2)	2802

*[1] For compound (XI) the chemical shifts of NCH_2Ph were δ 4.05 (d, J = 13.5 Hz) and 3.05 (d, J = 13.5 Hz), for (XII) δ 3.68 (d, J = 13.4 Hz) and 3.49 ppm (d, J = 13.4 Hz).

*[2] The PMR spectra of (III, IV) were recorded at 300 MHz. The spectra of (VII-X) were recorded at 45°C in deuterochloroform, and that of (XI) at 120°C in C_2HCl_5.

*[3] Solution in carbon tetrachloride at $5 \cdot 10^{-3}$ M. (The ratio of the half-width of the low-frequency half of the band to the half-width of the high-frequency half is given in parentheses.)

*[4] Determined by the INDOR method.

*[5] The value for the N-benzoyl derivatives of the isomer (I) is 3624 (1.0), and the value for the isomer (II) is 3622 (1.1).

TABLE 2. The Spin–Spin Coupling Constants of the Protons in the Stereoisomers (I-IV, VII-XII)

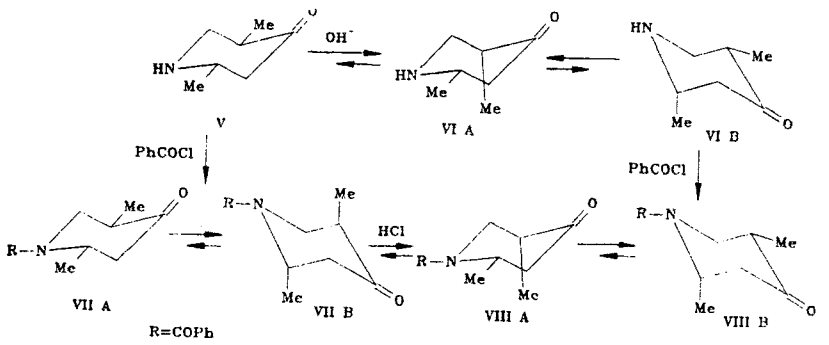
Compound	J, Hz																				
	2e,3e*1	2e,3a*1	2a,3e	2a,3a	3e,4e	3e,4a	3a,4e	3a,4a	4e,5e	4e,5a	4a,5e	4a,5a	5e,6e	5e,6a	5a,6e	5a,6a	3e,3a*2	6e,6a*2	2-CH$_3$, 2H	5-CH$_3$, 5-H
I	—	—	2,6	12,0	—	4,5	—	10,0	—	—	—	12,0	—	—	4,1	10,5	12,0	12,5	6,2	6,0
II	—	—	2,8	11,3	2,7	—	2,7	—	—	2,8	—	—	—	—	4,0	11,5	13,6	11,5	6,2	6,6
III	—	—	3,0	11,3	—	4,8	—	11,3	—	—	4,8	—	2,1	3,8	—	—	11,3	12,7	6,3	7,0
IV	—	—	13,0*5			9,2*3			4,7	—	—	—	5,0	4,0	—	—		13,0	6,0	6,8
VII	3,2	6,4	—	—	—	—	—	—	—	—	—	—	3,9	4,3	—	—	15,1	13,7	6,8	7,0
VIII	2,1	5,5	—	—	—	—	—	—	—	—	—	—	—	—	5,0	12,0	13,9	12,0	6,8	6,2
IX		bs	—	—		5,8*3			—	2,7	—	—	—	—	3,1	12,0		12,8	7,0	6,8
X		bq	—	—		15,0*4			—	—	—	10,0	—	—	4,2	11,5		13,7	7,0	6,2
XI	—	—	14,0*5			14,4*4			—	—	4,8	—	4,0	2,7	—	—		11,8	6,2	6,5
XII			—	—		14,6*4			—	—	—	7,4	—	—	4,4	8,9		12,1	7,0	7,0

*1The constant was not determined for (IX, X, XII).
*2The constant was not determined for (IV, IX-XII).
*3The sum of $J_{3e,4e}$ and $J_{3a,4e}$.
*4The sum of $J_{3e,4a}$ and $J_{3a,4a}$.
*5The sum of $J_{2a,3e}$ and $J_{2a,3a}$.

plan; the unstable cis-2,5-dimethyl-4-piperidone (VI) was obtained in the form of the N-benzoyl derivative (VIII), the equatorial amido alcohol (X) was obtained by stereoselective reduction, and the benzoyl stabilization was removed (schemes 1 and 2). Here we supposed that the presence of one "meta"-axial substituent to the carbonyl group in 1-benzoyl-cis-2,5-dimethyl-4-piperidone (VIII) (conformation B) in the case of reduction by reagents resulting in the preferential formation of the equatorial alcohols should lead to a higher yield of the equatorial alcohol, in contrast to reduction of the amido ketone of the cis-decahydroquinoline series with three "meta"-axial substituents [10]. The catalytic reduction of the cis isomer of the amido ketone (VIII) should give the axial alcohol (IX) preferentially.

Attempts to obtain the stereoisomers of 2,5-dimethyl-4-piperidone in the form of the N-acyl derivatives have been made before. Thus, the 1-benzoyl derivatives were obtained by the benzoylation of 2,5-dimethyl-4-piperidone with an excess of benzoyl chloride in benzene with heat or in an aqueous alkaline medium. One isomer was obtained in both cases (mp 64-65°C [3], 65.5-67.5°C [11]), and the authors first assigned it the trans configuration and then refrained from an assignment.

On the basis of familiar data on the higher stability of cis-N-acyldecahydro-4-quinolinones and on the conditions for their mutual trans,cis transformations [7, 8, 12, 13] it can be supposed that trans-1-benzoyl-2,5-dimethyl-4-piperidone (VII) will mainly be formed during the benzoylation of the mixture of isomers of 2,5-dimethyl-4-piperidone (which mainly represents the trans isomer) under mild conditions excluding the mutual transformations of the stereoisomers of the N-acylamino ketones. In fact, the benzoylation of the equilibrium mixture of amino ketones (V) and (VI) with an equivalent amount of benzoyl chloride in benzene at room temperature (by analogy with [8]) gave a mixture of the isomers of 1-benzoyl-2,5-dimethyl-4-piperidone, in which the liquid trans isomer (VII), isolated with a yield of 80% by chromatography, predominated significantly. During the isomerization of the mixture of isomers or of the pure trans isomer (VII) with dry hydrogen chloride in diethyl ether the crystalline cis isomer (VIII) is formed with a high yield. In the IR spectra both amido ketones give bands for the stretching vibrations of the two carbonyl groups, i.e., the ketone (at 1722 and 1713 cm^{-1} respectively) and amide (1638 and 1631 cm^{-1}) groups. In the PMR spectrum it is possible to interpret the signals of all the protons (Tables 1 and 2), and this makes it possible to determine the configurations and preferred conformations of the isomers reliably. Thus, in both isomers the 3e-H and 3a-H protons have two small constants in addition to the large geminal spin–spin coupling constant. This indicates the e orientation for the 2-H proton and the a-orientation for the 2-CH_3 methyl group. This is consistent with data on the preference for the axial orientation of the α,α' substituents in N-acyl-substituted piperidines and decahydroquinolines [9, 10, 14]. At the same time the coupling constants of the 6e-H and 6a-H protons show clearly that the 5-H proton is equatorial in the ketone (VII) and axial in the ketone (VIII) and, consequently, the ketone (VII) is the trans isomer while the ketone (VIII) is the cis isomer.



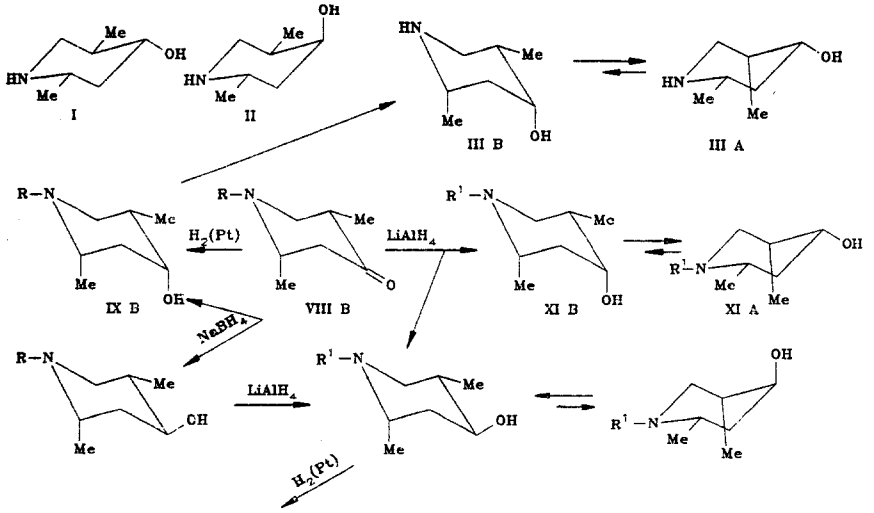
Since the epimerization of the amino ketones by keto–enol tautomerism under the influence of the basic characteristics of the amino group in the amino ketone is a slow process while benzoylation with benzoyl chloride in benzene is a very fast process (the hydrochloride of the amino ketone separates a few seconds after the reagents are mixed), it can be supposed that the ratio of the isomers of the N-benzoyl derivatives in the freshly obtained mixture of the acylamino ketones (VII) and (VIII) must correspond to the ratio of the isomers of the amino ketone (V) and (VI) in their equilibrium mixture. In the benzene solution of the acylamino ketones (VII) and (VIII) obtained after separation of the hydrochloride we

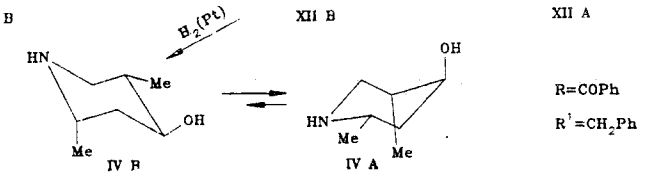
determined the ratio of the isomeric amides by measuring the intensities of the 2- and 6-H signals in the PMR spectrum. The ratio was 88 ± 2% for the trans isomer (VII) and 12 ± 2% for the cis isomer (VIII), and this agrees well with published data [15] [90% of the trans isomer (V) and 10% of the cis isomer (VI)]. We also determined the position of the equilibrium between the trans and cis isomers of the amino ketone from the intensity ratio of the signals for the carbon atoms in the ^{13}C NMR spectrum. Here we obtained 89.5 ± 0.5% of the trans isomer (V) and 10.5 ± 0.5% of the cis isomer (VI).

Using the ratios of the conformers of the cis isomer of the amino ketone [70% for (VIA) and 30% for (VIB) at 25°C] [15], we calculated the conformational energy of the β-methyl group in 2,5-dimethyl-4-piperidone ($\Delta G^0_{\beta\text{-}CH_3} = -1.47$ kcal/mole). Assuming that the energies of syn-axial CH_3/3-H 1,3-interaction in 3-methyl-4-piperidone and methylcyclohexane are equal (by analogy with their equality in methylcyclohexane and 2-methylcyclohexanone [16]), we determined the energy of syn-axial CH/unshared electron pair (UEP) 1,3-interaction ($\Delta G^0_{\beta\text{-}CH_3/UEP} = 0.62$ kcal/mole), and this was close to the corresponding values in 1-tert-butyl-3-methyl-4-piperidone ($\Delta G^0_{\beta\text{-}CH_3} = -1.54$, $\Delta G^0_{\beta\text{-}CH_3/UEP} = 0.69$ kcal/mole [17]).

In order to determine the conformational energy of the β-methyl group in 1-benzoyl-2,5-dimethyl-4-piperidone we equilibrated the amido ketones (VII) and (VIII) in a solution of dry hydrogen chloride in benzene (0.1 M) at 25°C. The equilibrium was reached both from the side of the cis and from the side of the trans isomer. The ratio of the isomers in the equilibrium mixture was determined from the area of the signals for the 2- and 6-H protons in the PMR spectrum in benzene and corresponded to 89.8% of the cis and 10.2% of the trans isomer (±1%). The calculated difference in the free energies of the trans and cis isomers of the amido ketones (VII) and (VIII) $\Delta G^0_{trans \rightleftarrows cis}$ was −1.28 kcal/mole.

Earlier we showed that as a result of the high energy of amide conjugation (∿20 kcal/mole [18]) the equatorial α substituents in the molecule of the cyclic amide, which hinder this conjugation, change to the axial position, and such a conformation is stable even if the repulsion energy of the 1,3-syn-axial substituents in the decahydroquinoline fragment amounts to about 10 kcal/mole [19]. This makes it possible to suppose that the fraction of the conformers (VIIA) and (VIIIA) is negligibly small and that the isomers (VII) and (VIII) exist almost entirely in the conformations (VIIB) and (VIIIB). Thus, the obtained difference in the free energies of the trans and cis isomers of (VII) and (VIII) can be attributed to the β-methyl group of the amido ketone. Hence, by analogy with 2,5-dimethyl-4-piperidone we obtain $\Delta G_{\beta\text{-}CH_3/UEP} = 0.43$ kcal/mole. The decrease in the conformational energy of the β-CH_3 and the energy of syn-axial CH_3/UEP 1,3-interaction in the series of piperidine (1.6 and 0.75 kcal/mole respectively) [20], 4-piperidone (1.47 and 0.62 kcal/mole), and N-acyl-4-piperidone (1.28 and 0.43 kcal/mole) is evidently due mainly to the weakening of the repulsive interaction between the axial β-CH_3 group and the p-pair of the nitrogen as a result of the flattening of the piperidine ring due to the increase of the exocyclic angles in the ketone and, particularly, in the amido ketone and to the displacement of the free electron pair of the nitrogen in the amide of the N–CO bond, the degree of double-bond character of which is significantly increased [9, 14, 19, 21].





The axial amido alcohol (IX), identical with an authentic sample [3], was obtained with a 95% yield during the hydrogenation of the cis-amido ketone (VIII) at platinum dioxide in anhydrous ethanol. The IR spectrum of this amido alcohol contained absorption bands for OH_{bond} (3422 cm^{-1}) and the amide carbonyl (1627 cm^{-1}). In the PMR spectrum (Tables 1 and 2) the equality of the chemical shifts of the 3e-H and 3a-H protons with their magnetic difference does not make it possible to determine all the numerical J values for the 4-H protons. However, the small $J_{4,5}$ value (2.7 Hz) and the small sum of $J_{3,4}$ (5.8 Hz) with the equal signs of $J_{3,4}$ (as shown by the form of the multiplet for the 4-H proton – a doublet of triplets with a strong average peak, combination peaks not visible) indicate the e-orientation for the 4-H proton. The a-orientation of the 4-OH is confirmed by the symmetrical absorption band of OH_{bond} (3635 cm^{-1}) in the IR spectrum of the solution. The $J_{5a,6a}$ value (12.0 Hz) indicates the e-orientation for the 5-CH_3 group. Thus, as a result of the a-orientation of the 2-CH_3 group, as supposed, the hydrogenation takes place mainly from the equatorial region and leads preferentially to the axial alcohol (IX), which exists in the conformation (IXB).

A mixture of the isomeric amido alcohols (IX) (64%) and (X) (35%) is formed during the reduction of the cis-amido ketone (VIII) with sodium borohydride. In the IR spectrum of the alcohol (X) there are the stretching vibrations of the OH_{bond} (3480 cm^{-1}) and the amide carbonyl (1625 cm^{-1}). In the PMR spectrum the proximity of the chemical shifts of the 3-H protons, which cannot be differentiated, does not make it possible to determine the coupling constants of the 2-, 3-, and 4-H protons. However, it is possible to determine $J_{4,5}$ (10 Hz) and the sum of $J_{3,4}$ (15 Hz). These data in conjunction with the identical signs of the vicinal $J_{3,4}$ constants [the signal of 4-H is a doublet of triplets, as in the alcohol (IX)] indicate the e-orientation for the 4-OH and 5-CH_3 groups [the conformation (XB)]. The e-orientation of the 4-OH is also confirmed by the smaller frequency of the OH_{free} vibration (3628 cm^{-1}) than in the axial alcohol (IX) and by the well defined asymmetry, while the equatorial orientation of the 5-CH_3 is confirmed by the larger $J_{5a,6a}$ value (11.5 Hz).

The debenzoylation of the amido alcohol (IX) by boiling with a 20% solution of hydrogen chloride gave the amino alcohol (III). The IR spectrum of the crystalline alcohol contains the OH_{bond} band at 3370 cm^{-1} (in solution the OH_{free} band at 3622 cm^{-1}) and the NH band at 3245 cm^{-1}. In the PMR spectrum the signal of the 4-H proton has two small constants ($J_{3e,4a}=J_{4a,5e}=4.6$ Hz) and a large constant ($J_{3a,4a}$ = 11.3 Hz); this indicates the a-orientation for the 5-CH_3 group and the e-orientation for the 4-OH group. The coupling constants $J_{2,3}$ of the protons (3.0 and 11.3 Hz) confirm the e-orientation of the 2-CH_3 group. Thus, the amino alcohol (III) exists preferentially in the 2e,4e,5a conformation (IIIA).

The amido alcohol (X) is stable when heated both with 20% hydrochloric acid and with a dioxane solution of dry hydrogen chloride. During the reduction of the benzoyl group with lithium aluminum hydride in diethyl ether the N-benzyl derivative (XII) was obtained with a 96% yield. Its IR spectrum contains the OH absorption band ($\nu_{OH_{free}}$ – an asymmetric band at 3626 cm^{-1}). The signals of the 2-, 3-, and 4-H protons in the PMR spectrum were not fully interpreted for the same reason as in the spectrum of the amido alcohol (X). However, the $J_{4a,5a}$ constants (7.4 Hz), the sum of the $J_{3,4}$ constants (14.6 Hz) and the $J_{5,6}$ coupling constants (4.4 and 8.9 Hz) show that the alcohol (XII), like the alcohol (X), exists preferentially in the 2a,4e,5e conformation (XIIB). The predominance of this conformation over the conformation (XIIA) is due to the larger sum of the conformational energies of the 4-OH and 5-CH_3 group of 1-alkylpiperidines (1.7 kcal/mole) [20].

The fourth isomer of 2,5-dimethyl-4-piperidol (IV) was obtained with an 85% yield during the hydrogenolysis of 1-benzylpiperidol (XII) at platinum dioxide in acetic acid. Its IR spectrum contains absorption bands for the OH groups (at 3360 cm^{-1} in the crystals, a symmetrical OH_{free} band at 3624 cm^{-1} in solution) and the NH group (3250 cm^{-1}). Like the spectrum of the alcohol (IX), the PMR spectrum (the 2-H signal is a sextet with splitting of 6.5 Hz, the 3-H signal a triplet with splitting of 4.5 Hz, and the 4-H signal a quartet with splitting of 4.7 Hz) corresponds to an AA'MX system, and this supports the "inaccurate" relationships for the peak intensities in the multiplets. Analysis of the higher-order spectra makes it

possible to obtain sufficient data (Tables 1 and 2) to determine the conformation of the alcohol (IV) reliably. Thus, the small $J_{5,6}$ constants indicate the e-orientation for 5-H. The small values of $J_{4,5}$ (4.7 Hz) and the sum of the $J_{3,4}$ constants (9.2 Hz) indicate the e-orientation for the 4-H proton, while the large value of the sum of the $J_{2,3}$ constants indicates the a-orientation for the 2-H proton. All these data indicate reliably a preponderance of the 2e,4a,5a conformation (IVA) for the alcohol (IV). In this case the factor which determines the conformation is the high conformational energy of the 2-CH_3 group in the piperidines not substituted at the nitrogen atom (in 2-methylpiperidine 2.5 kcal/mole [20]).

It is known that the equatorial alcohols are mainly formed during the reduction of unhindered cyclic ketones by lithium aluminum hydride. The amide group is also reduced. In fact, a mixture of N-benzylaminopiperidols, consisting of 56% of the isomer (XI) and 39% of the isomer (XII), was obtained during the reduction of the amido ketone (VIII) with lithium aluminum hydride in diethyl ether. The IR spectrum of the N-benzylamino alcohol (XI) contains an absorption band for OH_{free} (3625 cm^{-1}). The small values of the $J_{5,6}$ (4.0 and 2.7 Hz) and $J_{4,5}$ (4.8 Hz) constants and the large value of the $J_{3,4}$ constants (14.4 Hz) indicate the e-orientation for the 5-H proton and the a-orientation for the 4-H proton and show that the isomer of 1-benzyl-2r,5c-dimethyl-4c-piperidol exists preferentially in the 2e,4e,5a conformation (XIA). The benzyl group in the amino alcohol (XIA) occupies the e position, since in the a position it would experience stronger repulsion (about 4 kcal/mole) from the axial 5-CH_3 group. The benzyl group at the nitrogen atom of (XIIB) has the same orientation, as confirmed by the difference in the chemical shifts of their methylene protons [1.0 ppm in (XI) and 0.23 ppm in (XII)], since it is known [22] that they are larger in the e-orientation of the 2-CH_3 group and smaller in the a-orientation. Further evidence for the e-orientation of the benzyl group is provided by the presence of strong Boltzmann bands in the IR spectra for both isomers.

The IR and PMR spectra of the amino alcohols (I) and (II) (earlier [6] the δ and J values were only determined for 3a-H, 4-H, and 6a-H in pyridine) confirm their configurations and conformations as 2e,4e,5e and 2e,4a,5e.

It should be noted that the frequencies of the Boltzmann bands for the hydroxyamines depend on the orientation of the hydroxyl group; they are smaller in the equatorial alcohols (I, III, XI, XII) (2792-2805) and larger in the axial (II) and (IV) (2833, 2838 cm^{-1}).

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord IR-75 spectrometers for tablets with potassium bromide and in carbon tetrachloride solution ($5 \cdot 10^{-3}$ M). The ^{13}C NMR spectra were obtained on a Bruker WR-80 instrument at 20.155 MHz in deuterochloroform. The ^1H NMR spectra were obtained on a Tesla BS-487C instrument at 80 MHz with HMDS as internal standard. Double homonuclear and heteronuclear resonance were used to interpret the NMR spectra. When $(\nu_A - \nu_B)/J_{AB} < 6$, the chemical shifts and spin – spin coupling constants were calculated as in the spectra of higher orders. The quantitative determinations of the isomers were made by cutting out and weighing the signals of the protons and by measuring the heights of the signals for the carbon atoms. Thin-layer chromatography was conducted on alkaline aluminum oxide of III Brockman activity (A) and on Silpearl silica gel (B) with diethyl ether as eluant. The elemental analyses corresponded to the calculated compositions.

2,5-Dimethyl-4-piperidone was obtained from 2-methyl-1,4-hexadien-3-one and ammonia [23]. The ^{13}C NMR spectrum of the equilibrium mixture of isomers (without the solvent): trans isomer (V), 11.7 (q, 5-CH_3); 23.2 (q, 2-CH_3); 46.3 (d, $C_{(5)}$); 51.7 (t, $C_{(3)}$); 54.9 (t, $C_{(6)}$); 55.3 (d, $C_{(2)}$); 210.1 ppm (s, $C_{(4)}$); cis isomer (VI), 15.0 (q, 5-CH_3); 21.6 (q, 2-CH_3); 28.7 (d, $C_{(5)}$); 48.8 (t, $C_{(3)}$); 51.4 (t, $C_{(6)}$); 53.4 (d, $C_{(2)}$); 211.7 ppm (s, $C_{(4)}$). Contents of isomers: trans (V) 89.5 ± 0.5%; cis (VI) 10.5 ± 0.5%.

Stereoisomers of 1-Benzoyl-2,5-dimethyl-4-piperidone (VII, VIII). To a solution of 12.7 ml (0.10 mole) of the equilibrium mixture of isomers of 2,5-dimethyl-4-piperidone (V, VI) in 60 ml of dry benzene at room temperature we added with stirring 7.02 g (0.05 mole) of benzoyl chloride. After 1 h the precipitate was filtered off and washed with dry benzene. We obtained 7.93 g (97%) of 2,5-dimethyl-4-piperidone hydrochloride; mp 141-142°C. After evaporation of the filtrate 11.5 g of the mixture of isomers of the amidoketones (VII) and (VIII) remained in the form of a colorless oil. We chromatographed 1.0 g of this mixture in 10 ml of methanol on a column of silica gel (diameter 2 cm, 150 ml, eluant ether, 24 ml fractions). From fractions 11 and 12 we isolated 0.17 g (17%) of the cis isomer (VIII)

($C_{14}H_{17}NO_2$) in the form of colorless crystals; mp 71-72°C (from diethyl ether), R_f 0.54 (B). IR spectrum (potassium bromide): 1713 (C=O), 1631 (N–C=O), 696, 722, 745, 1580, 1605, 3055 cm^{-1} (Ph). From fractions 14-17 we isolated 0.80 g (80%) of the trans isomer (VII) ($C_{14}H_{17}NO_2$) in the form of a colorless oil; R_f 0.43 (B). IR spectrum (thin layer): 1722 (C=O), 1638 (N–C=O), 708, 737, 1580, 3026, 3058 cm^{-1} (Ph). To a solution of 10.5 g of the mixture of amido ketones (VII) and (VIII) in diethyl ether we added an ether solution of dry hydrogen chloride. The precipitates which separated on standing were recrystallized from ether. We obtained 10.0 g (95%) of the cis isomer (VIII); mp 71-72°C.

Epimerization of the Stereoisomers of 1-Benzoyl-2,5-dimethyl-4-piperidone (VII and VIII). To a benzene solution of the mixture of isomers (VII) and (VIII) [containing 88% of the trans isomer (VII)], obtained as described above, we added an equal volume of a benzene solution of dry hydrogen chloride (0.2 M). The equilibrium was established after 1.5 h at 25°C. The composition of the mixture was as follows: cis isomer (VIII) 89.7 ± 1%, trans isomer (VII) 10.3 ± 1%. During equilibration under the same conditions for the cis isomer (VIII) the equilibrium was established after 0.5 h: cis isomer 90.0 ± 1%, trans isomer (VII) 10.0 ± 1%.

1-Benzoyl-2r,5c-dimethyl-4c-piperidol (IX) ($C_{14}H_{19}NO_2$). A 5.00-g sample of the amido ketone (VIII) was hydrogenated in 20 ml of anhydrous ethanol at room temperature in the presence of 1 g of platinum oxide. After the usual treatment we obtained 4.8 g (95%) of the amido alcohol (IX) in the form of colorless crystals; mp 159-160°C (from acetone), R_f 0.35 (A); 0.30 (B). IR spectrum (potassium bromide): 1625 (N–C=O), 3422 (OH), 705, 732, 3050 cm^{-1} (Ph).

Reduction of 1-Benzoyl-2r,5c-dimethyl-4-piperidone (VIII) with Sodium Borohydride. To a solution of 10.0 g (0.04 mole) of the amido ketone (VIII) in 60 ml of ethyl alcohol we added 3.2 g of sodium borohydride in 15 ml of water. The reaction mixture was boiled for 1 h. To the cooled solution we added 70 ml of water. The solution was acidified to a weakly acidic reaction with concentrated hydrochloric acid, the reaction product was extracted with chloroform, and after drying the extract with sodium sulfate and distillation of the solvent the product was crystallized from acetone. We obtained 4.0 g of the amido alcohol (IX); mp 159-160°C. The residue was chromatographed on a column of silica gel (diameter 4 cm, 600 ml, eluant ether, 60-ml fractions). From fractions 12-22 we isolated 2.41 g of the amido alcohol (IX) [total yield of amido alcohol (IX) 64%]. From fractions 25-35 we obtained 3.53 g (35%) of 1-benzoyl-2r,5c-dimethyl-4t-piperidol (X) ($C_{14}H_{19}NO_2$) in the form of colorless crystals; mp 136-137°C (from acetone); R_f 0.25 (A); 0.18 (B). IR spectrum (potassium bromide): 1625 (N–C=O), 3480 (OH), 703, 747, 3065 cm^{-1} (Ph).

2r,5c-Dimethyl-4c-piperidol (III). We heated 10.0 g of the amido alcohol (IX) on a boiling water bath with 100 ml of 20% hydrochloric acid for 35 h. The benzoic acid was filtered off, the filtrate was evaporated to dryness, and the product was decomposed with a 50% solution of sodium hydroxide. The base was extracted with ether and dried with potassium carbonate. After removal of the solvent it was distilled under vacuum and recrystallized from acetone. We obtained 4.0 g (72%) of the piperidol (III) in the form of colorless needles; mp 86-87°C. A mixed melting test with an authentic sample did not give a depression. IR spectrum (potassium bromide): 3370 (OH_{bond}), 3255 cm^{-1} (NH).

1-Benzyl-2r,5c-dimethyl-4t-piperidol (XII) ($C_{14}H_{21}NO$). A 2.87-g sample (0.012 mole) of the amido alcohol (X) was extracted with ether in Soxhlet apparatus into a boiling suspension of 0.25 g of lithium aluminum hydride in 20 ml of anhydrous diethyl ether. The reduction was complete after 6 h. To the reaction mixture we added 30 ml of water. The mixture was acidified to a weakly acidic reaction with concentrated hydrochloric acid, and the aqueous solution was washed with ether. The amino alcohol was converted into the base and extracted with ether. The extract was dried with sodium sulfate, and the product was recrystallized from hexane. We obtained 2.51 g (96%) of the amino alcohol (XII) in the form of colorless crystals; mp 75-76°C; R_f 0.29 (A); 0.05 (B). IR spectrum (potassium bromide): 3430 (OH), 700, 744, 1600, 3033, 3065, 3077 cm^{-1} (Ph).

2r,5c-Dimethyl-4t-piperidol (IV) ($C_7H_{15}NO$). A solution of 2.50 g of benzylpiperidol (XII) in 15 ml of glacial acetic acid was hydrogenated in the presence of 0.2 g of platinum oxide at 70°C and atmospheric pressure. After separation of the catalyst the filtrate was diluted with water and treated with an excess of potassium carbonate. The base was extracted with ether, and after drying with sodium sulfate the product was recrystallized from acetone. We obtained 1.01 g (85%) of the piperidol (IV) in the form of colorless

crystals; mp 62-63°C. IR spectrum (potassium bromide): 3375 (OH), 3260 cm^{-1} (NH). The hydrochloride ($C_7H_{15}NO \cdot HCl$) formed colorless crystals; mp 144-145°C (from ethanol).

Reduction of 1-Benzoyl-2r,5c-dimethyl-4-piperidone (VIII) with Lithium Aluminum Hydride. To a suspension of 0.05 g of lithium aluminum hydride in 5 ml of diethyl ether we added a solution of 0.30 g of the amido ketone (VIII) in 6 ml of diethyl ether. The mixture was boiled and stirred for 2 h, 20 ml of water was added, the mixture was acidified with concentrated hydrochloric acid, and the aqueous solution was washed with ether. The amino alcohols were converted into the base with potassium carbonate and extracted with ether. After drying with sodium sulfate and removal of the solvent the reaction product was chromatographed on a column of aluminum oxide (diameter 1.5 cm, 100 ml, eluant benzene, 10 ml fractions). From fractions 1-5 we isolated 0.16 g (56%) of 1-benzyl-2r,5c-dimethyl-4c-piperidol (XI) ($C_{14}H_{21}NO$) in the form of crystal; mp 96-97°C (from hexane); R_f 0.40 (A); 0.05 (B). IR spectrum (potassium bromide): 3420 (OH), 697, 734, 3035, 3067, 3091 cm^{-1} (Ph). The hydrochloride ($C_{14}H_{21}NO \cdot HCl$) formed colorless crystals; mp 201-202°C (from ethanol). From fractions 7-9 we isolated 0.11 g (39%) of benzylpiperidol (XII); mp 75-76°C.

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