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REACTION OF ACETYLTETRAMIC ACID WITH *o*-PHENYLENEDIAMINE

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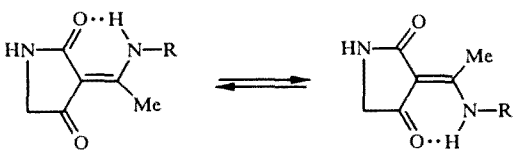
Acetyltetramic acid forms 3-[α-(2-aminophenylamino)ethylidene]-2,4-pyrrolidinedione (Ia) with o-phenylenediamine. NMR spectroscopy showed that compound Ia in solutions of $CDCl_3$ and DMSO exists as an equilibrium mixture of two rotational isomers caused by hindered rotation around an exocyclic double bond. The analysis of the ^{13}C NMR spectra of compounds of type I and the results of quantum chemical calculations indicate preferred chelation of amide carbonyl and predominance of the corresponding rotamer. The reaction of Ia with hydrochloric acid yields 10-methyl-1H-benzo[b]pyrrolo[3,4-f]-1,4-diazepin-1-one.

In continuing the studies on synthesis of 3-acyl-1,5-benzodiazepines in [1-3], we investigated the reaction of acetyltetramic acid with *o*-phenylenediamine. It was found that the reaction of equimolar quantities of these reagents in ethanol yields dark red 3-[α-(2-aminophenylamino)ethylidene]-2,4-pyrrolidinedione (Ia).



I a,b

I a R = *o*-$NH_2C_6H_4$; b R = Ph

The reaction of the N-nucleophile with the exocyclic carbonyl of acetyltetramic acid is in agreement with the published data [4, 5] and is confirmed by the data from the IR and NMR spectra.

A primary amino group (ν_{NH_2} 3470, 3380 cm^{-1}) and the NH group of the ring (ν_{NH} 3190 cm^{-1}) are clearly detected in the IR spectra of Ia.

Two sets of resonance signals of nonequivalent protons with an integral intensity ratio of 1.13 in $CDCl_3$ and 1.9 in DMSO-D_6 are observed in the ^1H NMR spectrum of compound Ia (Table 1). The signals of protons of the predominant isomer are located in a stronger field than the corresponding signals of the minor isomer.

It was previously experimentally shown in [6] that prototropic tautomerism is absent in compound Ib, the H-chelate proton is localized at the $N_{(9)}$ nitrogen atom ($^1J_{N,H}$ ~90 Hz), the significantly reduced order of the exocyclic $C_{(3)}=C_{(6)}$ double bond as a result of $p-\pi$ conjugation enables rotational isomerism relative to the $C_{(3)}=C_{(6)}$ bond in compounds of type I, and they can exist as an equilibrium mixture of rotamers A and B in certain conditions.

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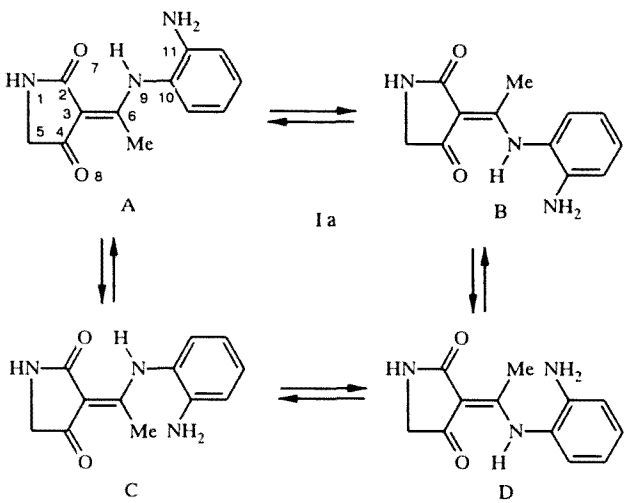
TABLE 1. PMR Spectra of Compounds Ia, b

Compound	Solvent	Chemical shifts, δ, ppm			Ratio of isomers
		CH_3	CH_2	NH	
Ia	$CDCl_3$	2,29*, 2,32	3,56*, 3,64	11,64*, 11,78	1,12
	DMSO	2,43*, 2,46	3,76*, 3,82	11,61*, 11,97	1,89
	DMSO + CF_3COOD	2,23	3,78	10,3	—
Ib*[2]	DMSO	2,17*, 2,20	3,56*, 3,64	12,22*, 12,31	2,57
	$CDCl_3$	2,53*, 2,57	3,76*, 3,82	12,09*, 12,03	1,13
	CF_3COOD	2,85	4,18	—	—

*Predominant isomer.

*[2]The PMR spectral data from [7] were used.

The data in the ^1H NMR spectra, including the ratio of isomers determined in [6, 7] for compound Ib, are close to the data from the spectra of compound Ia, which demonstrates the similarity of these structures. However, they are insufficient for solving the problem of the structure of the predominant isomer, since they do not allow assigning the observed signals to concrete rotamers (A or B). The opinions on this question differ. Saito et al. [6, 8] give preference to isomer B in compounds of type I, while Gelin [5] states the opposite. Not two, but a larger number of isomers are theoretically possible for compound Ia which we synthesized (in consideration of the possible orientation of the *o*-substituent in the phenyl ring).



We calculated the possible geometric isomers of compounds Ia and Ib in the LCAO MO approximation with the AM1 method [9] by varying the $\alpha(C_{(6)}-N_{(9)}-C_{(10)}-C_{(11)})$ torsion angle with a 30° step and optimizing all geometric parameters, including this torsion angle, to refine the information on the predominant rotamer in compounds of type I and to obtain data on their relative thermodynamic stability in the ground state. As the heats of formation (ΔH_f) obtained as a result of the calculations show, of the four isomers (A, B, C, and D), A and B are energetically the most advantageous for compound Ia. In turn, isomer A is the most stable in pairs of rotamers A and B for both compounds Ia and Ib (Table 2).

Additional information on the structure of type I compounds can be obtained from the ^{13}C NMR spectra of compounds Ia (DMSO) and Ib ($CDCl_3$) [8], which also consist of a double set of signals. The observed signals were assigned in consideration of the character of the spin–spin interaction in the proton-bound spectra (Table 3). Note the actual equality of the ^{13}C chemical shifts in both compounds, despite the difference in solvents and substituents. The low-pole part of the ^{13}C NMR spectrum of compound Ia corresponding to the signals of $C_{(2)}$, $C_{(4)}$, and $C_{(6)}$ atoms is shown in Fig. 1. A similar absorption picture was reported for compound Ib in [8]. It should be noted that the greatest difference in the ^{13}C chemical shifts of both isomers is observed for $C_{(4)}$ and $C_{(2)}$ atoms. In going from the predominant rotamer to the minor rotamer, the signal of the $C_{(2)}$ atom is shifted to the strong field almost as much as the signal of the $C_{(4)}$ atom is shifted to the weak field. In the

TABLE 2. Data from Quantum Chemical Calculations of Compounds Ia, b

Compound	Isomer	Optimized bond lengths, Å									ΔH_f, kcal/mole	$(C_{(6)}-N_{(9)}-C_{(10)}-C_{(11)})$, deg
		$N_{(1)}-C_{(2)}$	$C_{(2)}-C_{(3)}$	$C_{(3)}-C_{(4)}$	$C_{(4)}-C_{(5)}$	$C_{(2)}-O_{(7)}$	$C_{(4)}-O_{(8)}$	$C_{(3)}-C_{(6)}$	$C_{(6)}-N_{(9)}$	$N_{(9)}-C_{(10)}$		
Ia	A	1,401	1,481	1,460	1,541	1,248	1,232	1,385	1,362	1,415	-27,095	122,40
	B	1,408	1,481	1,459	1.537	1,243	1,235	1,384	1,364	1,415	-26,665	122,65
	C	1,403	1,481	1,460	1,540	1,246	1,233	1,384	1,361	1,417	-24,447	72,80
	D	1,407	1,481	1,459	1,537	1,243	1,235	1.384	1,362	1.417	-26,015	70,80
Ib	A	1,401	1,482	1,461	1,540	1,247	1,232	1,383	1,364	1,413	-26,015	52,12
	B	1,407	1,483	1,461	1,536	1,243	1,235	1,383	1,366	1,412	-25,479	47,86

TABLE 3. Charges on Atoms of Different Forms of Compounds Ia, b

Compound	Isomer	Charges on atoms									
		$N_{(1)}$	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$O_{(7)}$	$O_{(8)}$	$N_{(9)}$	$C_{(10)}$
Ia	A	−0,375	0,366	−0,437	0,291	−0,086	0,249	−0,409	−0,319	−0,254	−0,047
	B	−0.373	0,365	−0,436	0,284	−0,088	0,242	−0,373	−0,338	−0,258	−0,043
	C	−0,375	0,364	−0,437	0,289	−0,086	0,233	−0,394	−0,323	−0,251	−0,055
	D	−0,374	0,365	−0,435	0,285	−0,086	0,234	−0,377	−0,336	−0,253	−0,057
Ib	A	−0,377	0,365	−0,428	0,290	−0,085	0,242	−0,398	−0,318	−0,260	0,038
	B	−0,374	0,365	−0,425	0,284	−0,086	0,243	−0,372	−0,337	−0,261	0,040

TABLE 4. Data from ^{13}C NMR Spectra of Compounds Ia (DMSO-D_6) and Ib ($CDCl_3$)

Compound	Chemical shift, δ, ppm				
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$
Ia	175,4*, 172,0	96,3*, 98,2	193,7*, 197,1	50,5*, 48,9	167,3*, 167,9
Ib*2	176,1*, 173,4	96,5*, 98,4	194,3*, 197,3	51,0*, 49,6	166,6*, 167,0
	SSCC, ^nJ (^{13}C, ^1H), Hz				
	$^3J_{C_4,H}$	$^2J_{C_4,H}$	$^1J_{C_5,H}$	$^2J_{C_5,H}$	$^2J_{C_6,H}$
Ia	2,8	5,7	142,8	4,0	5,7
Ib*2	2,8	4,5	—	—	—

*Predominant isomer.

*2The ^{13}C NMR spectral data from [8] were used.

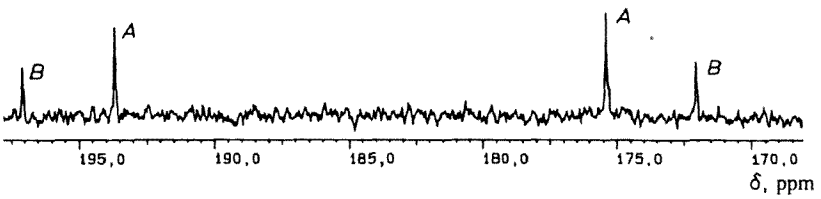


Fig. 1. Low-pole part of the $^{13}C-\{^1H\}$ NMR spectra of compound Ia in DMSO-D_6.

studies of compound Ib by Saito et al. [8], the more intense signals (see Fig. 1) are assigned to isomer B. However, this assignment is doubtful, as it is known [10-12] that formation of intramolecular hydrogen bonds is accompanied by a shift in the signal of the carbonyl and amide group carbon atom to the weak field in comparison to the absorption of the group not contained in the H-chelate ring. The difference in the chemical shifts of bound and free carbonyl and amide groups in rotamers A and B of compounds Ia, b is of almost the same magnitude and is opposite in sign, and its value is close to the difference in the ^{13}C chemical shifts of free and bound carbonyl groups observed in 2-aminomethylene-1,3-diketones [11, 12]. The signals of higher intensity thus correspond to a free carbonyl group and bound amide carbonyl, i.e., the predominance of structure A (and not B, as stated in [6-8]) for the predominant isomer in type I compounds is convincingly supported. The preferred chelation of the amide carbonyl in type I compounds, as well as in tetramic acids [13, 14], can be attributed to the fact that the amide carbonyl group is characterized by high electron density on the oxygen atom in comparison to the ketone group as a result of the resonance contribution of $HRN_1-C_2=O_7 \rightleftarrows HRN^+=C_2-O_7^-$. This is also confirmed by the data from the quantum chemical calculations reported in Table 4.

Note the basic properties of the steric and electronic structure of compounds Ia, b. It should be expected that the equilibrium conformations of the molecule will be determined by both factors which attempt to make the molecule planar (hydrogen bond, $p-\pi$ conjugation) and steric hindrances which displace the phenyl substituent from the plane of the remainder of the molecule. As the calculations show, the heterocyclic and enamine fragments of molecules Ia, b are in virtually the same plane, while the nonplanar orientation of the phenyl substituent relative to the plane of the remainder of the molecule reduces the steric hindrances to the minimum ($\alpha(C_{(6)}-C_{(9)}-C_{(10)}-C_{(11)})$ torsion angle of approximately 122.4° and 52.12° for the most stable conformations A of compounds Ia and Ib). A comparison of the geometric characteristics of both compounds shows that incorporation of an amino group in the *o*-position of the substituent is not actually accompanied by a change in both the geometry of the molecule and the distribution of charges in it (Tables 2 and 4). A tendency toward equalization of the bond lengths is observed in the heterocycle and enamine fragment: the double bonds are formally strongly lengthened in comparison to the standard values [15], and the single bonds are significantly shortened, indicating effective delocalization of π-electrons in these molecules. The small difference in the calculated heats of formation of forms A and B of compound I and the equilibrium character of A $\rightleftarrows$ B isomerization suggest the possibility of a comparatively easy transition between the two ro-

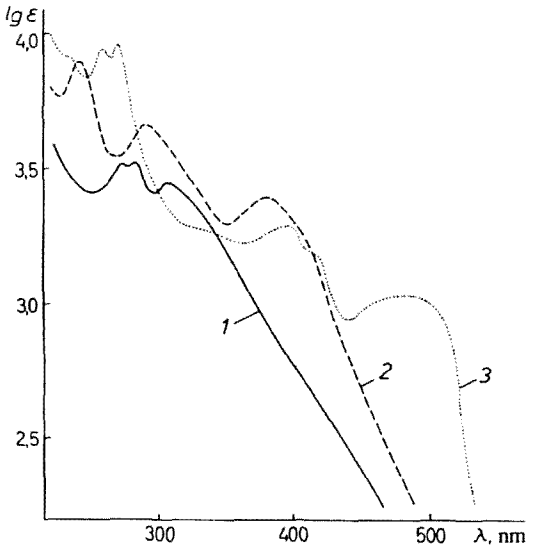
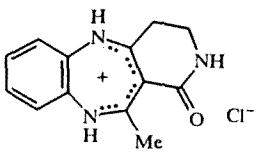


Fig. 2. Electronic absorption spectra: 1) Ia in ethanol; 2) II in 50% ethanol in the presence of NaOH; 3) Ia and II in 50% ethanol in the presence of HCl.

tamers when the external conditions change. For example, addition of trifluoroacetic acid to a solution of compound Ia in DMSO results in coalescence of the resonance signals in the ^1H NMR spectrum (Table 1), which indicates that hindered rotation around the exocyclic double bond becomes rapid on the NMR scale, and the rotamers are almost indistinguishable.

Treatment of an ethanol solution of compound Ia with concentrated hydrochloric acid results in the formation of black-wine-red 10-methyl-1H-benzo[*b*]pyrrolo[3,4-*f*]-1,4-diazepin-1-one hydrochloride (II), whose structure was confirmed by the IR and PMR spectra data reported in the experimental section.



II

The UV spectra of solutions of compounds I and II in strongly acid medium (Fig. 2) are identical and characterize the diazepine cation with an absorption maximum at 485 nm [1, 3].

EXPERIMENTAL

The IR spectra were made on a Specord 75-IR for suspensions of the substances in Nujol and hexachlorobutadiene and the electronic absorption spectra were made on a Specord M-40 spectrophotometer with a 10^{-5} M concentration of the solutions. The ^1H NMR spectra were recorded on Bruker WH-90/DS and Bruker AM-360 instruments with a working frequency of 90 and 360 MHz, respectively, and the ^{13}C and ^{13}C-{^1H} NMR spectra were made on a Bruker Am-360 in DMSO solution. The ^1H and ^{13}C chemical shifts were measured against TMS internal standard.

The data from elemental analysis of compounds I and II for C, H, Cl and N corresponded to the calculated data.

3-[α-(2-Aminophenylamino)ethylidene]-2,4-pyrrolidinedione (Ia, $C_{12}H_{13}N_3O_2$). A solution of 0.54 g (5 mmole) of *o*-phenylenediamine in 20 ml of ethanol at the same temperature was added to a solution of 0.70 g (5 mmole) of acetyltetramic acid in 20 ml of ethanol at 70-75°C and left at 20°C for 24 h. A rotary evaporator was used to distill 15-20 ml of ethanol from the darkened reaction mixture, the sediment was left for 24 h, the dark red residue was filtered off, and 0.63 g (55%) of Ia was obtained, mp = 189-191°C (from ethanol).

IR spectrum (3600-2000 cm^{-1} region without indication of the frequencies of the C–H bond stretching vibrations and 1800-1500 cm^{-1}): 3470, 3380, 3190, 1680, 1665, 1630, 1590, 1580, 1550 cm^{-1}.

10-Methyl-1H-benzo[*b*]pyrrolo[3,4-*f*]-1,4-diazepin-1-one Hydrochloride (II, $C_{12}H_{11}$, ClN_3O). Here 2 ml of conc. hydrochloric acid was added to a solution of 0.46 g (2 mmole) of compound Ia in 20 ml of ethanol, held for 24 h at 5°C, the black-wine-red crystals of II were filtered off and washed on the filter with diethyl ether. Yield of 0.35 g (70%). Mp = 252-256°C. IR spectrum: 3190, 2900-2700, 1710, 1695, 1665, 1625, 1610, 1560, 1520 cm^{-1}. PMR spectrum (DMSO-D_6): 2.35 (3H, s, CH_3), 3.65 (2H, s, CH_2), 6.50-7.00 (4H, m, C_6H_4), 7.60 (1H, NH), 10.89 (1H, NH), 11.11 ppm (1H, NH).

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