INVESTIGATION OF THE REACTIVITIES AND TAUTOMERISM OF AZOLIDINES.

46.* PMR SPECTRA AND STRUCTURES OF THE PRODUCTS OF HYDROXYMETHYLATION AND AMINOMETHYLATION OF 2-IMINO-5-ARYLIDENE-4-THIAZOLIDINONES

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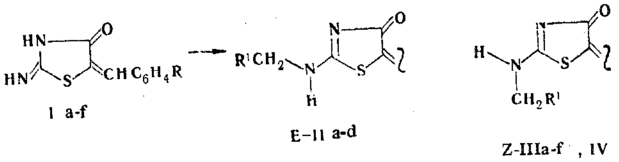
On the basis of dual reactivity concepts, it is shown that the hydroxy- and aminomethylation of ambifunctional 2-imino-5-R-benzylidene-4-thiazolidinones (R = H, p-Cl, p-OCH_3, p-Br, and p-F) should be directed to the same reaction center. On the basis of PMR spectroscopic data, it was confirmed that this center is the exocyclic nitrogen atom. It was established that 2-piperidinomethylamino-5-R-benzylidene-4-thiazolinones (R = H, p-Cl, p-NO_2, p-OCH_3, p-Br, and p-F) exist in d_6-DMSO primarily in the form of E conformers of the amino form. The E conformers of the latter compounds are chelate structures with an intramolecular hydrogen bond.

We have previously shown [2] that 2-imino-5-arylidene-4-thiazolidinones (Ia-d) react with piperidine and aqueous formaldehyde in dioxane to give 2-piperidinomethylamino-5-arylidene-4-thiazolinones (IIa-d). The reaction of Ia-f with formalin in the same solvent leads to the formation of 2-hydroxymethylamino-5-arylidene-4-thiazolinones (IIIa-f).



I a R=H, b *p*-Cl, c *p*-NO_2, d *p*-OCH_3, e *p*-Br, f *p*-F; IIa-d R^1=piperidyl; IIIa-f R^1=OH; IV R^1=H

In addition to the proof of the structures of II and III [2], confirmation of the alkylation at the same reaction center, viz., the exocyclic nitrogen atom, was presented in [2].

From the assumptions of dual reaction theory [3] the ratios of the possible isomeric products in hydroxy- and aminomethylation should be close, both in the case of kinetic and thermodynamic control of the reaction; there is no need to postulate aminomethylation through the initial addition of the ambident anion to formaldehyde, as was done in [4]. The carbonium-immonium ion (CII), like the formaldehyde molecule, is a "hard" electrophile [5], and both electrophilic particles will attack primarily the "harder" center of the ambident anion of I. Precisely the close values of the α and β parameters on the Davis oxy base scale [6] ($\alpha_{CD_2O} \approx \alpha_{CII}$, $\beta_{CH_2O} \approx \beta_{CII}$) rather than localization of the negative charge in the ambident anion on a certain heteroatom, as follows from the schemes presented in [7], are responsible for the identical regioselectivity of hydroxy- and aminomethylation in the case of kinetic control. If, however, as a consequence of reversibility of the reactions under consideration [5], thermodynamic control occurs, a bond with a more basic (with respect to the proton) ambident anion atom, i.e., once again with a "harder" atom of this sort, is primarily formed as a result, since a more stable isomer is obtained in this case than in the reaction of a "hard" electrophile and a "soft" ambident anion center.

Thermodynamic control evidently occurs in the case under consideration, for II and III are unstable and readily undergo decomposition to give the starting thiazolidones I (for example, in the case of solvolysis in ethanol [2]).

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*See [1] for communication 45.

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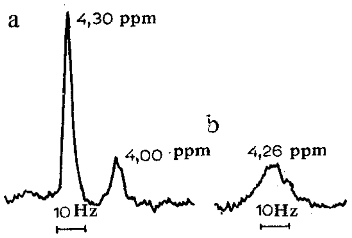

Fig. 1

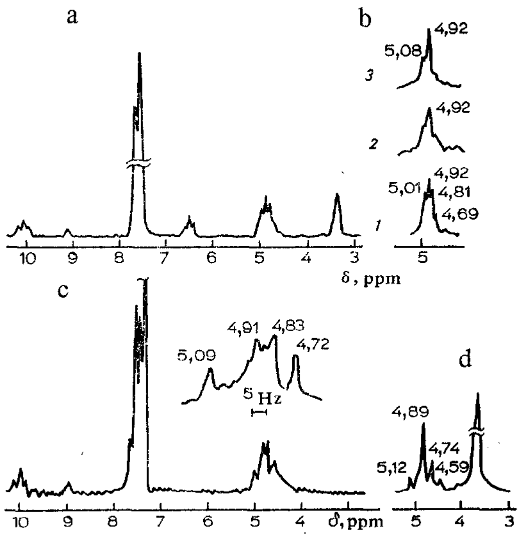

Fig. 2

Fig. 1. Signals of methylene protons in the PMR spectrum of IIa in d_6-DMSO (60 MHz): a) 29°C; b) 92°C.

Fig. 2. PMR spectra of IIIa in d_6-DMSO: a) overall form (60 MHz); b) temperature dependence of the multiplet signal of the methylene protons of the hydroxymethyl group (60 MHz): 1) 29°C; 2) 65°C; 3) 73°C; c) overall form (80 MHz); d) multiplet signal of the methylene protons of the hydroxymethyl group after the addition of D_2O (80 MHz).

A number of structural peculiarities of the structures of II and III are displayed as a result of an examination of their PMR spectra. Two peaks of methylene protons with chemical shifts of 4.03-4.09 and 4.33-4.40 ppm with an intensity ratio of ~1:3 are observed in the PMR spectra of IIa-d at ~30°C. In the case of IIa at 92°C both peaks merge to give one broad signal at 4.26 ppm (Fig. 1). This sort of pattern should be expected if it is assumed that II exist in the form of two configurational (or conformational) isomers; the E isomer is more favorable for steric reasons. It is clear that the observed character of the absorption of the methylene protons is impossible to explain for the isomeric 3-substituted compound. The E,Z-isomerization process may occur both for the imino form via planar inversion at the $N_{(2')}$ atom or via rotation of the substituent attached to the exocyclic nitrogen atom about the $C_{(2)}=N_{(2')}$ bond and for the amino form as a result of retarded rotation about the $C_{(2)}\overset{\cdots}{-}N_{(2')}$ partially double bond [8].

The PMR spectra of hydroxymethyl derivatives IIIa-f also constitute evidence in favor of hydroxymethylation of I at the exocyclic $N_{(2')}$ atom. In the PMR spectrum of IIIa (Fig. 2) the signal of the NH proton (10.08 ppm) is an asymmetrical triplet with J ≈ 5 Hz and is shifted to weak field as compared with the signal of the NH proton in the spectrum of **2-methylamino-5-benzylidene-4-thiazolinone (IV) at** 9.54 ppm [2]. Multiplet character of the signal of the NH proton at 10.08 ppm is possible only for the amino form of 2-hydroxymethyl derivative IIIa. The signal at 9.16 ppm, the intensity of which is smaller by a factor of about three than the intensity of the triplet at 10.08 ppm, was assigned to the resonance of the NH proton of the second form of IIIa. If it is assumed that the second form is the 3-hydroxymethyl derivative of Ia, the proton of the $H{-}N_{(2')}{=}C_{(2)}$ imino group of the 3-hydroxymethyl isomer would absorb at weaker field, like the proton of the imino group of 2-imino-3-methyl-5-benzylidene-4-thiazolidinone (9.93 ppm [2]).

The signal of the hydroxy proton (6.37 ppm) is a distorted triplet with an intensity ratio of 1:2:1 (J ~ 6-8 Hz), which, like the signals of the NH protons, vanishes upon deuteration. If an impurity that catalyzes exchange of the hydroxy proton with the protons of the residual water is present in the d_6-DMSO, the signal of the OH proton of IIIa is displayed in the form of a broad line that is superimposed on the signal of the methylene protons of the hydroxymethyl group (Fig. 2).

TABLE 1. 2-Imino-5-R-benzylidene-4-thiazolidinones and Their Derivatives

Compound	R	R'	mp, deg C (dec.)	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}		PMR spectrum, ppm				Found, %		Empirical formula	Calculated, %		Yield, %
					C=O	C=N+Het	NH	OH	CH, Ar	CH_2	N	S		N	S	
Ib	p-Cl	—	>300 (230 [10])	241 (4,12), 290 (4,22), 335 (4,44)	1675	1510	9,17	—	7,50—7,68	—	11,8	13,2	$C_{10}H_7ClN_2OS$[a]	11,7	13,4	93
Ie	p-Br	—	>300	244 (3,79), 290 (3,96), 335 (4,26)	1670	1510	9,30; 9,62	—	7,52—7,90	—	10,2	11,9	$C_{10}H_7BrN_2OS$[b]	9,9	11,3	92
If	p-F	—	>300	230 (4,17), 285 (4,16), 331 (4,35)	1690	1520	9,13; 9,50	—	7,15—7,73	—	13,3	15,0	$C_{10}H_7FN_2OS$[c]	12,6	14,5	95
IIb	p-Cl	Piperidyl	228	231 (4,06), 293 (4,12), 345 (4,31)	1675	1500, 1590	No signal observed	—	7,55 м	4,03; 4,33	13,2	9,4	$C_{16}H_{18}ClN_3OS$[d]	12,5	9,6	75
IIIb	p-Cl	OH	269	241 (4,15), 291 (4,25), 334 (4,52)	1700	1585	10,03 t	6,38 t	7,53—7,58	4,63—5,02	10,5	12,5	$C_{11}H_9ClN_2O_2S$[e]	10,4	11,9	99
IIIe	p-Br	OH	270	243 (3,99), 290 (4,12), 335 (4,37)	1700	1590	10,10	6,33 t	7,35—7,76	4,75—5,00	9,4	10,8	$C_{11}H_9BrN_2O_2S$[f]	9,0	10,2	94
IIIf	p-F	OH	282	238 (3,84), 285 (3,99), 330 (4,19)	1705	1590	10,16 t	6,35 t	7,21—7,59	4,71—5,08	11,3	13,2	$C_{11}H_9FN_2O_2$[g]	11,1	12,7	96

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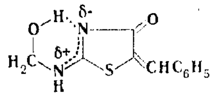
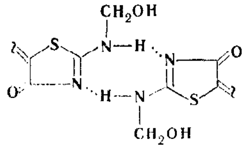
[a] Found: Cl 14.9%. Calculated: Cl 14.8%. [b] Found: Br 28.3%. Calculated: Br 28.2%. [c] Found: F 7.9%. Calculated: F 8.6%. [d] Found: Cl 10.7%. Calculated: Cl 10.6%. [e] Found: Cl 13.0%. Calculated: Cl 13.2%. [f] Found: Br 26.0%. Calculated: Br 25.5%. [g] Found: F 7.4%. Calculated: F 7.5%.

The appearance of spin–spin coupling of the vicinal $N_{(2')}H{-}CH_2$ protons is due to slowing down of the rate of exchange of the NH protons owing to the presence of a positive charge on the nitrogen atom. The paramagnetic shift of the signal of the NH proton in the PMR spectrum of IIIa as compared with the analogous signals of IIa (9.65 ppm) and IV (9.54 ppm) constitutes evidence for its pronounced deshielding, possibly as a result of the formation of a chelate structure with an intramolecular hydrogen bond (HB).



E–IIIa



Z–IIIa

Chelation is possible only for the E conformer and should stabilize it; the E conformer is also more sterically favorable. Moreover, dimerization as a result of the formation of intermolecular HB should stabilize the Z conformer, also leading to a weak-field shift of the signal of the NH proton.

The splitting of the signal of the hydroxy proton by the vicinal methylene protons is due to its retarded exchange owing to participation in hydrogen bonding. The paramagnetic shift is considerably greater than one might have expected in the case of the formation of HB with the solvent and is almost independent of the concentration, on the basis of which it may be assumed that the triplet at 6.37 ppm belongs to the hydroxy proton of the chelated form of the E conformer of IIIa, which is stabilized by a weak intramolecular HB [9].

The multiplet of the methylene protons of the hydroxymethyl group of IIIa (4.72-5.09 ppm) is complex in character (Fig. 2), and the reason for this may be as follows: 1) spin–spin coupling with the vicinal NH and OH protons; 2) the possibility of tautomeric equilibrium; 3) retarded or completely hindered rotation about the double (in the imino tautomer), partially double (in the amino tautomer), or single (in the rigid ring system owing to the formation of intramolecular HB) bond, which leads to the existence of two isomers (conformers) or to nonequivalence of the methylene (axial and equatorial) protons.

The additon of D_2O to the ampul simplifies the form of the multiplet of the methylene protons (Fig. 2) owing to the disappearance of the effects of their coupling with the vicinal protons. However, deuteration does not disrupt the HB, and the nonequivalence of the geminal CH_2 protons of the chelated E conformer should be retained. This evidently actually occurs, whereas the multiplet at 4.59-5.12 ppm is the superimposition of the signals of the methylene protons of the hydroxymethyl groups of at least two forms of IIIa. The part of the multiplet that corresponds to the AB system of the chelated E conformer cannot be isolated.

Raising the temperature should lead to the following results: 1) an increase in the rate of exchange of the labile NH and OH protons and suppression of the effects of vicinal spin–spin coupling; 2) elimination of the reason for the nonequivalence of the CH_2 protons of the chelated E conformer, if this nonequivalence is actually due to the formation of a rigid ring structure, for in this case the rate of exchange of the axial and equatorial protons increases, and the strength of the HB is weakened. In addition to averaging of the signals of the H_a and H_e protons, one should also expect changes in the ratios between the various forms of IIIa (between the E and Z conformers, between the chelated and nonchelated forms of the E conformer, between the monomers and the dimers, etc.). In fact, the form of the multiplet under discussion changes as the temperature is raised, and the predominant form at 73°C is the form with a signal at 4.92 ppm (Fig. 2). As expected, raising the temperature leads to disappearance of the multiplet character and broadening and diamagnetic shift of the signal of the hydroxy proton at 6.37 ppm.

Thus, hydroxymethyl derivative IIIa is a mixture of at least two conformers of the amino form; at room temperature the predominant form is the E conformer, which is stabilized by an intramolecular HB. The character of the PMR spectra of the remaining hydroxymethyl derivatives IIIb-f does not differ essentially from that for IIIa. It should be noted that, because of the low solubility of IIIc-e, the multiplet structure of the signals of the NH and OH protons in their PMR spectra is not always detected.

Compounds IIa-d evidently also exist in the amino form in d$_6$-DMSO, for there is no basis to assume that replacement of the hydroxy group by a piperidino group may lead to a change in the position of the tautomeric equilibrium.

EXPERIMENTAL

The PMR spectra of solutions in d$_6$-DMSO were recorded with Tesla BS-467 (60 MHz) and Tesla BS-487C (80 MHz) spectrometers with tetramethylsilane as the internal standard.

The preparation of Ia,c,d, IIa,c,d, and IIIa,c,d was described in [2]. Compounds Ib,e,f, IIb, and IIIb,e,f (see Table 1) were obtained by a similar method.

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CONDENSED HETEROCYCLES WITH A THIAZOLE RING.

5.* THIAZOLO[3,4-b][1,2,4]TRIAZOLIUM SALTS

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The reaction of α-cyanobenzyl benzenesulfonate with N-acyldithiocarbazinates gives thiazolo[3,4-b][1,2,4]triazolium salt derivatives, which are readily converted to mesoionic compounds by the action of bases. The structures of the synthesized substances were proved by data from the IR and PMR spectra.

Continuing our research on the synthesis and study of analogs of our previously synthesized [2] new heterocyclic system, viz., thiazolo[3,4-b][1,2,4]triazole, we studied the reaction of α-cyanobenzyl benzenesulfonate (I) with derivatives of acid hydrazides (IIa-d). Inasmuch as it is known [3, 4] that 4-aminothiazoles are formed in the reaction of sulfonate I with dithiocarbamates, one also might have expected the formation of substituted thiazolium salts of the IIIB type in the case under consideration. However, we found that the reaction does not stop at this stage but proceeds further to give new thiazolotriazole derivatives (IVa-d, Table 1). (Scheme, following page.)

The structures of the compounds obtained are confirmed by data from the IR and PMR spectra. The IR spectra of the condensation products do not contain bands of stretching vibrations of the C=O and N—H bonds of starting dithiocarbazinates II (1660, 3160-3315 cm^{-1}) or of the C≡N bond of sulfonate I (2200 cm^{-1}), but the spectra do contain absorption bands of a C=N bond (1630-1635 cm^{-1}). Signals of protons of methylthio groups (2.50 ppm) and other substituents are observed in the PMR spectra of IVa-c (the p-nitro-substituted compounds are

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*See [1] for communication 4.

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