BASICITIES OF STEREOISOMERIC DERIVATIVES OF PIPERIDINE AND THE STEREOPOLAR EFFECT

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UDC 541.132'62:547.822.3

The basicities of the geometrical isomers of some piperidine derivatives in 50% (by volume) aqueous methanol at 25° were studied. Compounds with an axial OH group have higher basicities than their epimers with an equatorial OH group. The observed principles can be explained either by the existence of two other effects that are responsible for the different effectiveness of transmission of the induction effect from the axial and equatorial positions or by the variable magnitude of the stereopolar effect, which changes as a result of geminal interaction of the substituents attached to C_4 of the piperidine ring.

In recent years in [1-5] it has been convincingly shown that the basicities of stereoisomers of substituted piperidines and their bicyclic analogs depend substantially on the orientation of the substituents attached to C_4 of the piperidine ring. In connection with the remote character of these substituents from the reaction center, this phenomenon could not be explained by steric factors, and the rigidity of the skeleton of a number of investigated compounds [1, 3, 4] excluded conversion of their rings. This made it possible to assert that the difference in the basicities of the stereoisomers is associated with different polar effects of the substituents attached to C_4, which occupy equatorial or axial positions; this is not in agreement with the classical concepts of the inductive effect. Various assumptions [1, 5] have been expressed in connection with the nature of the observed phenomenon, which we have called the "stereopolar effect," but the available experimental data were inadequate for a discussion of them. In the present paper we present the results of a study of the basicities of geometrical isomers of 4-monosubstituted 1-tert-butyl-3-methylpiperidines (I-X, Table 1) and 4-substituted 1-tert-butyl-3-methyl-4-hydroxypiperidines (XI-XX, Table 2).

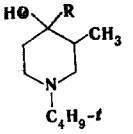
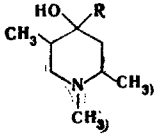
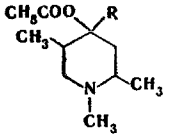
A comparison of these data with data previously obtained [5] for 4-substituted 1,2,5-

TABLE 1. Basicities of the Geometrical Isomers of 4-Monosubstituted 1-tert-Butyl-3-methylpiperidines in 50% (by volume) Aqueous Methanol (at 25°C)

R	$\sigma^*_{RCH_2}$	γ-Isomers		β-Isomers	
		compound	pK_a	compound	pK_a
H	0	I	10,42	—	—
$OCOCH_3$	0,83	II	9,36	VII	8,94
$OCOC_6H_5$	0,83	III	9,32	VIII	8,96
Cl	1,05	IV	9,23	—	—
ONO_2	1,36	V	8,76	IX	8,42
OH	0,555	VI	10,07	X	9,62

M. V. Lomonosov Moscow Institute of Fine-Chemical Technology. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 89-93, January, 1975. Original article submitted December 2, 1974.

TABLE 2. Basicities of the Geometrical Isomers of 4-Substituted Piperidines in 50% (by volume) Aqueous Methanol (at 25°C)

R	σ^* RCH_2												
		γ-Isomers		β-Isomers		γ-Isomers		β-Isomers		γ-Isomers		β-Isomers	
		compound	pK_a	compound	pK_a	compound	pK_a	compound	pK_a	compound	pK_a	compound	pK_a
H	0	VI	10,07	X	9,62	XXI	8,99	XXVIII	8,52	XXXIV	8,28	XL	7,90
C_2H_5	−0,115	XI	10,04	XVI	9,82	XXII	9,05	XXIX	8,59	XXXV	8,43	XLI	8,22
C_6H_5	0,215	XII	9,72	—	—	XXIII	8,69	XXX	8,34	XXXVI	**8,02**	XLII	7,88
C≡CH	0,6	XIII	9,39	XVII	9,01	XXIV	8,28	XXXI	8,00	XXXVII	7,69	XLIII	7,50
$COCH_3$	0,6	XIV	9,08	XVIII	9,40	XXV	8,11	XXXII	8,30	XXXVIII	7,48	XLIV	7,83
$COOCH_3$	0,71	XV	9,24	XIX	9,23	XXVI	8,09	XXXIII	8,16	—	—	—	—
CN	1,3	—	—	XX	7,89	XXVII	6,94	—	—	XXXIX	6,70	—	—

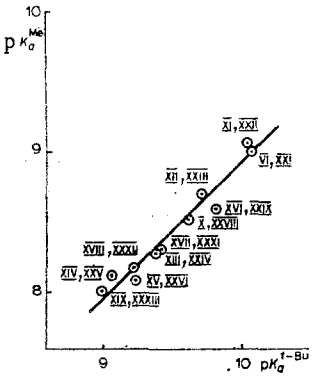


Fig. 1

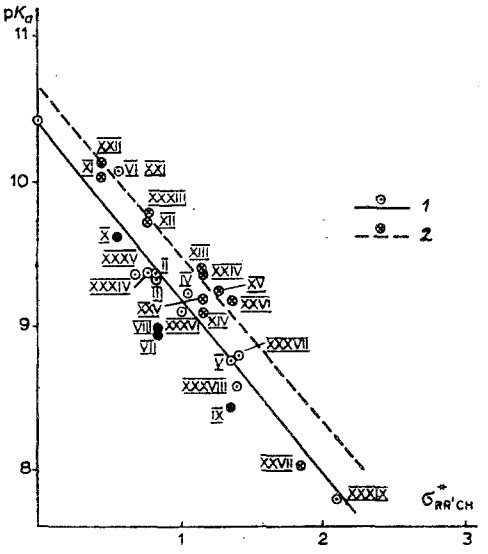


Fig. 2

Fig. 1. Relationship between the pK_a values of substituted 1-tert-butyl-3-methylpiperidines (pK_a^{t-Bu}) and 1,2,5-trimethylpiperidines (pK_a^{Me}).

Fig. 2. Relationship between the pK_a values of substituted piperidines and the σ^* constants: 1) compounds that do not contain OH groups; 2) compounds that contain an OH group attached to C_4.

trimethyl-4-hydroxy- and 1,2,5-trimethyl-4-acetoxy piperidines (XXI-XLIV, Table 2) makes it possible, in our opinion, to formulate more clearly the principles of the stereopolar effect.

The synthesis and establishment of the three-dimensional structures of II, III, VI-VIII, and X-XX were described in [6, 7]; the preparation of I, IV, V, and IX and the study of their configurations will be published in a separate communication. In all cases the stereoisomers containing axial Cl, OH, or OR groups are designated as the γ isomers, and their eipmers containing the same substituents in the equatorial position are designated as the β isomers. The basicities were determined by potentiometric titration in 50% (by volume) aqueous methanol at 25°C. The mean-square error in the pK_a values presented in Tables 1 and 2 is no more than ±0.03 units. All of the correlations were calculated by the method of least squares with a Mir computer, during which the C_4 atom of the piperidine ring with the R and R' geminal substituents attached to it was considered to be an RR'CH< group, the σ^* constant for which was calculated as an additive value from the equation

$$\sigma^*_{RR'CH} = \sigma^*_{RCH_2} + \sigma^*_{R'CH_2}. \quad (1)$$

A comparison of the data presented for the geometrical isomers of 4-substituted piperidines VI, X-XX, and XXI-XXXIII shows (see Table 2) that all of the principles of the effect of the structure of the compounds on their basicities are identical in both series. This is confirmed by Fig. 1, from which it is seen that a good correlation, described by the following equation, exists between the pK_a values of the geometrical isomers of substituted 1-tert-butyl-3-methylpiperidines (VI-XX, pK_a^{t-Bu}) and 1,2,5-trimethylpiperidines (XXI-XXXIII, pK_a^{Me}) with identical substituents attached to the ring C_4 atom:

$$pK_a^{t\text{-}Bu} = (1.08 \pm 0.05) + pK_a^{Me} \quad (2)$$

This makes it possible to examine the data on the basicities for both series jointly using a conversion with respect to Eq. (2).

An analysis of the results shows that in the investigated compounds all of the sub-

TABLE 3. Parameters of the Correlation of the Basicities of 4-Substituted Piperidines with Respect to the Taft Equation

Compounds included in the correlation	ρ^*	r	s	pK_a^0
I—V, XXXIV—XXXIX	1.22±0.04	0.995	0.07	10.40
VI, XI—XV, XXI—XXVI	1.17±0.08	0.975	0.09	10.64

stituents attached to C_4 can be divided into principal types from the point of view of their effect on the basicity: type A — R_A = Cl, ONO_2, and OCOR, i.e., substituents bonded to the piperidine ring through an atom with a high electronegativity (O, Cl) (the OH group occupies a special position) and type B — R_B = C_2H_5, C_6H_5, $COCH_3$, $COOCH_3$, C≡CH, and C≡N, i.e., substituents connected to the piperidine ring through the weakly electronegative C atom (and also the H atom).

It is apparent from Fig. 2 and Tables 1 and 2 that the basicities of all of the geometrical isomers with type A substituents (R_A) in the axial position and type B substituents (R_B or H) in the equatorial position (II-V and XXXIV-XXXIX) comply satisfactorily with the Taft equation, and the point for unsubstituted 1-tert-butyl-3-methylpiperidine (I) lies on the same correlation line, which can be called the principal line. The pK_a values for geometrical isomers that contain an axial OH group (VI, XI-XV, and XXI-XXVI) lie on a straight line passing parallel to the principal line and above it by 0.27 ± 0.12 pK_a units (cyanohydrin XXVII constitutes an exception), whereas the points that correspond to the geometrical isomers having equatorial substituents of the A type (R_A) (VII-IX) lie below the principal line by 0.37 ± 0.05 pK_a units. The slopes of the lines are identical (see Table 3) and practically coincide with the theoretical value 1.3 ± 0.2 calculated from the ρ^* value for the basicities of tertiary amines in 50% methanol (2.98 ± 0.04 [5]) and z^* values for the piperidine ring (0.44 [8]).

This makes it possible to assume that equatorially oriented substituents R_B and axially and equatorially oriented substituents R_A are characterized by normal efficiency of transmission of the inductive effect; however, at the same time, in the latter case there is a certain additional effect that brings about a decrease in the basicities of the compounds as compared with their epimers having axial R_A substituents. It is important to emphasize that this effect does not depend on the σ^* constant of substituent R_A. Geometrical isomers with axial R_B substituents (XVI-XX, XXVIII-XXXIII, and XL-XLIV) do not lie on either of the above-indicated lines (Fig. 3), and it can be seen from Table 2 that the effect of axial R_B substituents on the pK_a value is very small (except for cyanohydrin XX). In [2, 3, 5] this was interpreted as a reduced efficiency of transmission of the inductive effect of the substituents attached to the ring C_4 atom from the axial position; however, as we have shown above, this phenomenon is absent when substituents R_A are attached to the ring C_4 atom in the axial position.

The peculiarities of the OH group have been previously noted [9] and are apparently associated with specific interaction of it with the solvent, as a result of which the magnitude of σ^* for the OH group is not constant but takes on different effective values as a function of the character of the medium (in our case $\sim$ 0.35 for $HOCH_2$). This is confirmed by the fact that the difference in the pK_a values of geometrical isomers having axial and equatorial OH groups attached to the ring C_4 atom (VI, X) is 0.45 pK_a units, i.e., it does not differ substantially from the value indicated above for other stereoisomeric pairs (II and VII, III and VII, and V and IX).

Insofar as the remaining values noted above are concerned, two alternative explanations can be proposed for them.

1. There are two different steric effects, one of which is responsible for the increased electron-acceptor properties of the equatorial substituents of the R_A type attached to C_4, the other of which brings about a decrease in the efficiency of transmission of the inductive effect for axial substituents of the R_B type.

2. Transmission of the inductive effect of all of the substituents attached to C_4 in the

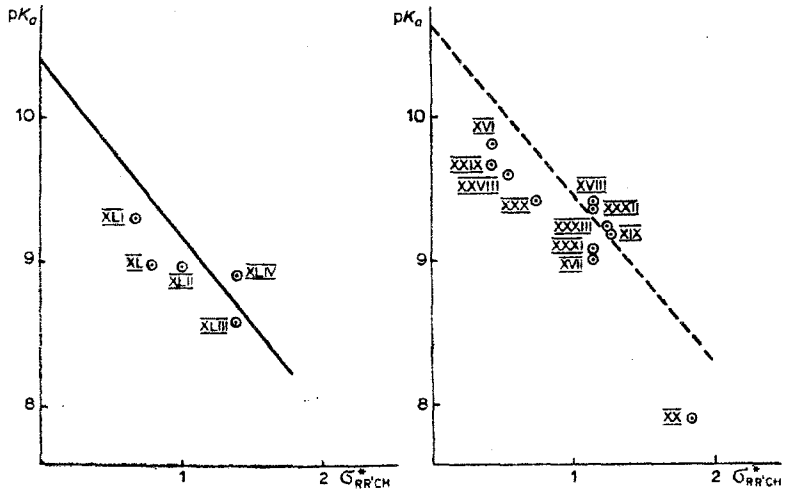


Fig. 3. Effect of axial substituents of the B type on the basicities of substituted piperidines: left) compounds that do not contain an OH group; right) compounds containing an OH group attached to C_4 (the lines are drawn in conformity with the parameters in Table 3).

investigated compounds independently of their three-dimensional orientation is realized identically, and there is one one stereopolar effect characteristic for equatorial R_A substituents; however, its magnitude is not constant but changes as a result of geminal interaction of substituents of the R_A and R_B types, decreasing as the electronegativity of substituents R_B increases.

The second assumption seems simpler to us and therefore more attractive, although the nature of the stereopolar effect and of the contribution of geminal interaction to it remains as yet far from clear.

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