SYNTHESES OF DI- AND TETRAHYDROPYRROLES.

XIII.* THERMODYNAMIC CHARACTERISTICS OF THE RING–CHAIN TAUTOMERIC EQUILIBRIUM OF 2,3,3-TRIMETHYL-1-ARYL-2-HYDROXY-5-PYRROLIDONES

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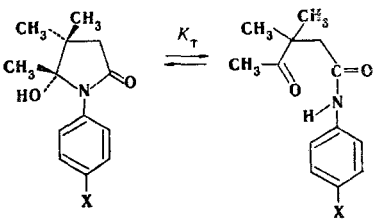
The constants and thermodynamic parameters of the ring–chain tautomeric equilibrium of p-substituted (benzene ring) 2,3,3-trimethyl-1-aryl-2-hydroxy-5-pyrrolidones in aqueous pyridine solution were determined by PMR spectroscopy. Conversion of the ring tautomer to the open form is accompanied by an increase in the enthalpy and entropy. The ΔH value decreases by a factor of 2.8 kcal/mole on passing from electron-donor substituents to electron-acceptor substituents, whereas the ΔS value remains approximately constant and decreases by 2-4 eu only for strong electron acceptors ($COOCH_3$, CN, and NO_2). The correlation between the free energies and the σ substituent constants in the benzene ring is discussed.

We have previously shown [1] that a ring-chain tautomeric equilibrium is established in solutions of 2,3,3-trimethyl-1-aryl-2-hydroxy-5-pyrrolidones (I). In the present research we have determined the effect of the substituents in the benzene ring on the constants and thermodynamic parameters of this equilibrium. For this, in analogy with [1, 2] we accomplished the synthesis of a number of previously undescribed p-substituted (benzene ring) 1-aryloxypyrrolidones Ia,d-f and keto amide IIg. The cyclic structure of Ia,d-f was established on the basis of IR and PMR spectral data. Broad absorption bands of OH groups at 3200-3400 cm^{-1} and intense absorption bands of C=O groups in lactams at 1665-1690 cm^{-1} are observed in the IR spectra of Ia,d-f. According to the PMR spectral data, these compounds exist exclusively in the cyclic form in freshly prepared solutions in chloroform (see [1, 2]). The 1-(p-cyanophenyl)-substituted derivative was isolated in the form of open tautomer IIg. Absorption at 1695-1705 cm^{-1} (ketone and amide C=O) is observed in its IR spectrum, but absorption is absent at 3200-3400 cm^{-1} (OH); singlets of a CH_3CO group at 2.21 ppm and of a 2-CH_2 group at 2.60 ppm, the position and intensity of which are close to those of the corresponding signals in the PMR spectrum of a specially synthesized compound with a "fixed" open form – 3,3-dimethyllevulinic acid N-methyl-N-phenylamide (CH_3CO 2.20 ppm and 2-CH_2 2.40 ppm) – are present in the PMR spectra of solutions in $CDCl_3$. The tautomeric equilibrium constants (K_T)



I a-h II a-h

I–II a X=$N(C_2H_5)_2$; b X=OCH_3; c X=H; d X=Cl; e X=COOH; f X=$COOCH_3$; g X=CN; h X=NO_2

*See [1] for communication XII.

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TABLE 1. Parameters of the PMR Spectra of Tautomeric Forms I and II of 1-Aryloxoypyrrolidones in 50% Aqueous Pyridine

Compound	X*	Chemical shifts, δ, ppm									
		form I						form II			
		3-$(CH_3)_2C$		2-CH_3, S	4-CH_A	4-CH_B	aryl, m	3-$(CH_3)_2C$, S	CH_3CO, s	2-CH_2, s	aryl, m
Ii	—	1,03	1,26	1,60	2,22	2,80	—†	1,26	2,35	2,77	— †
Ia	$N(C_2H_5)_2$	1,24	1,38	1,40	2,44	2,98	6,4—7,3	— †	2,41	—†	— †
Ib	OCH_3	1,22	1,38	1,40	2,49	3,03	6,9—7,7	— †	2,47	3,03	6,9—7,7
Ic	H	1,20	1,33	1,40	2,49	3,03	7,5—7,6	1,30	2,44	3,00	—†
Id	Cl	1,20	1,38	1,38	2,48	3,00	7,4—7,5	1,37	2,43	3,01	7,4—7,5
Ie	COOH	1,20	1,38	1,38	2,48	3,00	7,4—8,4	1,37	2,43	3,01	7,4—8,4
If	$COOCH_3$	1,24	1,41	1,41	2,51	3,05	7,5—8,2	1,38	2,45	3,08	8,0
Ig	CN	1,23	1,40	1,40	2,51	3,05	7,5—8,2	1,38	2,45	3,08	7,5—8,2
Ih	NO_2			1,43 (m)	2,53	3,09	7,5—8,5	1,43 (m)	2,48	— †	7,5—8,5

*Signals of the protons of substituents X: Ia, $(C_2H_5)_2$ 1.25 (t, 6H) and 3.30 (q, 4H); Ib, OCH_3 3.89 (s, 3H); If, $COOCH_3$ 4.04 (s, 3H). Signals of the protons of 3,3-dimethyl-2-methylene-5-pyrrolidones; Ii, 3-$(CH_3)_2C$ 1.19 (s, 6H), 2-CH_3 2.38 (s, 2H); CH_AH_B=C 4.17 (d, 1H) and 4.59 (d, 1H) (J_{AB} = 2.8 Hz); Ic, 3-$(CH_3)_2C$ 1.39 (s, 6H); 2-CH_3 2.67 (s, 2H); CH_AH_B=C 4.01 (d, 1H) and 4.13 (d, 1H) (J_{AB} = 2.3 Hz); Ih, 3-$(CH_3)_2C$ 1.46 (s, 6H); 2-CH_3 2.74 (s, 2H); CH_AH_B=C 4.20 (d, 1H) and 4.45 (d, 1H) (J_{AB} = 2.6 Hz).
†The signals were not isolated.

TABLE 2. Constants and Thermodynamic Characteristics of the Ring–Chain Tautomeric Equilibrium of p-Substituted Aryloxy-pyrrolidones Ia-i in 50% Aqueous Pyridine Solutions

X	K_T (34°)	$\Delta G - \Delta G°$ (15°C), kcal/mole	ΔH, kcal/mole	ΔS, eu
$N(C_2H_5)_2$	0,061±0,070*	−0,675	5,2±0,2	11,2±0,7
OCH_3	0,058±0,027	−0,604	5,1±0,2	11,1±0,7
H	0,171±0,071	0	4,7±0,2	11,8±0,7
Cl	0,190±0,010	0,075	4,8±0,3	12,4±0,8
COO−	0,229±0,010	0,298	4,5±0,3	12,1±1,0
$COOCH_3$	0,469±0,015	0,770	3,2±0,2	9,3±0,8
CN	0,601±0,030	0,928	3,1±0,4	9,5±1,0
NO_2	0,617±0,055	0,978	2,4±0,1	7,0±0,3
2,3,3-Trimethyl-2-hydroxy-5-pyrrolidone	0,068±0,009	—	5,3±0,2	11,9±0,6

*This is the K_T (40°) value.

of Ia-h and IIa-h in 50% aqueous pyridine solutions were determined from the ratios of the integral intensities of the signals of the tautomeric forms, the PMR spectral parameters of which are presented in Table 1. The presence of water in the solvent is necessary to avoid dehydration of the cyclic tautomer, particularly at high temperatures (see [1]).

It is apparent from Table 2 that electron-donor substituents in the para position of the benzene ring lower the K_T values as compared with unsubstituted 1-phenyl hydroxypyrrolidone derivative Ic, whereas electron-acceptor substituents raise them.

The enthalpies (ΔH) and entropies (ΔS) (Table 2) were obtained from the temperature dependences of the tautomeric equilibrium constants (see Fig. 1). The increase in entropy on conversion of the cyclic tautomer to the open tautomer (in agreement with the increase in the conformational freedom of the molecules) for most of the compounds, except for If-h, is practically independent of the nature of the substituent in the benzene ring and is close to 11-12 eu. A symbatic decrease in ΔH and ΔS (of 2-2.8 kcal/mole and 3-5 eu, respectively) is

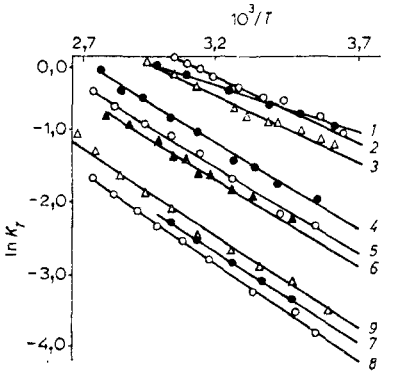

Fig. 1. Temperature dependence of the tautomeric equilibrium constants of hydroxypyrrolidones Ia-i in 50% aqueous pyridine: 1) X = NO_2, correlation coefficient r = 0.99; 2) X = CN, r = 0.96; 3) X = $COOCH_3$, r = 0.98; 4) X = COOH, r = 0.98; 5) X = Cl, r = 0.99; 6) X = H, r = 0.99; 7) X = OCH_3, r = 0.99; 8) X = $N(C_2H_5)_2$, r = 0.99; 9) Ii, r = 0.99.

observed for compounds with strong electron-acceptor substituents (If-h) ($COOCH_3$, CN, and NO_2). The decrease in ΔS, i.e., the decrease in the conformational freedom of the open tautomers for IIf-h, is possibly associated with the formation of a stronger intramolecular hydrogen bond of the C=O...H—N type because of the reduced basicity of the nitrogen atom in these compounds as a consequence of the electron-acceptor effect of substituents X. The K_T, ΔH, and ΔS values of N-unsubstituted 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone Ii, which are presented in Table 2 for comparison, are close to the corresponding values of Ia,b (i.e., compounds containing electron-donor groups in the para position of the benzene ring).

Good correlation with the electrophilic σ^+ substituent X constants is observed for the changes in the free energy $\Delta\Delta G$ (or, correspondingly, log K/K_0) (log $K/K_0 = 1.38\sigma^+$, r = 0.96, s = 0.18, and F = 2.08*).† However, the points corresponding to the electron-donor substituents are shifted markedly to the left from the $\Delta\Delta G - \sigma^+$ line drawn through the points corresponding to the remaining substituents. Thus for coincidence of these values with the line the σ values should be lower in absolute value than the σ^+ values (see [3]).

Satisfactory correlations were also obtained when σ_p values (log $K/K_0 = 1.85\sigma_p$, r = 0.93, s = 0.33, and F = 1.14) and nucleophilic σ_p^- substituent constants (log $K/K_0 = 1.45\sigma_p^-$, r = 0.935, s = 0.24, and F = 1.25) were used. Comparison of the correlation coefficients (r) and the Fischer coefficients (F) does not make it possible to make an unambiguous choice between the σ_p and σ_p^- substituent constants. However, it should be noted that although the use of σ^- constants is required for a number of reaction series in the aniline series (ionization of the anilinium ions and acylation and alkylation of anilines) [3], in the case of acylated anilines, to which class both of the tautomeric forms under consideration belong, direct polar conjugation of the electron-acceptor substituents with the free electron pair of the nitrogen atom becomes less likely (because of their conjugation with the carbonyl group). In this connection, in this case one should evidently prefer a correlation of $\Delta\Delta G$ with the σ_p substituent constants.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra of solutions (0.4 mole/liter) of the compounds were recorded with a Hitachi—Perkin—Elmer R-20A spectrometer (60 MHz); the internal standard was hexamethyldisiloxane (sodium 2,2-dimethyl-2-silapentane-5-sulfonate for aqueous pyridine solutions of the compounds). It was shown that the position of the ring-chain equilibrium depends very slightly on the concentration of the 1-aryloxypyrrolidones at concentrations from 0.1 to 0.4 mole/liter. The percentages of the tautomers at 0-100° were determined from the ratios of the integral intensities of the signals of the 4-CH_AH_B, 2-CH_3, and 3-$(CH_3)_2$ groups of the cyclic tautomer and the corresponding signals of the linear tautomer. No less than 10 integ-

*The F value is the Fischer coefficient and is equal to the ratio of the reproducibility errors to the linear regression errors with allowance for the number of degrees of freedom (see [4]).

†The compliance with Brown's equation (i.e., correlation with the σ^+ constants) noted during a study of the ring—chain tautomeric equilibrium of 2-aryl-4,4-dimethyloxazolidines and 3-arylamino-3-phthalides, as well as the keto-enol tautomerism of ethyl esters of substituted benzoylacetic acids [4-6], is associated with the structures of these compounds rather than with the type of tautomeric transformations.

ral curves with subsequent statistical treatment in a 95% probability interval were recorded at each temperature. The samples were maintained at a fixed temperature for 15 min. It was shown that the spectra remained unchanged when the samples were maintained at the fixed temperature for longer periods (up to 2-3 days), and this served as a criterion for the achievement of equilibrium. A small (equilibrium) amount of the corresponding 3,3-dimethyl-2-methylene-1-aryl-5-pyrrolidones is formed in addition to the tautomers in the case of 1-aryloxypyrrolidones Ic,h. Potassium bicarbonate (0.11 mole/liter) was added to the samples in a number of cases to accelerate the achievement of equilibrium. In this case we observed conformity between the data obtained with potassium bicarbonate and the data obtained in its absence. Potassium chloride (0.11 mole/liter) was added to the samples that did not contain potassium bicarbonate in order to maintain a solution with constant ionic strength. The calculation of the ΔH and ΔS values and the correlation of the $\Delta\Delta G$ values with the σ^+, σ^-, and σ_p substituent constants were effected by the method of least squares.

Aryloxypyrrolidone Ic was obtained by the method in [2] and aryloxypyrrolidones Ib,h were obtained by the method in [1].

4-Chloro-3,3,4-trimethyl-4-butanolide. A solution of 14.1 g (0.1 mole) of dimethyllevulinic acid and 16.6 g (0.14 mole) of thionyl chloride in 140 ml of chloroform was maintained at 20° for 2 days, after which it was vacuum evaporated (at 20°) to give 16.2 g (100%) of 4-chloro-3,3,4-trimethyl-4-butanolide with mp 85-85.5° (mp 86° [7]). The PMR spectrum in CCl_4 was identical to the spectrum of a sample obtained by the method in [8].

2,3,3-Trimethyl-1-(p-diethylaminophenyl)-2-hydroxy-5-pyrrolidone (Ia). A solution of 12.8 g (80 mmole) of 4-chloro-3,3,4-trimethyl-4-butanolide and 12.2 g (75 mmole) of diethylaminoaniline in 30 ml of pyridine was heated at 100-110° for 80 h, after which the solvent was removed by distillation, and the residue was dissolved and washed with 10% aqueous KOH and 15% HCl solution. The hydrochloric acid extract was made alkaline to pH 10-11 with KOH and extracted with chloroform. Workup of the chloroform extract gave 15.9 g (69.5%) of hydroxypyrrolidone Ia. To obtain an analytically pure sample, the reaction product was dissolved in ethyl acetate, and the solution was allowed to evaporate freely to give white crystals with mp 124-124.5°. PMR spectrum (in $CDCl_3$): 3-$(CH_3)_2C$ and 2-CH_3 1.18 (s, 9H); CH_3CH_2O 1.18 (t, 3H); 4-CH_AH_B 1.89/2.16/2.45/2.75 (q, AB system, 2H, J_{AB} = 16.2 Hz); OH 3.70 (s, 1H), C_6H_4 6.50, 6.66, 6.93, and 7.08 (q, 4H, J = 9.6 Hz) ppm. IR spectrum: 1665 (lactam CO); 3170-3240 (OH, broad band) cm^{-1}. Found, %: C 70.2; H 9.1; N 10.2. $C_{17}H_{26}N_2O_2$. Calculated, %: C 70.3; H 9.0; N 9.6.

2,3,3-Trimethyl-1-(p-chlorophenyl)-2-hydroxy-5-pyrrolidone (Id). This compound was similarly prepared from 2.5 g (20 mmole) of p-chloroaniline, 1.0 g of a mixture of hydroxypyrrolidone Id and 3,3-dimethyl-2-methylene-1-(p-chlorophenyl)-5-pyrrolidone. The components were dissolved in 10 ml of 80% aqueous methanol, 0.25 ml of concentrated HCl was added, and the mixture was heated at 80-90° for 5 h. Potassium carbonate (0.05 g) was added and the mixture was evaporated to dryness at 20°. The residue was dissolved in chloroform, the solution was filtered, and the filtrate was evaporated at 20° with a rotary evaporator. Workup gave 0.8 g (15.8%) of hydroxypyrrolidone Id as a slowly crystallizing light-brown oil. To obtain an analytical sample, a portion of the crystallized substance was washed with cold ethyl acetate until white crystals formed on the filter. The pure product had mp 105-105.5°. PMR spectrum (in $CDCl_3$): 3-$(CH_3)_2C$ 1.09 (s, 3H) and 1.15 (s, 3H); 2-CH_3 1.15 (s, 3H); 4-CH_AH_B 1.91/2.18/2.47/2.74 (q, AB system, 2H, J_{AB} = 16.7 Hz), C_6H_4 7.06-7.59 ppm (m, 4H). IR spectrum: 3390 (OH), 1680 (lactam CO) cm^{-1}. Found, %: C 6.19; H 6.3; N 5.1. $C_{13}H_{16}ClNO_2$. Calculated, %: C 61.5; H 6.3; N 5.5.

2,3,3-Trimethyl-1-(p-carboxyphenyl)-2-hydroxy-5-pyrrolidone (Ie). The alkaline aqueous extract from the preceding experiment (obtained after washing the chloroform solution of the reaction mixture with 10% aqueous KOH solution) was acidified to pH 2 with HCl and extracted with chloroform. When the chloroform solution was allowed to stand for a long time, it yielded 0.25 g (2%) of white crystals of Ie with mp 196-197°. PMR spectrum (in CD_3OD): 3-$(CH_3)_2C$ and 2-CH_3 1.15 (s, 3H) and 1.22 (s, 6H); 4-CH_AH_B 2.05/2.32/2.61/2.88 (q, AB system, 2H, J_{AB} = 16.2 Hz); C_6H_4 7.36/7.51/8.02/8.17 (q, 4H, J = 9 Hz) ppm. PMR spectrum (in C_5D_5N): 3-$(CH_3)_2$ and 2-CH_3 1.05 (s, 3H); 1.27 (s, 3H) and 1.37 (s, 3H); 4-CH_AH_B 2.10/2.37/2.70/2.97 (q, AB system, 2H, J_{AB} = 16.2 Hz); C_6H_4 7.27/7.88/8.29/8.45 (q, 4H, J = 9.6 Hz), NH and OH 11.30 ppm. IR spectrum: 1685 (shoulder at 1635; lactam and acid CO), 3315 and 3405 (lactam OH), and 2300-3500 cm^{-1} (COOH). Found,%: C 63.7; H 6.5; N 4.8. $C_{14}H_{17}NO_4$. Calculated, %: C 63.9; H 6.5; N 5.3.

3,3-Dimethyllevulinic Acid N-(p-Cyanophenyl)amide (IIg). The method used to prepare Ia was used to synthesize this compound from 2.4 g (20 mmole) of p-aminobenzonitrile. Workup gave 2.0 g of an oily product, which was dissolved in 20 ml of methanol—water—chloroform saturated with HCl (15:2:1), and the resulting solution was heated at 80° for 3 h. It was then evaporated with a rotary evaporator at 20°, and the residue was dissolved in 15 ml of chloroform and reprecipitate by the addition of hexane to give 1.5 g (31%) of anilide IIg with mp 150-151°. PMR spectrum (in $CDCl_3$): 3-$(CH_3)_2C$ 1.29 (s, 6H); CH_3CO 2.21 (s, 3H); 2-CH_2 2.60 (s, 2H); C_6H_4 7.58 (m, 4H) ppm. IR spectrum: 1695-1705 (amide and ketone CO), 2220 (CN), and 3325 cm^{-1} (NH). Found, %: C 68.8; H 6.4; N 11.3. $C_{14}H_{16}N_2O_2$. Calculated, %: C 68.8; H 6.6; N 11.4.

3,3-Dimethyllevulinic Acid N-Methyl-N-phenylamide. This compound was obtained by the method in [2] from 1.52 g (15 mmole) of N-methylaniline anilide, which was removed by vacuum distillation. Workup gave 2.1 g (90.3%) of a product with bp 105-107° (0.08 mm). PMR spectrum (in $CDCl_3$) : 3-$(CH_3)_2C$ 1.10 (s, 6H); CH_3CO 2.20 (s, 3H); 2-CH_2 2.40 (s, 2H), N-CH_3 3.21 (s, 3H); C_6H_5 7.01-7.40 (m, 5H) ppm. IR spectrum (in a thin layer): 1710 (ketone CO) and 1660 cm^{-1} (amide CO). Found, %: C 71.8; H 7.8; N 5.8. $C_{14}H_{19}NO_2$. Calculated, %: C 72.0; H 8.2; N 6.0.

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MASS SPECTROMETRIC STUDY OF ISATINS.

II.* N-PROPYL(ALLYL, PROPARGYL)ISATINS

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UDC 543.51:547.756

The mass spectra of N-propyl- (I), N-allyl- (IV), and N-propargylisatin (VII) and their 5-methyl (II, V, VIII) and 7-methyl (III, VI, and IX) derivatives were recorded. It is shown that a portion of the $[M-2CO]^+$ ions in the mass spectra of N-propargylisatins undergo rearrangement to give ions with a quinoline structure. A scheme for the fragmentation of the investigated compounds is presented. The mass spectra of the 5- and 7-methyl derivatives are compared.

*See [1] for communication I.

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