Contributions to the study of some heterocycles. XLV. Configuration of the ketoximes of some 4-acetyl-2-(*p*-X-phenyl)-5-Y-thiazoles

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The configuration of the ketoximes of some 4-acetyl-2-(*p*-X-phenyl)-5-Y-thiazoles was studied. Chemical proofs (Beckmann rearrangement) confirmed by mass spectra and u.v. measurements demonstrate the *anti* thiazole (*E*) configuration of the investigated oximes. The remarkable negative solvatochromy of the oxime *IIa*, acetylated oxime *VI*, as well as of the ketones *Ia—d*, points out a particular behaviour of the proton in the position 5 of the thiazole ring, assigned to the existence of a weak C—H---Z (Z = O, N) interaction. The ^{1}H-n.m.r. spectra confirm the particularity of the H-5 proton and the study of the dependence of chemical shifts on concentration and temperature suggests a weak intramolecular hydrogen bond interaction between the oximic nitrogen and the heteroaromatic H-5 proton.

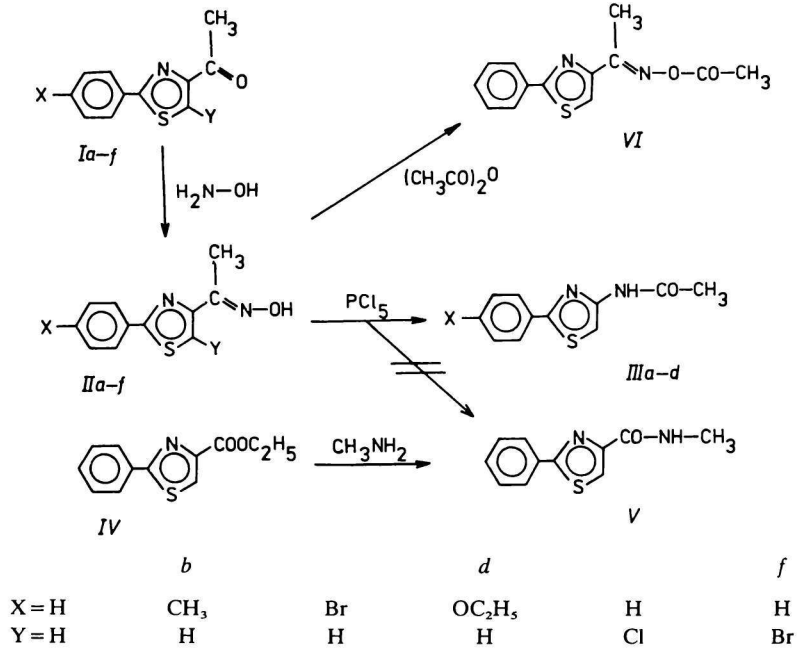
Была изучена конфигурация кетоксимов некоторых 4-ацетил-2-(*п*-X-фенил)-5-Y-тиазолов. Химические доказательства (перегруппировка Бекмана), подтвержденные масс-спектрами и УФ спектрами показали, что исследованные оксимы обладают конфигурацией *анти*-тиазола (*E*). Отличительная отрицательная сольватохромность оксима *IIa*, ацетилированного оксима *VI*, а также кетонов *Ia—d* указывает на особенное поведение протона в положении 5 тиазольного кольца, которое приписывается слабому взаимодействию C—H---Z (Z = O, N). Спектры ^{1}H-ЯМР подтверждают отличаемость протона H-5 и зависимость химического сдвига от концентрации и температуры обуславливается слабой внутримолекулярной водородной связью между азотом оксима и гетероароматическим протоном H-5.

In previous papers, the preparation and behaviour of some 2-benzoyl-4-R-thiazoles [1], 4-acetyl-2-arylthiazoles [2, 3], and 5-acetyl-2-aryl-4-R-thiazoles [1, 4] were studied.

According to some earlier observations [5—9], the condensation of mixed ketones with hydroxylamine leads to the formation of one or both isomeric oximes in different proportions, depending upon the kind of the heterocycle, position of the ketone function relative to the heteroatom, as well as upon the presence of some substituents attached to the heterocycle.

The asymmetry of the thiazole ring, with its possible involvement in the field of configurational studies of ketoximes, stimulated us to carry out a complex investigation in connection with the configuration of the ketoximes of 4-acetyl-thiazoles.

By condensation of 4-acetyl-2-phenylthiazole *Ia* with hydroxylamine, we obtained only one oxime. By means of the phosphorus pentachloride in anhydrous ether, this oxime turns into compound *IIIa*, which is not identical with compound *V*, obtained by the reaction of ester *IV* with methylamine (Scheme 1). A similar behaviour was observed for compounds *Ib—f*.



Scheme 1

On the basis of these results, according to Scheme 1, we can conclude that the oximes *IIa—f* have the *anti* thiazole configuration.

In order to confirm the structure of the amide *IIIa*, we recorded its mass spectrum which was compared with the spectrum of the isomeric amide *V* (Table 1).

Table 1

Mass spectral data of compounds *IIIa* and *V*

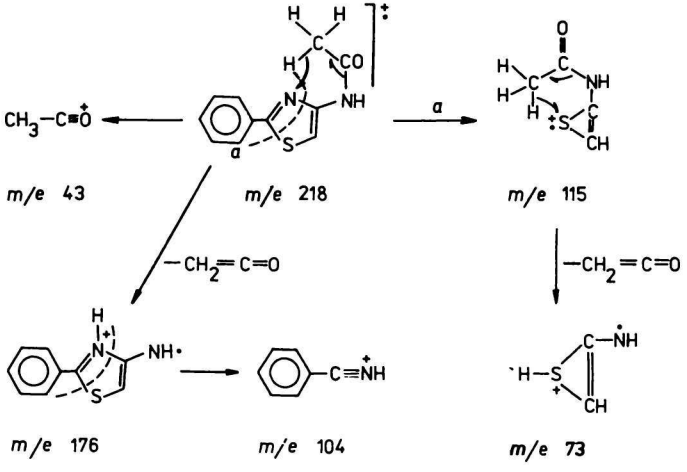
m/e		43	44	45	46	51	57	58	73	76	77	86	103
I (%)	*IIIa*	63	20	28	23	11	15	—	76	11	22	—	16
	V	10	20	9	4	16	32	30	17	14	32	5	16
m/e		104	105	115	116	121	160	161	162	176	188	189	218
I (%)	*IIIa*	100	13	1	—	—	—	—	—	99	—	—	30
	V	22	17	3	16	52	14	100	12	17	17	30	41

Table 1 gives only the peaks of relative abundance greater than 10% (except the peaks which represent structural proofs).

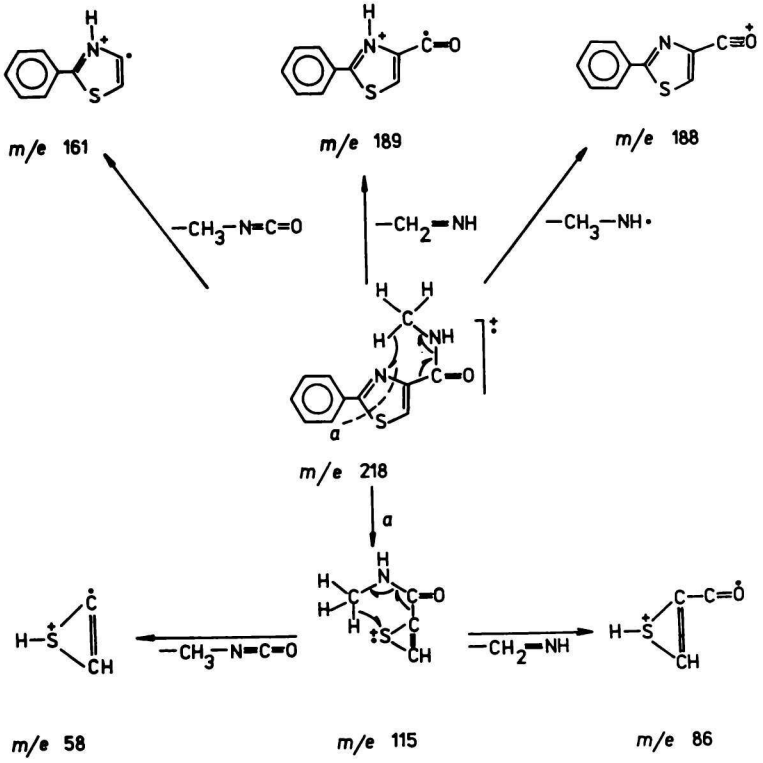
As some mass spectra of 2-arylthiazoles have been already described [3, 10, 11], only fragmentation patterns representing structural proofs will be discussed (Schemes 2 and 3).

Noteworthy is the low intensity of the ion at *m/e* 115 (fragmentation *a*) arising from the classical fragmentation of thiazole derivatives (breaking of 1—2 and 3—4 bonds with keeping of the positive charge on the sulfur atom). This behaviour could be the result of the subsequent McLafferty transposition (with the formation of ions at *m/e* 73 and *m/e* 86 and 58, respectively) arising at once after the breaking of the bonds.

The results obtained by the Beckmann rearrangement and confirmed by mass spectrometry, demonstrate the *anti* thiazole (*E*) configuration of oximes *IIa—d*.



Scheme 2



Scheme 3

In order to avoid the possible objection that the determination of the configuration of oximes by means of the Beckmann rearrangement could be altered by possible isomerizations [12, 13], we confirmed our arguments by means of physical investigations.

The u.v. spectra run in solvents of different polarities (heptane and methanol), render evident, as in the case of other disubstituted thiazole derivatives [4], the existence of two absorption bands. Table 2 shows λ_{max} only for the long wavelength

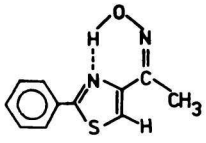
Table 2

Influence of the solvent polarity upon λ_{max} in the u.v. spectra of chosen compounds

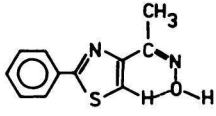
Compound		*IIa*	*IIf*	*VI*	*Ia*	*Ib*	*Ic*	*Id*
λ_{max}	Heptane	304	311	294	289	294	293	299
	Methanol	296	310	284	278	287	283	295
$\Delta\lambda$		8	1	10	11	7	10	4

bands, because the influence of the solvent is experienced particularly by those ones.

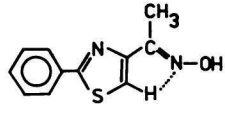
Surprisingly, in the case of the oxime of 4-acetyl-2-phenylthiazole *IIa* we noticed a remarkable negative solvatochromy. The fact that a similar effect in the case of the 2-(*o*-hydroxyphenyl)benzimidazole [14] was assigned to the formation of a hydrogen bond, made us consider the possibility of the existence of a similar interaction in the case of our oximes. Depending upon the configuration of the oximes, either an interaction between the hydrogen of the oxime and heterocyclic nitrogen (*syn* configuration, structure *A*) or an interaction between the nitrogen of the oxime and the hydrogen in the position 5 of the thiazole (*anti* configuration) could be possible (Scheme 4)



syn configuration
structure *A*



syn configuration
structure *B*



anti configuration

Scheme 4

In order to clear up the problem, we recorded the u.v. spectra of the oxime of the 4-acetyl-5-bromo-2-phenylthiazole (*IIf*) and of the acetylated oxime of the 4-acetyl-2-phenylthiazole (*VI*). If the configuration of the oxime were *syn* and the hydrogen bond were formed through the heterocyclic nitrogen (structure *A*), as a result of the acetylation, the negative solvatochromy should disappear. The value of the negative solvatochromy for compound *VI* does not change (Table 2), but if the hydrogen in the position 5 is substituted by a bromine atom (compound *IIf*), the negative solvatochromy practically disappears. Theoretically, it would be possible to consider structure *B* too, but because of the electronic effects of the acetyl group, a hydrogen bond in this case is very unlikely.

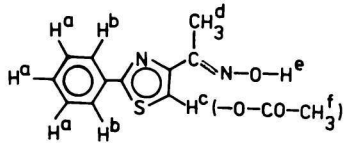
These results represent, in addition, an argument for the *anti* configuration of our oximes and at the same time confirm the involvement of the hydrogen in the position 5 in the negative solvatochromy.

In order to establish whether this involvement is particular only for oximes, we recorded the u.v. spectra of the 4-acetyl-2-(*p*-X-phenyl)thiazoles *Ia—d* (Table 2) and found that not only the negative solvatochromy is maintained but also that $\Delta\lambda$ depends upon the substituent X, which is in good agreement with the conclusion concerning the transmission of the electronic effects of the *para* substituents of the benzene ring upon the position 5 of the thiazole [15]. The similar behaviour of the ketones represents another argument concerning the particularity of the hydrogen in the position 5, since the ketones are usually mentioned as classical example of positive solvatochromy [16].

The observations above, as well as the mentioned examples in the literature [17—19] concerning the existence of hydrogen bonding of C—H groups (C—H---Z, in which the hydrogen is more acidic than usual and Z = O, N), made us to study the behaviour of the hydrogen in the position 5 in the thiazole, using the ^{1}H-n.m.r. spectroscopy (Table 3).

Table 3

Solvent effect on chemical shifts of protons H^{a-f} of compounds *Ia*, *IIa*, and *VI*



Compound	H^a	H^b	H^c	H^d	H^e	H^f	Solvent	$\Delta\lambda$ p.p.m., for H^c (Solvent effect)
Ia	7.27	7.84	7.84	2.51	—	—	CCl_4	0.63
	7.49	7.94	8.47	2.60	—	—	$DMSd_6$	
IIa	7.42	7.98	7.50	2.31	10.44	—	$CDCl_3$	0.64
	7.42	7.80	8.14	2.23	11.45	—	$DMSd_6$	
VI	7.19	7.69	7.69	2.50	—	2.22	$CDCl_3$	0.56
	7.40	8.00	8.25	2.51	—	2.25	$DMSd_6$	

The ^{1}H-n.m.r. spectra point out the same specific behaviour of the proton in the position 5 (H^c), which shows in the case of the ketone *Ia* as well as the oximes *IIa* and *VI* an obvious dependence upon the polarity of the solvent. Thus, the aromatic H^a, H^b, and methyl CH_3^d protons show much smaller differences in the chemical shifts than the proton H^c, as well as the proton H^e, which are shifted 0.6—0.7 and 1 p.p.m. downfield, respectively. The mobility of the H^c proton confirmed in this way too, represents a further argument for the assumption of an intramolecular C—H---Z type interaction.

Because of the insolubility of the oxime *IIa* in nonpolar solvents, the studies concerning these interactions were carried out on the acetyl derivative of the oxime *VI* which shows a considerable negative solvatochromy, too. In order to clear up the nature of these interactions, we recorded its spectra on the one hand at different concentrations (Table 4) and on the other hand at different temperatures (Table 5) in nonpolar solvents (CCl_4 and decalin).

Table 4 does not show any significant differences for the signals of the proton H^c in comparison with the signals of the other aromatic protons (H^a and H^b) as the concentration (in CCl_4) decreases from 20 to 2.5%. Hence, intermolecular interactions cannot be assumed.

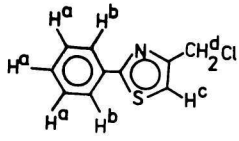
Table 4

Concentration dependence of the chemical shifts of protons of compound *VI*

Conc %	H^a	H^b	H^c	H^d	H^f
20	7.19	7.69	7.69	2.32	2.04
17	7.20	7.72	7.72	2.34	2.05
13	7.22	7.72	7.72	2.35	2.05
10	7.22	7.74	7.74	2.36	2.05
5	7.22	7.76	7.76	2.37	2.05
2.5	7.23	7.77	7.77	2.39	2.07
$\Delta\delta_{max}$	0.04	0.08	0.08	0.07	0.03

Table 5

Temperature dependence of the chemical shifts of protons of compounds *C* and *VI*



C

T, °C	*C*				*VI*		
	H^a	H^b	H^c	H^d	H^a	H^b	H^c
22	7.07	7.69	6.91	4.44	7.21	7.79	7.79
50	7.08	7.69	6.92	4.45	7.19	7.76	7.74
80	7.08	7.69	6.92	4.44	7.24	7.81	7.71
100	7.10	7.71	6.94	4.44	7.20	7.80	7.66
140	7.08	7.69	6.92	4.44	7.17	7.76	7.61

The study concerning the dependence of the chemical shifts of proton H^c upon temperature was carried out in decalin on the same acetylated oxime (*VI*) as compared to the 4-chloromethyl-2-phenylthiazole (*C*) [20] for which intramolecular interactions are not possible (Table 5).

In the case of chloromethylated compound *C* no dependence of the chemical shift upon temperature can be observed (Table 5). On the other hand, for the acetylated oxime *VI* the only signal dependent upon temperature is that one corresponding to the proton H^c, the total difference in chemical shift being $\Delta\delta = 0.18$ p.p.m. It is interesting to point out the linear dependence of the chemical shift of proton H^c upon temperature (Fig. 1), the linear equation having a high correlation coefficient

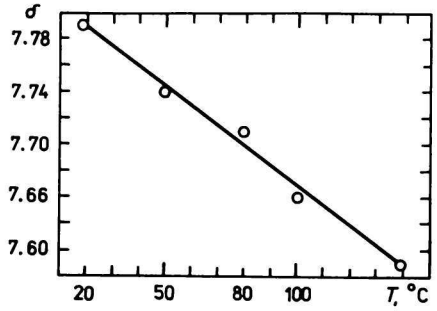


Fig. 1. Dependence of the chemical shift of proton H^c upon temperature.

$$\delta_{H^c} = 7.82\ T - 0.0015;\quad n = 5;\quad r = 0.994$$

This dependence of the chemical shifts upon temperature is well known for the case of the hydrogen bonds [21, 22]. The difference of chemical shifts ($\Delta\delta = 0.18$ p.p.m.), much smaller than that one for the usual hydrogen bonds [23] points out much weaker interaction in the case of our compounds.

EHTMO calculations [24] point out that among the possible configurations and conformations in Scheme 4 the most stable is the *anti* configuration, in which the distance between the oxime nitrogen and the hydrogen in the position 5 of the thiazole (0.263 nm) is favourable for such interactions.

Experimental

The u.v. spectra were recorded with a VSU 2P spectrometer (Zeiss, Jena) in the range 200—380 nm. The mass spectra were recorded with a VARIAN MAT 111 spectrometer at an ionizing potential of 80 eV (40°C). The ^{1}H-n.m.r. spectra were recorded with a TESLA BS 487C 80 MHz spectrometer using CCl_4, $CDCl_3$ or $DMSd_6$ as solvents and TMS as external standard. The i.r. spectra were recorded in KBr pellets with an IR 27 G Shimadzu spectrometer.

Oximes of 4-acetyl-2-(p-X-phenyl)thiazole (IIa—f)

4-Acetyl-2-(*p*-X-phenyl)thiazole (0.01 mole) dissolved in ethanol (50 ml) and hydroxylammonium chloride (0.015 mole) dissolved in water (30 ml), neutralized with sodium acetate, were refluxed for 30 min. After cooling, the condensation product was washed with water and purified by crystallization from ethanol. The characterization of *IIa—f* is given in Table 6.

4-Acetylamino-2-(p-X-phenyl)thiazoles (IIIa—d)

0.01 mole of the corresponding *II* was dissolved in cold anhydrous ethyl ether (250 ml) and PCl_5 (4 g) was added in small portions keeping the temperature at 0°C. After 24 h of stirring at 0°C, the formed amide was filtered, put into ice and after filtration and washing with water, was crystallized from 40% ethanol. The characterization of *IIIa—d* is given in Table 7.

Table 6

Characterization of the oximes *IIa—f*

Compound	X	Y	Formula	*M*	Calculated/found % N	M.p., °C
IIa	H	H	$C_{11}H_{10}ON_2S$	218.28		179—180
IIb	CH_3	H	$C_{12}H_{12}ON_2S$	232.30		165—166
IIc	Br	H	$C_{11}H_9ON_2SBr$	297.17	9.42 9.32	153—154
IId	OC_2H_5	H	$C_{13}H_{14}O_2N_2S$	262.33	10.67 10.41	163—164
IIe	H	Cl	$C_{11}H_9ON_2SCl$	252.72	11.08 10.84	163—164
IIf	H	Br	$C_{11}H_9ON_2SBr$	297.17	9.42 9.11	180—181

Compounds *IIa*, *IIb* are known in the literature [25] but we obtained them by a different method.

Table 7

Characterization of acetylaminothiazoles *IIIa—d*

Compound	X	Formula	*M*	Calculated/found % N	M.p., °C
IIIa	H	$C_{11}H_{10}ON_2S$	218.28		168—169
IIIb	CH_3	$C_{12}H_{12}ON_2S$	232.31		178—179
IIIc	Br	$C_{11}H_9ON_2SBr$	297.17	9.42 9.18	225—226
IIId	OC_2H_5	$C_{13}H_{14}O_2N_2S$	262.33	10.67 10.65	193—194

Compounds *IIIa*, *IIIb* are known in the literature [25].

N-Methyl-2-phenyl-4-thiazolylcarboxamide (V)

4-Ethoxycarbonyl-2-phenylthiazole (0.01 mole) dissolved in 19% methanolic methylamine solution (30 ml) was kept at room temperature for 48 h, then the mixture was refluxed for a few minutes, poured into water, filtered and crystallized from 40% ethanol.

For $C_{11}H_{10}ON_2S$ (218.28) calculated: 12.83% N; found 12.56% N. M.p. 124—125°C.

Acetylated 4-acetyl-2-phenylthiazole oxime (VI)

Compound *IIa* was refluxed with acetic anhydride for 2—3 min, poured into water, filtered and crystallized from 40% ethanol. M.p. 76—77°C.

For $C_{13}H_{12}O_2N_2S$ (260.32) calculated: 10.76% N; found: 10.52% N; ν(C=O)= $= 1755\ cm^{-1}$, ν(N—O) = 960 cm^{-1}.

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