EFFECT OF THE CHARACTER OF RING FUSION ON THE BASICITY OF BICYCLIC HYDRAZIDES

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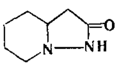
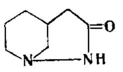
The ionization constants of a number of 1,2-diazabicyclo-3-alkanones were measured. It was found that the basicity of 2-aza-3-quinuclidones is 1.5-2 orders of magnitude lower than in the remaining compounds. An assumption was made regarding the substantial effect of the character of ring fusion on the basicity of bicyclic hydrazides.

In a study of the chemical properties of a number of 1,2-diazabicyclo-3-alkanones, which are bicyclic hydrazides, we encountered considerable effect of the character of ring fusion on the basicity of these compounds. While 1,2-diazabicyclo[3.0.4]-3-nonanone (I) [1], 1,2-diazabicyclo[3.1.3]-3-nonanone (II) [1], 1,2-diazabicyclo[4.0.4]-3-decanone (III) [2], and 1,2-diazabicyclo[2.1.3]-3-octanone (IV) [3] have close pK_a values ranging from 2.2 to 2.8, 1,2-diazabicyclo[2.2.2]-3-octanone (2-aza-3-quinuclidone) (Va) [3] is a much weaker base (pK_a 0.81).



I



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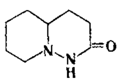

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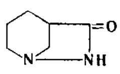

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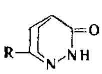
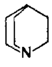


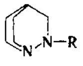
Va,b

a R=H; b $R=CH_3$

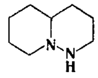
The introduction of a methyl group into the α-position relative to the angular nitrogen in Va somewhat increases the basicity due to the inductive effect of the substituent, but the pK_a value for Vb is one order of magnitude lower than for I-IV. The protonation center in the examined substances is apparently the angular nitrogen atom. As should have been expected, a second nitrogen adjacent to the angular nitrogen lowers the pK_a owing to its −I effect, while the additional electron-acceptor carbonyl group leads to a further reduction in the basicity of the compound. Similar regularities in the change in the basicity are also observed on passing from quinuclidine (VI) to 2-azaquinuclidine (VIIa) and its N-acyl (VIIc, d) or N-nitroso (VIIe) derivatives, as well as on passing from 1,2-diazabicyclo[4.0.4]decane (VIII) to its oxo derivative (III).



VI



VIIa-e



VIII

a R=H; b $R=CH_2C_6H_5$; c $R=COCH_3$; d $R=3,4,5\text{-}(OCH_3)_3C_6H_2CO$; e R=NO

However, the indicated electromeric effect cannot explain the anomalously low pK_a values of 2-aza-3-quinuclidone (Va) and its C-methyl derivative (Vb), especially since the closest analogs of these compounds, which have an exocyclic carbonyl grouping (VIIc, d), are characterized by higher (by an order of magnitude) pK_a values and are extremely close in basicity to the 1,2-diazabicyclo-3-alkanones (I-IV) examined above.

In this connection, the assumption arises that the anomalously low pK_a values of Va, b are caused by steric factors and are associated with the character of the ring fusion, which rigidly fixes their configura-

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TABLE 1. pK_a Values

Compound	pK_a		Compound	pK_a	
	potentiometry	spectrophotometry		potentiometry	spectrophotometry
I	—	2,21±0,7	VI	10,9±0,06[5]	—
II	2,31±0,05	2,27±0,05	VIIa	7,71±0,02	—
III	2,80±0,04	2,75±0,03	VIIb	6,70±0,04	—
IV	2,67±0,07	2,69±0,05	VIIc	2,29±0,06	2,20±0,07
Va	—	0,81±0,04	VIId	2,20±0,04	2,19±0,05
Vb	—	1,25±0,06	VIIe	—	0,40±0,06
			VIII	7,32±0,03	—

tion. It may be thought that the introduction of a carbonyl function into the 1,2-diazabicyclic system, which is associated with transition from sp^3 to sp^2 hybridization of the $C_{(3)}$ atom, leads to a certain distortion of the valence angles of the angular nitrogen atom. Compensation for such distortions of the valence angles occurs due to the certain freedom of the conformational transitions in rings of the I-IV type. In Va, b, where there is ring fusion of the quinuclidine type, the molecular conformation is rigidly fixed, and disruption of the valence angles of the angular nitrogen atom cannot be compensated and is manifested in appreciable reduction of the basicity of the compounds. It is interesting that the character of ring fusion in the bicyclic system in the absence of a carbonyl function does not have such a significant effect on the basicity of VIIa and VIII.

EXPERIMENTAL

The synthesis and physical constants of the substances presented in this paper are described in [1-3]. The ionization constants were measured potentiometrically and spectrophotometrically. An LPU-01 potentiometer with glass and silver chloride electrodes was used for the potentiometric determinations. Carbon dioxide-free $1 \cdot 10^{-2}$-$5 \cdot 10^{-3}$ M aqueous solutions of the investigated substances were titrated with 0.1 N hydrochloric acid at 20± 1°C and constant ionic strength (0.1 N KCl). The pK_a values were calculated by the usual method [4]. The pK_a values were determined spectrophotometrically with an SF-4A spectrometer using aqueous solutions ($1 \cdot 10^{-3}$-$4 \cdot 10^{-3}$ M). The pH values were determined by known methods. The results of the determinations by both methods were in quite satisfactory agreement. The pK_a values found are presented in Table 1.

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