CHEMICAL TRANSFORMATIONS AND EVALUATION OF THE BASICITIES OF 4,5-DIHYDROPYRROLO[1,2,3-e,f][1,5]BENZODIAZEPIN-6(7H)-ONES

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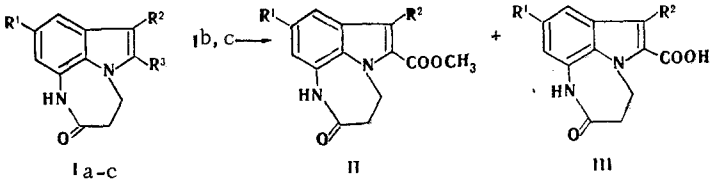
UDC 547.759.3'892.07

The alkaline hydrolysis, amidation, and methylation of 4,5-dihydropyrrolo[1,2,3-e,f][1,5]benzodiazepin-6(7H)-one derivatives under various conditions were investigated. The ionization constants (pK_α) for 1,2-dimethyl-4,5-dihydro[1,2,3-e,f][1,5]benzodiazepin-6(7H)-one were calculated by the Hammett indicator method, and two values, viz., $pK_\alpha^1 = -2.37$ and $pK_\alpha^2 = 5.53$, which were ascribed to protonation of the diazepine ring and the indole ring of the molecule, respectively, were obtained.

A study of the chemical properties of physiologically active substances seems of considerable interest both within the framework of modification of the existing structures and in order to synthesize possible products of metabolism; this ultimately makes it possible to obtain information regarding the dependence of the biological activity on the structures of the compounds and their chemical properties.

We studied some chemical transformations of representatives of the 4,5-dihydropyrrolo-[1,2,3-e,f][1,5]benzodiazepin-6(7H)-one series (Ia-c), which have pronounced tranquilizing activity.

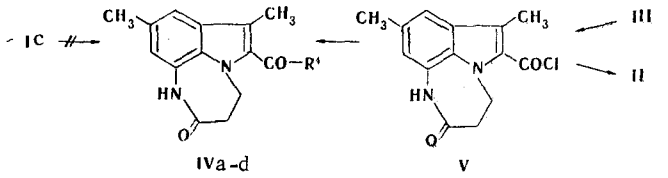
We showed that the alkaline hydrolysis of 2-ethoxycarbonyl derivatives (Ib, c) in an aqueous methanol solution leads to two products (II and III), the formation of which is readily explained by the presence of two nucleophiles, viz., CH_3O^- and HO^-, in the reaction medium. As expected, an increase in the reaction time gives only III in high yields.



Ia-c II III

Ia $R^1=H$, $R^2=R^3=CH_3$; b $R^1=H$, $R^2=CH_3$, $R^3=COOC_2H_5$; c $R^1=CH_3$, $R^2=C_2H_5$, $R^3=COOC_2H_5$

Despite the use in the reaction of such strong amines as diethylamine and piperidine, we were unable to realize the direct amidation of benzodiazepines Ib, c. However, amides IV and esters II are readily formed through the corresponding acid chloride V, which is used in the reaction without isolation and purification.



IVa-d V

IV a $R^4=N(C_2H_5)_2$; b $R^4=NHC_6H_5$; c $R^4=NC_5H_{10}$; d $R^4=\overline{NCH_2CH_2OCH_2CH_2}$

The methylation of Ia was carried out with methyl iodide in the presence of sodium hydride. We were unable to isolate 7-methyl derivative in dry benzene, but the reaction takes place readily in dry dimethylformamide (DMF); this is explained, in all likelihood, by the effect of the solvent.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 983-986, July, 1981. Original article submitted July 30, 1980.

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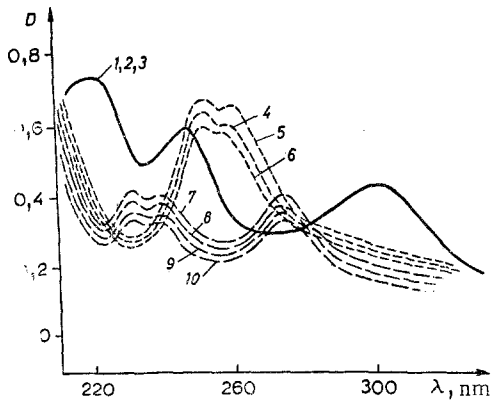


Fig. 1

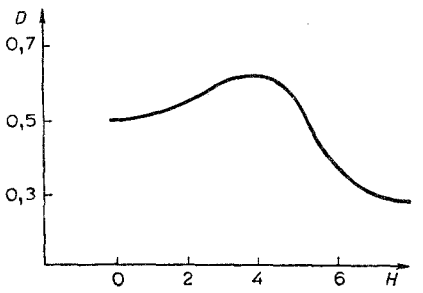
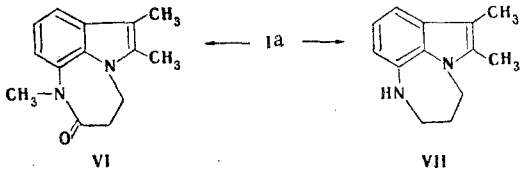


Fig. 2

Fig. 1. UV spectrum of 1,2-dihydro-4,5-dihydropyrrolo[1,2,3-e,f][1,5]-benzodiazepin-6(7H)-one: 1) in ethanol; 2) 16.9%; 3) 31.5%; 4) 44.1%; 5) 55.1%; 6) 64.8%; 7) 73.4%; 8) 81.1%; 9) 88.1%; 10) 94.3% H_2SO_4 solutions.

Fig. 2. Graph of the dependence of the optical density on the acidity function (H) at a wavelength of 252 nm for Ia.

The corresponding tetrahydro derivative VII was obtained by the action of lithium aluminum hydride in dry ether on Ic.



VI VII

The compositions and structures of all of the synthesized compounds (II-VII) were confirmed by spectral methods, the results of elementary analysis, and, in some cases, by alternative synthesis.

We evaluated the acid–base properties of representatives of the benzodiazepinone series (Ia-c) in the case of Ia. The basicity was estimated by means of the Hammett indicator method.

The ionization constants (pK_α) were measured by spectrophotometry by the standard method [1].

To calculate the ionization constants we used Eqs. (1) and (2):

$$pK_\alpha = H + \log\frac{d-d_m}{d_i-d}, \quad \text{if} \quad d_i > d_m \tag{1}$$

$$pK_\alpha = H + \log\frac{d_m-d}{d-d_i}, \quad \text{if} \quad d_m > d_i \tag{2}$$

where d_m is the optical density of a solution of the neutral molecule, d_i is the optical density of a solution containing the completely ionized form, and d is the optical density of a solution containing a mixture of the ion and the neutral molecule.

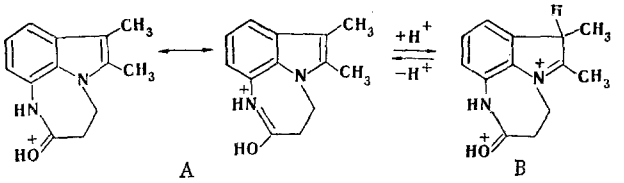
To obtain the absorption spectra of both acid-base forms we recorded the UV spectra at sulfuric acid concentrations from 16.9 to 94.3% (Fig. 1). The graph of the dependence of the optical density (D) for the analytical wavelength (λ 252 nm) on the H values (the acidity function) gives approximate values of the ionization constants (Fig. 2). The ionization constants were calculated precisely by means of Eq. (1) or (2) with the use of data obtained by measurements of the optical densities of five solutions of Ia in sulfuric acid with H values that are approximately distributed over the range H = pK_α ±0.5 (see Table 1).

Two pK_α values, viz., −2.37 ± 0.04 and −5.53 ± 0.02, were obtained. The first pK_α value corresponds to protonation of the amide group of the diazepine ring and the formation

TABLE 1. Results of the Determination of the Ionization Constants of 1,2-Dimethyl-4,5-dihydropyrrolo[1,2,3-e,f][1,5]-benzodiazepin-6(7H)-one

H	d	d_i	d_m	pK_α	C_H, g-eq/liter
			From Eq. (1)		
−2,07	0,563			−2,41	4,0
−2,24	0,578			−2,36	4,4
−2,45	0,594	0,650	0,523	−2,35	4,8
−2,61	0,604			−2,36	5,3
−2,74	0,613			−2,35	5,7
				$pK_\alpha^1 = -2,37 \pm 0,04$	
			From Eq. (2)		
−5,13	0,570			−5,55	10,0
−5,39	0,532			−5,54	10,4
−5,63	0,484	0,360	0,650	−5,51	10,8
−5,87	0,452			−5,52	11,2
−6,18	0,412			−5,52	11,7
				$pK_\alpha^2 = -5,53 \pm 0,02$	

of cation A. An analysis of the literature data indicates preponderant protonation at the oxygen atom [2, 3], although cases involving protonation at the nitrogen atom of the diazepine ring are also not excluded [4].



Protonation at the oxygen atom is characteristic for cyclic benzolactams [5], since in this case mesomeric bonding of the electron pair of the nitrogen atom with the p-electron sextet of the benzene ring is not disrupted, and this makes cation A energically more favorable than in the case of the cation formed by protonation at the nitrogen atom.

The pK_α value of −5.53 corresponds, in all likelihood, to protonation of the indole part of the molecule. The significant decrease in the pK_α values in the case of Ic as compared with, for example, the ionization constant of 2,3-dimethylindole (pK_a = − 3.3 [6]) is evidently associated with the electron-donor effect of the $-NH-\underset{|}{C}=\overset{+}{O}H$ on the distribution of the electron density over the entire molecule and the formation of cation B.

EXPERIMENTAL

The IR spectra of KBr pellets of the synthesized compounds were recorded with a Perkin–Elmer spectrometer. The UV spectra of solutions of the compounds in alcohol (in sulfuric acid in the case of Ia) were recorded with a Specord UV-vis spectrophotometer.

1,9-Dimethyl-2-carboxy-4,5-dihydropyrrolo[1,2,3-e,f][1,5]benzodiazepin-6(7H)-one (III). A 0.22-g (0.004 mole) sample of potassium hydroxide dissolved in the minimum amount of water was added to a solution of 0.35 g (0.0012 mole) of Ia in 35 ml of ethanol, and the reaction mixture was refluxed for 30 min. It was then cooled, and the solvent was evaporated *in vacuo*. The residue was dissolved in water and acidified to pH 4-5 with hydrochloric acid, and the resulting precipitate was removed by filtration and dried to give 0.26 g (85%) of a product with mp 345-347°C. Found: C 65.1; H 5.4; N 10.8%. $C_{14}H_{14}N_2O_3$. Calculated: C 65.2; H 5.4; N 10.7%.

1,9-Dimethyl-2-(morpholinocarbonyl)-4,5-dihydropyrrolo[1,2,3-e,f][1,5]benzodiazepin-6(7H)-one (IVd). A 0.15-ml sample of thionyl chloride and three to four drops of DMF were added to 0.25 g (0.001 mole) of III in 50 ml of dry chloroform, and the mixture was heated

TABLE 2. 1,9-Dimethyl-2-R^4-carbonyl-4,5-dihydropyrrolo[1,2,3-e,f][1,5]benzodiazepin-6(7H)-ones

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IVa	255—256	68,9	7,2	13,5	$C_{28}H_{23}N_3O_2$	69,0	7,4	13,4	80
IVb	343—345	72,0	5,8	12,7	$C_{20}H_{19}N_3O_2$	72,1	5,7	12,6	73
IVc	251—253	70,3	7,0	12,8	$C_{19}H_{23}N_3O_2$	70,1	7,1	12,9	82
IVd	273—275	66,2	6,5	12,7	$C_{18}H_{21}N_3O_2$	66,1	6,4	12,8	75

until the solid had dissolved completely, after which the solution was refluxed for 30 min. It was then cooled, and 7 ml of morpholine was added dropwise. The resulting mixture was diluted with water, and the excess morpholine was neutralized with dilute hydrochloric acid (1:1). The organic layer was separated and evaporated, and the residue was recrystallized from acetone.

Compounds IVa-c were similarly obtained. Data on IVa-d are presented in Table 2.

1,7,9-Trimethyl-4,5-dihydropyrrolo[1,2,3-e,f][1,5]benzodiazepin-6(7H)-one (VI). A 0.15-g sample of sodium hydride was added to a solution of 1.54 g (0.0054 mole) of Ia in 50 ml of dry DMF, and the mixture was heated at 60°C for 1 h. It was then cooled and treated with a solution of 0.84 g of methyl iodide in 9 ml of dry ether. The mixture was then allowed to stand at room temperature for 18 h, after which the solvent was evaporated *in vacuo*, and the residue was washed with water and extracted with methylene chloride. The extract was dried with potassium carbonate and evaporated, and the residue was purified by chromatography on silica gel [elution with acetone—ethyl acetate (1:1)] to give 0.6 g (40%) of VI with mp 103-105°C. Found: C 73.9; H 7.1; N 12.1%. $C_{14}H_{16}N_2O$. Calculated: C 73.7; H 7.0; N 12.3%.

1,2-Dimethyl-4,5,6,7-tetrahydropyrrolo[1,2,3-e,f][1,5]benzodiazepine (VII). A suspension of 0.9 g of lithium aluminum hydride in 50 ml of tetrahydrofuran (THF) was added with cooling (ice water) to a solution of 1.4 g (0.005 mole) of Ia in 50 ml of dry THF, after which the mixture was refluxed in a nitrogen atmosphere for 18 h. It was then cooled and treated with 0.9 ml of a 15% solution of potassium hydroxide and 10 ml of water, and the mixture was filtered. The filtrate was evaporated, and the residue was recrystallized from ethyl acetate to give 0.7 g (53%) of a product with mp 63-64°C. Found: C 78.2; H 8.1; N 14.3%. $C_{13}H_{16}N_2$. Calculated: C 78.0; H 8.0; N 14.0%.

LITERATURE CITED

1. A. Albert and E. Serjeant, Ionization Constants of Acids and Bases, Methuen (1962).
2. G. Fraenkel and G. Franconi, J. Am. Chem. Soc., 82, 4478 (1960).
3. R. Drago and D. Bafus, J. Phys. Chem., 65, 1066 (1961).
4. H. Fracejus, Chem. Ber., 92, 988 (1956).
5. R. Huisgen, J. Ugi, H. Brade, and E. Rauchenbusch, Ann., 586, 30 (1954).
6. G. Berti, A. Settino, and D. Segnini, Gazz. Chim. Ital., 91, 571 (1961).