Reduction of 2-benzylideneindane-1,3-dione (II) by Tetrahydropyridine (V). A 0.04 ml portion of concentrated HCl is added to a solution of 0.12 g (500 mmoles) of compound II and 0.17 g (500 mmoles) of compound V in 10 ml of 80% ethanol, and the mixture is boiled for 20 h. The reaction mixture is diluted with water and extracted by chloroform (2 × 30 ml). The chloroform extract is dried and evaporated. According to the data of liquid chromatography (Zorbah SIL; ethyl acetate—hexane, 35:15), the residue contains 49% of 2-benzylindane-1,3-dione III.

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1,2,5-TRIMETHYL-4-(p-HYDROXYARYL)-Δ^3-TETRAHYDROPYRIDINES AND THEIR SPATIAL STRUCTURE

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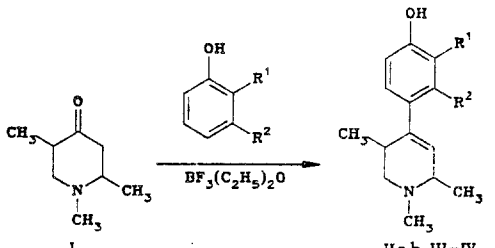
The condensation of 1,2,5-trimethylpiperidine-4-one with phenol and isomeric cresols yields 1,2,5-trimethyl-4-(p-hydroxyphenyl)- and (p-hydroxytolyl)-Δ^3-tetrahydropyridines, the structure and conformation of which have been studied by proton NMR spectroscopy.

The condensation of γ-piperidones with phenol (cresols) is of interest for the preparation of piperidine derivatives containing hydroxyphenyl groups in the γ-position. Compounds of this type are examined for their physiological activity [1].

We have studied the compounds formed by condensation of 1,2,5-trimethylpiperidine-4-one (I) with phenol and isomeric cresols in the presence of boron trifluoride etherate. In all cases, the compounds obtained were dehydration products of 1,2,5-trimethyl-4-(p-hydroxyaryl)-piperidine-4-ones.



I — IIa,b, III–IV

II a,b $R^1=R^2=H$; III $R^1=H$, $R^2=CH_3$; IV $R^1=CH_3$, $R^2=H$

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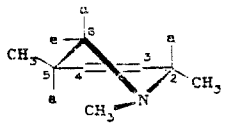
TABLE 1. Chemical Shifts of Protons in Substituted Δ^3-Tetrahydropyridines (δ, ppm)

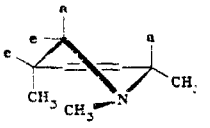
Compound	2-H	3-H	5-H	6-H_a	6-H_e	N—CH_3	2-CH_3	5-CH_3	Protons of the 4-substituent
IIa	2,88	5,52	3,01	2,19	3,06	2,42	1,23	0,83	System AA′BB′: 7,10 (2H, d); 6,81 (2H, d)
IIb	2,85	5,65	2,78	2,64	2,74	2,41	1,24	1,11	7,25 (2H, d); 6,78 (2H, b)
III	2,84	5,49	3,00	2,17	3,04	2,40	1,21	0,84	2,23 (CH_3); 7,01 (2′-H) 6,70 (5′-H); 6,88 (6′-H)
IV	2,83	5,47	3,09	2,16	2,98	2,43	1,19	0,76	2,28 (CH_3); 6,65 (3′-H); 6,64 (5′-H); 6,90 (6′-H)

The structure and stereochemistry of the substituted tetrahydropyridines obtained were established by examination of the proton NMR spectra (Tables 1 and 2).

It follows from these results that in all cases Δ^3-tetrahydropyridines are formed, not the Δ^4-isomers as would be expected. This can be unambiguously deduced, for example, from the fact that the methylene protons at the α-carbon atom of the tetrahydropyridine ring have as a neighbor the 5-H methylene proton with which vicinal spin-spin coupling is observed (Table 2). Taking into account the fact that the initial piperidone (I) is a mixture of trans- and cis-isomers, according to the position of the methyl groups, with a considerable predominance of the first [2], the formation of isomers of the tetrahydropyridines would be expected. However, only in the case of the condensation of the piperidone (I) with phenol was the separation accomplished, with the aid of column chromatography, into the individual isomers, precominantly the trans-2,5-isomer IIa with very small amounts of the cis-2,5-isomer IIb. Examination of the spin-spin coupling constants J_{HH} (Table 2) enables one also to determine the preferred conformation of these configurational isomers. In the case of the trans-isomers of IIa, III, and IV this is semi-chair, with equatorial orientation of the 2- and 5-methyl substituents, and in the case of the cis-isomer of IIb, semi-chair with 2e,5a-orientation of these substituents:



IIa, III, IV



IIb

Change in the orientation of the 5-methyl substituent on transition from the trans-isomers IIa, III, and IV to the cis-isomer IIb can be traced in terms of the values of the two vicinal spin-spin coupling constants of the protons on $C_{(5)}$ and $C_{(6)}$ (Table 2). Thus, in the trans-isomers the large value of one of these constants (9-10 Hz) points to trans-biaxial orientation, and the value of the second constant (5.5 Hz) could be ascribed to gauche interaction which in the aggregate supports the equatorial orientation of the 5-methyl group. The small value of one of these constants in the cis-isomer (2.5 Hz) can be explained only by gauche-biequatorial orientation of the corresponding protons, which have between them a dihedral angle close to 90° and this also leads to a minimal value of the vicinal spin-spin coupling constant according to the Karplus relationship [3]. The value of the second of these constants in the cis-isomer (4.2 Hz, Table 2) is such that one can assign it to the gauche-interaction $^3J_{ae}$ whence the axial orientation of the 5-methyl substituent in the cis-isomer IIb can be unequivocally deduced.

It is interesting to note that change in the orientation of the methyl substituent from equatorial to axial on transition from isomer IIa to IIb leads to deshielding of its protons, in contrast to a saturated six-membered ring, which can be explained by the vicinity of the π-electron system of the double bond. The exceptionally large values of the long-range spin-spin coupling constants — homoallylic $^5J_{2,5}$ = 2.5-3, and $^4J_{5,3}$ = 1.5-1.7 Hz (Table 2) — are characteristic for the spatial structure of the trans-isomers and result from the effect of σ-π overlap [4] with axial orientation of the interacting protons in the vicinity of the

TABLE 2. Spin-Spin Coupling Constants of Protons in the Tetrahydropyridine Ring of Compounds IIa, IIb, III, and IV (Hz)

Compound	Proton interactions							
	$6_a,6_e$	$6_a,5$	$6_e,5$	2,3	5,2	5,3	2,2-CH_3	5,5-CH_3
IIa	−11,5	9,0	5,5	2,0	3,0	1,5	7,0	7,0
IIb	−11,5	4,2	2,5	2,5	1,8	2,0	6,5	7,0
III	−11,5	9,5	5,5	2,0	2,5	1,5	7,0	7,0
IV	−11,0	10,0	5,5	1,7	3,0	1,7	6,8	7,1

double bond. In contrast, the vicinal spin-spin coupling constant $^3J_{2,3}$ in both trans- and cis-isomers has the small value of 1.7-2 Hz (Table 2) on account of the dihedral angle between protons 2-H and 3-H being close to 90°.

The orientation of the N-methyl group must be considered differently on account of the low energy barrier for inversion of the nitrogen atom in a six-membered ring [5]. The PMR results which we obtained give support to its preferentially equatorial position, both in the trans-isomers IIa, III, and IV and in the cis-isomer IIb. Evidence of this is the large difference in the chemical shifts of the methylene protons on $C_{(6)}$ in the trans-isomers (0.8-0.9 ppm, Table 1) because of supplementary deshielding of the 6_e proton in the gauche-orientation with respect to the unshared electron pair of nitrogen. Leveling of the chemical shifts of these protons in the cis-isomer IIb (2.64 and 2.75 ppm, Table 1) can be explained by selective shielding of the 6_e proton by the 5-methyl group in the cis-ae-orientation with respect to this proton. Equatorial orientation of the N-methyl group in the trans- and cis-isomers is also supported by the difference in the vicinal $^3J_{ae}$ of the protons at $C_{(5)}$ and $C_{(6)}$ in these isomers. The substantially greater value of this coupling constant in the trans-isomers (5.5 Hz, Table 2) in comparison with the cis-isomers (4.2 Hz) is explained by the positive contribution in the gauche-orientation of one of the interacting protons (6_e) with the unshared electron pair of the heteroatom [6] in the trans-isomer. The reason for the predominance of the trans-1e,2e-configuration of the methyl groups could be steric 1,2-interaction, making their cis-configuration much more disadvantageous at the strain angles (smaller than those of saturated six-membered rings) of a semi-chair configuration in cyclic mono-enes [7] such as Δ^3-tetrahydropyridine.

Thus, it follows from our PMR data that the dehydration products which we have studied are, in all cases, Δ^3-tetrahydropyridines, the molecules of which have semi-chair configuration, the 1e,2e,5e-orientation of the methyl substituents predominating in the trans-2,5-isomers IIa, III, and IV, and the 1e-2e,5a-conformer in the cis-isomer IIb.

EXPERIMENTAL

A WH-360 spectrometer (360 MHz) was used to obtain the proton NMR spectra of 2-5% solutions in $CDCl_3$. First-order analysis of the spectra was performed. The double resonance method was used for unambiguous assignment of the signals and for determining the spin-spin coupling constants.

1,2,5-Trimethyl-4-(p-hydroxyphenyl)-Δ^3-tetrahydropyridine (II). To a mixture of 18.8 g (0.2 mole) phenol and 3.34 g (24 mmoles) borontrifluoride etherate at 0°C was added 5.1 g (0.03 mole) piperidone (I). The reaction mixture was kept at 20°C for 10 days. Water (500 ml) was added and the solution shaken in a separating funnel with 100 ml ether. The aqueous solution was saturated with sodium carbonate. The reaction product was extracted with four 50 ml portions of ether and the extract dried over sodium sulfate. The residue after distilling off the ether was 3.72 g (47%) of a glass-like mass. A portion of the residue (0.56 g) was taken for chromatographic separation, using aluminum oxide of activity II in a column with h = 60 cm, d = 3.5 cm; the eluent was a mixture of 1:1 hexane:ethyl acetate. The separation yielded 0.06 g (10.7%) compound IIb, colorless crystals, mp 136-137°C from heptane, R_f 0.75. Found, %: N 6.4; M^+ 217. $C_{14}H_{19}NO$. Calculated, %: N 6.4; M^+ 217. Further elution gave 0.31 g (55.4%) compound IIa, colorless crystals, mp 130-131°C from heptane, R_f 0.72. Found, %: N 6.4; M^+ 217. $C_{14}H_{19}NO$. Calculated, %: N 6.4; M^+ 217. Hydrochloride of compound IIa, mp 189-191°C (from 3:1 acetone:alcohol).

1,2,5-Trimethyl-4-(4-hydroxy-3-methylphenyl)-Δ^3-tetrahydropyridine (II). The reaction mixture was made up from 12.8 g (0.12 mole) o-cresol, 11.7 g (0.08 mole) BF_3 etherate, and

5.85 g (0.042 mole) piperidone (I), and the experiment carried out in a similar manner to the preceding. From the ether extract there was obtained 3.5 g residue in which TLC (the same system) showed two compounds with R_f 0.72 and 0.69. The residue was crystallized from heptane, yielding 2.98 g (31%) compound III, mp 160-161°C; R_f 0.69. Found, %: N 6.0; M^+ 231. $C_{15}H_{21}NO$. Calculated, %: N 6.1; M^+ 231.

1,2,5-Trimethyl-4-(4-hydroxy-2-methylphenyl)-Δ^3-tetrahydropyridine (IV) was prepared by a similar condensation of piperidone (I) with m-cresol using the same molar proportions of reactants, the yield being 3.05% of (IV), mp 120-121°C from heptane; R_f 0.51. Found, %: N 6.1; M^+ 231. $C_{15}H_{21}NO$. Calculated, %: N 6.1; M^+ 231.

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SYNTHESIS OF 1,5-METHANO-2-BENZAZOCINES FROM 3-HYDROXY-1,3-DIMETHYL-6-PHENYL-4-PIPERIDONE

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Reaction of 3e-hydroxy-1e,3a-dimethyl-6e-phenyl-4-piperidone with cyanoacetic ester affords 6e,8a-dimethyl-2-oxo-5e-phenyl-3-cyanofuro[2,3-c]piperidine, the epoxide of which undergoes intramolecular cyclization on treatment with 80% H_2SO_4 to give 1,2,5,6-tetrahydro-2-endo-4-dimethyl-1,5-methano-6-oxo-2-benzazocin-3-ene. It has been found that the latter is formed via the intermediate 3-hydroxy-6e,8a-dimethyl-2-oxo-5e-phenylfuro[2,3-c]piperidine.

1,5-Methano-2-benzazocines have so far received little attention as a result of the lack of satisfactory methods for their preparation. Compounds of this type have been obtained by adding amidines to di-, tri-, and tetranitronapthalenes [1]. We have developed a new method for the synthesis of 1,5-methano-2-benzazocines based on the acid-catalyzed reaction of the epoxy-lactone (II). The latter compound was obtained by condensing the α-ketol (I) with ethyl cyanoacetate.

The conversion of the epoxylactone (III) into the ketone (V) evidently involves hydrolysis of the cyano-group and the epoxide ring, decarboxylation, and dehydration to give the intermediate lactone (IV). Subsequent intramolecular reactions of the lactone (IV) involve opening of the lactone ring, decarbonylation, and dehydration (see scheme on following page).

Reduction of the ketone (V) with complex hydrides of aluminum and boron showed that attack on the carbonyl group by the hydride ion takes place from the sterically more accessible exo-position, subsequent reduction of the double bond with sodium borohydride in ethanol taking place from the endo-position.

The structures of all the compounds obtained were confirmed by their elemental analyses and their IR, PMR, and mass spectra. For example, in the PMR spectra of (II-IV), the protons of the piperidine ring are seen as two spin systems, AMX and AX, examination of which shows

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