EQUILIBRIUM NH-ACIDITY OF 1,4-DIHYDROPYRIDINES AND 4,5-DIHYDROINDENO[1,2-b]PYRIDINES

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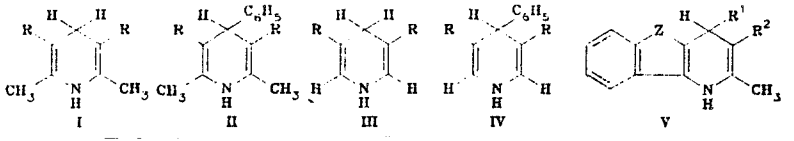
The patterns governing the dependence of NH-acidity on the presence of α-, β- and γ-substituents in the 1,4-dihydropyridine ring and on their nature have been established by comparison of the pK_a values of monocyclic 1,4-dihydropyridines and 4,5-dihydroindenopyridines. Additional data were obtained on the influence of the the electronic effects of sulfur-containing substitutents on the reaction center in the dihydropyridine molecules.

We have previously measured the equilibrium NH-acidity of compounds in the series of 2,6-dimethyl-1,4-dihydropyridines (1,4-DHP) and certain dihydroindenopyridines (indeno-DHP) [1-3]. Considering their high biological activity and the uniqueness of their chemical properties [4, 5], we have in the present work considerably extended the range of compounds included in these series. To obtain additional data on the influence of the electronic effects of substituents, particularly, of sulfur-containing substituents on the reaction center and the possibility of predicting the reactivity of the compounds, we studied the equilibrium NH-acidities of 1,4-DHP (I-IV) and indeno-DHP (V).



I II III IV V

The equilibrium NH-acidity of compounds I-V was determined in DMSO by the transmetallation method, used in [6] (Tables 1 and 2). The pK_a values were related to the acidity of 9-phenylfluorene, the pK_a of which was accepted as equal to 18.5.

On comparing the pK_a values of compounds of series I and III, II and IV, it was found that 1,4-DHP III and IV are stronger NH-acids than their 2,6-dimethyl-substituted analogs.

There is a good linear correlation between the pK_a values of NH-acids in series I and III:

$$pK_a(I) = 1.002pK_a(III) + 1.4; \quad r = 0.993; \; s = 0.19; \; n = 5. \qquad (1)$$

Equation (1) and a direct comparison of the pK_a values of compounds I and III or II and IV for the corresponding substitutents R show that the methyl groups in the 2 and 6-positions reduce the acidity by approximately 1.4 ± 0.2 pK_a units. The above indicated influence of the methyl groups is probably caused mainly by their electron-donor action, although some steric influence on the conjugation of substitutents R with the heterocyclic ring should not be included. This is indicated by some increase in the difference between the pK_a values (pK_a(I) − pK_a(III)) on transition from R = CN (ΔpK_a = 1.2) and the bulkier R = $COOC_2H_5$, $CSOC_2H_5$ (ΔpK_a = 1.4...1.6).

The phenyl group in the 4-position displays weakly pronounced electron-acceptor properties. When it is introduced into 2,6-dimethyl-1,4-DHP (IIa-c) or 1,4-DHP (IVa,b), a slight increase in the NH-acidity is observed (ΔpK_a ~0.5...0.2 pK_a units).

Indeno-DHP (Va-f) (Table 2) are stronger NH-acids than the cyclic 1,4-DHP Ia-h. The character of the influence of the β-substituents on the equilibrium NH-acidity is the same for series I and V, and with respect to their acidifying effect, the substituent can be arranged according to the following series: $C(O)OC_2H_5$ < $C(O)SC_2H_5$ < $C(S)OC_2H_5$ < CN < < $C(S)SC_2H_5$ < NO_2.

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TABLE 1. Equilibrium NH-Acidity of 1,4-DHP in DMSO

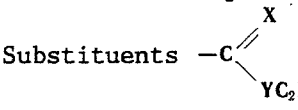
Compound	R	pK_a*	Compound	R	pK_a
Ia	$COOC_2H_5$	20,1	II b	CN	16,2
Ib	$COCH_3$	19,5	II c	NO_2	11,9
Ic	$C(O)C_6H_5$	18,3	III a	$C(O)OC_2H_5$	18,7
Id	$C(O)SC_2H_5$	17,7	III b	$C(O)CH_3$	18,0
Ie	$C(S)OC_2H_5$	17,3	III c	$C(O)SC_2H_5$	16,1
If	CN	16,7	III d	$C(S)OC_2H_5$	15,7
Ig	$C(S)SC_2H_5$	14,8	III e	CN	15,5
Ih	NO_2	12,1	IV a	$C(O)OC_2H_5$	18,0
II a	$C(O)OC_2H_5$	19,6	IV b	$C(S)OC_2H_5$	15,1

*The pK_a values of compounds Ia-f were determined in [1].

TABLE 2. Equilibrium NH-Acidity of Indeno-DHP in DMSO

Compound	Z	R^1	R^2	pK_a*
V a	CO	C_6H_5	$C(O)OC_2H_5$	15,2
V b	CO	C_6H_5	$C(O)SC_2H_5$	14,0
V c	CO	C_6H_5	$C(S)OC_2H_5$	14,0
V d	CO	C_6H_5	$C(S)SC_2H_5$	13,7
V e	CO	C_6H_5	$C(O)CH_3$	14,8
V f	CO	C_6H_5	CN	13,2
V g	CO	H	$C(O)OC_2H_5$	15,4
V h	CO	CH_3	$C(O)OC_2H_5$	15,5
V i	SO_2	C_6H_5	$C(O)OC_2H_5$	15,0
V j	CS	C_6H_5	$C(O)OC_2H_5$	11,2

*The pK_a values of compounds Va-d were determined in [1].

TABLE 3. The σ_1 and σ_R Values of Substituents 

Substituent	σ_I	σ_R^-
$C(O)OC_2H_5$	0,30	0,38
$C(O)SC_2H_5$	0,41	0,40
$C(S)OC_2H_5$	0,18	0,70
$C(S)SC_2H_5$	0,27	0,76

Introduction of the sulfonyl group in place of the carbonyl into the indeno-DHP (V) does not lead to a noticeable change in the NH-acidity in DMSO (Table 2), while the pK_a value of the sulfonyl derivatives V, determined spectrophotometrically in 50% ethanol, is on the average 0.5...0.7 pK_a units higher than the pK_a of the carbonyl analogs [3].

Replacement of the cyclic carbonyl group in compound Va by a thiocarbonyl group (Vj) leads to a decrease in the pK_a value by 4 units, which correlates well with the data for the change in the NH-acidity on transition from urea [7] or N-phenyl carbamate [8] to their thiono analogs.

Analysis of the pK_a values of compounds I within the bounds of a two-parametric correlation with σ_1 and σ_R^- [9] shows (equation (2)) that the NH-acidic center is more sensitive to an inductive effect than to the resonance effect of the 3,5-substituents, as is often observed for NH-acids [6].

$$pK_a(I) = 31.3 - 18.2\sigma_I - 15.2\sigma_R^0; \quad r = 0.985, \; s = 0.26, \; n = 4. \qquad (2)$$

TABLE 4. Equilibrium Constants (K_{eq}) of Reactions of 1,4-DHP and Indene-DHP with Potassium-Substituted Derivatives of Indicator Acids and Characteristics of Long-Wave Absorption of Their Anions in DMSO

Compound	Indicator	pK_a of indicator	K^*_{eq}	λ_{max}, nm	$\varepsilon \cdot 10^{-4}$
Ic	Imidazole	18,9	3,7±0,4	537	1,48
Ih	2-Phenyl-4,5-dibromoimidazole	11,0	0,077±0,01	590	2,60
IIa	2-Methylimidazole	19,9	2,05±0,10	452	1,67
IIb	2-Phenylbenzimidazole	16,2	1,0±0,15	420	1,08
IIc	2-Phenyl-4,5-dibromoimidazole	11,0	0,135±0,005	565	1,02
IIIa	2-Phenylimidazole	18,1	0,23±0,1	474	1,16
IIIb	2-Phenylimidazole	18,1	1,3±0,1	500	1,30
IIIc	2-Phenylbenzimidazole	16,2	1,12±0,05	540	1,70
IIId	2-Phenylbenzimidazole	16,2	3,35±0,05	645	2,30
IIIe	1,2,4-Triazole	15,4	0,84±0,04	445	1,00
IVa	Imidazole	18,9	8,9±0,4	460	1,42
IVb	Triazole	15,4	1,8±0,1	610	3,45
Ve	Triazole	15,4	3,6±0,4	598	1,40
Vf	Benzotriazole	12,6	3,6±0,4	598	1,40
Vg	Triazole	15,4	1,03±0,1	617	0,64
Vh	Triazole	15,4	0,83±0,06	590	1,06
Vi	Triazole	15,4	2,3±0,3	483	0,40
Vj	2-Phenyl-4,5-dibromoimidazole	11,0	0,6±0,1	630	0,95

*The pK_{eq} values of compounds Ia,b,d-g and Va-d were determined in [1].

Equation (2) can be used for an approximation of the contribution of the sulfur-containing substituents into the direct polar conjugation with an NH-acidic center of 1,4-DHP. For this purpose, the σ_1 values of the C(X)YR substituents, previously determined in [1] by the NMR method, were converted to the σ_1 scale using the values of this parameter for $C(O)OC_2H_5$: 0.19 in the NMR scale, and 0.30 on the conventional scale [9]. Using the thus obtained σ_1 values and the corresponding pK_a values in equation (2) gives the values of σ_R^- for sulfur-containing groupings $C(X)YC_2H_5$ (Tables 3 and 4).

It is seen that when the ether oxygen atom in the -COOR group is replaced by sulfur, the resonance of the group practically does not change. However, this effect substantially increases when the carbonyl oxygen atom is similarly replaced, which is possibly due to the participation of d-orbitals of the sulfur atom in the conjugation or its ready polarization. As a result, the resonance contribution of the substituents R = $C(S)XC_2H_5$ to the stabilization of the N-anion of DHP considerably exceeds the contribution of their inductive component, in contrast with the cases of the remaining substituents considered here.

Since the 1,4-DHP studied had a relatively limited set of β-substituents, the σ_R^- constants presented here should be considered as values by which the relationship between the resonance contributions of sulfur-containing groupings studied can be evaluated qualitatively only.

EXPERIMENTAL

The pK_a values of the NH-acids were measured in dilute solutions ($\leq 1.10^{-3}$ mole) of potassium substituted derivatives of indicator acids in thoroughly dried DMSO, using a fully welded evacuated (1×10^{-4} mm Hg) apparatus. The position of the equilibrium of the transmetallation reaction was recorded spectrophotometrically in quartz cuvettes on an "SF-4A" spectrometer. The spectral characteristics of the potassium-substituted indicators have been published in [10]. The colors of the solutions of the potassium-substituted 1,4-DHP vary from bright-red to blue.

The monocyclic 1,4-DHP were obtained by modified Hantzsch methods: Ia,b,d-g – according to [1, 11-16], IIa,b – according to [12, 17], IIIa-e – according to [18-20], IVa,b – according to [19, 21], Va-h – according to [2, 14, 22, 23], Vi, j – according to [3, 24]. The data of the elemental analysis correspond to the calculated values.

2,6-Dimethyl-3,5-dinitro-1,4-dihydropyridine (Ih, $C_7H_9N_3O_4$). A mixture of 0.92 g (10 mmoles) of nitroacetone [25], 0.75 g of hexamethylenetetramine and 0.4 g of ammonium acetate in 5 ml of acetic acid was heated for 30 min. The solvent was evaporated under vacuum, the residue was dissolved in 2 ml of acetone and the solution was deposited on a chromatographic column (silica gel L 40/100μ), using a 9:7:3:1 chloroform–hexane–acetone–ethanol mixture as

eluent. An orange fraction was collected. After evaporation of the solvents, the residue was crystallized from methanol. Yield, 0.37 g (37%) of pyridine Ic, mp 222°C (dec). UV spectrum (ethanol), λ_{max} 217(sh), 260, 323, 357, 450 nm (for the anion λ_{max} 570 nm), PMR spectrum (in DMSO-D_6): 2.40 (s, 6H, 2,6-$(CH_3)_2$); 3.76 (s, 2H, 4-H); 9.67 ppm (s, 1H, NH).

2,6-Dimethyl-4-phenyl-3,5-dinitro-1,4-dihydropyridine (IIc, $C_{13}H_{13}N_3O_4$). A mixture of 0.92 g (10 mmoles) of nitroacetone [25], 0.54 g (5 mmoles) of benzaldehydes and 4.3 g (50 mmoles) of ammonium acetate in 10 ml of acetic acid was boiled for 2 h, then cooled, and poured into 100 ml of water. The mixture was neutralized using sodium bicarbonate and extracted with ethyl acetate (3 × 50 ml). The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated under vacuum, and the residue was crystalized from methanol. Yield, 0.97 g (71%) of pyridine IIc, mp 178°C. UV spectrum (ethanol), λ_{max}: 207, 247, 263 (sh.), 304, 432 nm (for the anion λ_{max} 550 nm). PMR spectrum (DMSO-D_6): 2.40 (s, 6H, 2,6-$(CH_3)_2$); 5.56 (s, 1H, 4H); 7.22 (s, 5H, arom); 10.02 ppm (s, 1H, NH).

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