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Reaction of Thioureidomethylenebisphosphonic Acids with α-Haloketones: I. Effect of Substituents on the Reaction Pathway

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Abstract—Substituted thioureidomethylenebisphosphonic acids react with haloketones to form thiazoles. The cyclization direction is predictably controlled by the size of the substituent. The NMR spectra of the resulting isomeric tetrazoles have well-defined differences and allow reliable structural assessment of the products.

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We earlier showed [1] that the reaction of methylthioureidomethylenebisphosphonic acid **Ia** with haloketones leads to formation of (3-methyl-4-substitited-2-thiazolylimino)methylenebisphosphonic acid (**V**), whereas phenyl-substituted analog **Ib** affords a mixture of the two possible isomers **V** and **VI** (Scheme 1).

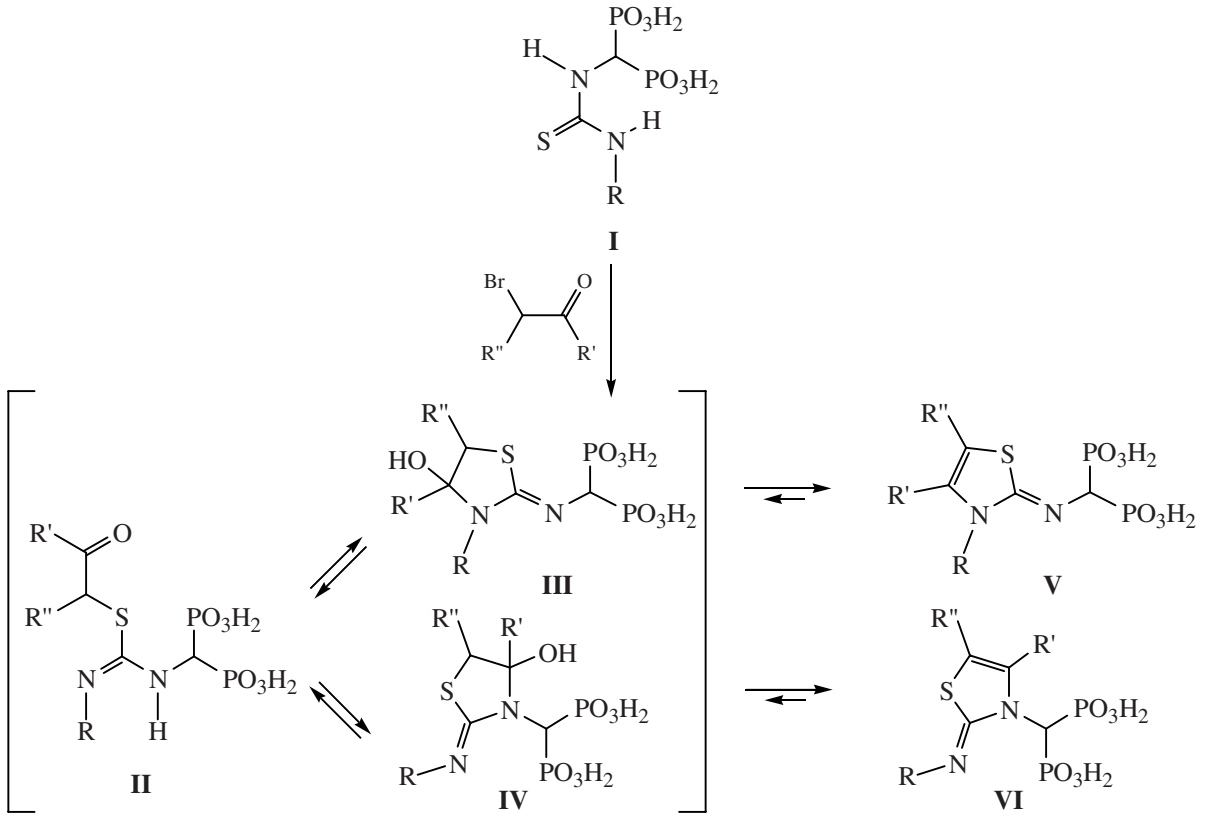
In this connection we set ourselves the task to study the effect of the size of substituent R at the N^3 atom of the thioureido group on the cyclization pathway. Despite a huge number of substituted thiazoles described in the literature [2], the effect of substituents in thiourea on the cyclozation pathway is poorly understood. It has been noted that mono-substituted thiourea derivatives and *N*-phenyl-*N*'-methylthiourea react with haloketones by one certain pathway that leads to cyclization at the least sterically hindered direction [3]. However, addition to the reaction mixture of strong acid changes the reaction mechanism and results in formation of both the possible thiazole isomers [3, 4].

We studied reactions with bromoketones of a series of disodium thioureidomethylenebisphosphonates we described earlier [5] or salts with triethylamine, which were not isolated individual and used in the reaction mixtures where they formed. Depending on substituents R at N^3, the reactions gave either one of the two possible isomers or their mixture. In the last case we observed crystallization of one product or, more often, a mixture whose components could be easily recognized by NMR spectroscopy.

We found that the reaction with α-haloketones of thioureidomethylenebisphosphonates **Ia**, **Ib,** and **Id** bearing at the N^3 atom a CH_2R group sterically less bulky than the bisphosphonomethyl group always took a single pathway and formed (thiazol-2-ylideneamino) methylenebiphosphonates **V**. Therewith, intermediate thiazolines **III** and **IV** (Scheme 1) whose signals were registered in the NMR spectra of the reaction mixtures further underwent dehydration under the reaction conditions at 20°C to form thiazoles, within 2–3 h at R' = Me and a few days at R' = Ar.

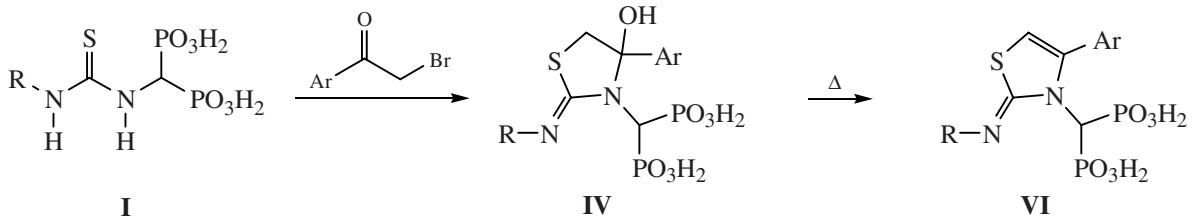
Thioureids **If** and **Ig** with bulky substituents (*t*-Bu, Ad) afford no other products than thiazoles **VI** (Scheme 2). Therewith, the reaction with arylhaloketones stops at the step of formation of thiazolines **IV** that are stable at room temperature and in some cases could be isolated from the reaction mixtures (Tables 1 and 2). The reaction of thioureids **If** and **Ig** with bromoacetone at room temperature gives thiazoles after ca. one month, but the reaction under reflux was complete in 2–5 days. At R' = Ar, boiling in aqueous methanol for 10–20 days is necessary, and, therewith, there occur up to 30% of side decomposition to aminomethylene-bisphosphonic acid or desulfurization to ureids that were identified using reference compounds prepared by other methods [6].

Scheme 1.



I: R = Me (**a**), Ph (**b**), Et (**c**), $CH_2CH{=}CH_2$ (**d**), cyclohexyl (**e**), *t*-Bu (**f**), adamantyl (**g**), 4-Cl-C_6H_4- (**h**), 4-O_2N-C_6H_4- (**i**); R' = Me, Ar; R" = H, Me, CO_2Et, $CON(CH_3)_2$.

Scheme 2.



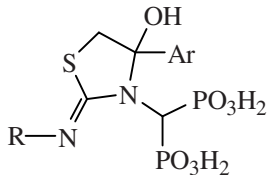
IV: R = *t*-Bu, adamantyl; Ar = Ph, 4-Cl-C_6H_4, 4-H_3C-C_6H_4.

Even though some by-products are formed, thiazoles **VI** generally crystallize pure from the mixtures.

With thioureidomethylenebisphosphonates **Ib**, **Ie**, and **Ih** bearing aryl or cyclohexyl groups at N^3, simultaneous formation of both thiazole isomers is observed (Scheme 1). Finally, crystallization of either one less soluble isomer or a mixture of two isomers is observed. The rates of formation of thiazoles from thioureids with aryl substituents turned to be slightly lower that those from unhindered substances **Ia**, **Ic,** and **Id** but 1–2 orders of magnitude higher than from **Ie**–**Ig** (R' = cyclohexyl, *t*-Bu, Ad). With bromoacetone, the reaction is complete in 1 h, with arylhaloketones in 1–3 days at room temperature in water–methanol–acetic acid mixtures. When disodium thioureidomethylenebisphosphonates in water are applied, dehydration proceeds several times slower.

It should be noted that the formation of thiazoles is reversible, and some thiazoline can remain n the reaction mixture. We found that dehydration proceeds

Table 1. [1]H NMR data for the synthesized thiazolinomethylenebisphosphonates of the general formula



Comp. no.	R	Ar	P	δ(CHP_2, d.d), ppm (*J*, Hz)	δ(CH_2, d.d), ppm ($^2J_{PH}$, Hz)	Other proton signals, δ, ppm
IVa	*t*-Bu	Ph	A	3.44 (21.5+25.3)	3.57+3.83 (1.8)	1.46 s (9H, *t*-Bu), 7.42–7.67 m (5H, Ph)
IVb	*t*-Bu	*p*-Cl-C_6H_4	A	3.40 (21.4+25.0)	3.59+3.90 (11.8)	1.46 s (9H, *t*-Bu), 3.17 s (3H, CH_3), 7.51 d + 7.65 d (4H, *p*-C_6H_4)
IVc	Ad	Ph	A	3.37 (~23 + ~23)	3.47+3.67 (11.8)	1.17 t+q + 3.09 (1½ Et), 1.56–2.19 m (Ad), 7.38–7.74 m (5H, Ph), 9.12 br.s (OH)
IVd	Ad	*p*-Cl-C_6H_4	C	2.91 (~21 + ~23)	–[a]	0.60 t + q + 2.52 (7½ H, 1½ Et), 1.0–1.6 m (Ad), 6.88 d + + 7.01 d (4H, *p*-C_6H_4)
IVe	Ad	*p*-H_3C-C_6H_4	C	2.97 (20.8+24.6)	–[a]	0.61 t + q + 2.53 (7½ H, 1½ Et), 1.0–1.63 m (Ad), 6.73 d + + 6.92 d (4H, *p*-C_6H_4)

[a] Signals were not found, probably due to overlap with a water signal. Compounds **IVd** and **IVe** are insoluble in DMSO and decompose on heating. Here and in further tables with NMR data: (A) DMSO-d_6, (B) DMSO-d_6 + NEt_3 (4–5 equiv per solute), and (C) D_2O + Na_2CO_3 (soda was added until it dissolved).

Table 2. [31]P NMR data for selected synthesized thiazolinomethylenebisphosphonates

Comp. no.	R	Ar	P	δ(PO_3 + PO_3), ppm ($^2J_{PH}$, Hz)
IVa	*t*-Bu	Ph	A	8.53 m + 12.25 d.d (21 + 25)
IVd	Ad	*p*-Cl-C_6H_4	C	8.83 d.d (~15 + 23) + 11.75 d.d (~15 + 21)
IVe	Ad	*p*-H_3C-C_6H_4	A	7.2 m
IVe	Ad	*p*-H_3C-C_6H_4	C	9.7 d.d (~19 + ~24) + 11.26 d.d (~19 + ~20)

almost completely in mixtures containing more than 20% of water: No thiazoline signals are observed in the [31]P NMR spectra. At the same time, dehydration in anhydrous mixtures does not proceed completely, and up to 10% of thiazoline remained in the equilibrium mixture. This effect of water on the state equilibrium contradicts the law of mass action and is probably connected with the fact that thiazolium salts **V** or **VI** are stabilized by solvation with water molecules.

The reversibility of dehydration into thiazoles leads to the possibility of interconversion of isomeric thiazoles in an acidic medium. The most facile interconversion occurs at R = cyclohexyl and R' = Me. In this case, the 1:1 mixture of isomeric thiazoles, formed initially in the reaction mixture with pH ~4, converts in a few days at room temperature to a single product **V**. Conversion proceeds slower at R = Ar and R' = Me and practically does not occur at R' = Ar.

Due to the reversible hydration of thiazoles to thiazolines, their NMR spectra are impossible to measure in CF_3COOD. When dissolved in this acid, the thiazole ring is rapidly hydrated by the residual water in the solvent to form an equilibrium mixture containing up to 15% of thiazoline. In DMSO or water, no such hydration occurs .

The synthesized thiazolium or thiazolino-substituted bisphosphonic acids are high-melting substances (commonly, above 200°C, with ill-defined melting points). They are poorly or moderately soluble in DMSO or acetic acid, moderately soluble in water at R' = Me and almost insoluble at R' = Ar, and insoluble in alcohols and acetone. They are readily soluble in water in the presence of bases, forming salts. Bisphosphonates poorly soluble in DMSO dissolve on addition of triethylamine, and some of the NMR spectra were registered in such mixtures.

Isomeric thiasoles **V** and **VI** are easily distinguishable by NMR spectroscopy. The signals of the P_2CH protons of thiazoles **V** in DMSO appear in the range 3.33–3.96 ppm and are split by spin–spin coupling with $^2J_{PH}$ 18.8–20.2 Hz (Tables 3 and 4), and the corresponding signals of compounds **VI** are observed in the range of 4.5–4.8 ppm ($^2J_{PH}$ 22.5–23.1 Hz) (Tables 5 and 6). In D_2O in the presence of Na_2CO_3, the characteristic $^2J_{PH}$ constants of thioazoles **V** are 17.6–19.2 Hz and those of **VI** are ~22.8 Hz. In ^{31}P NMR spectra of the reaction mixtures, thiazoles **V** induce doublets at 9.8–10.4 ppm ($^2J_{PH}$ 18.5–20 Hz) and thiazoles **VI,** at 8.2–8.7 ppm ($^2J_{PH}$ 23– 24 Hz).

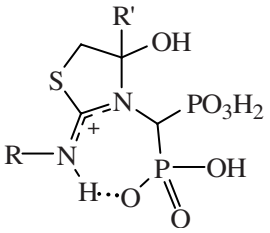
Thiazolines **III** and **IV** appear as two characteristic doublets of doublets from two different phosphorus atoms in the unsymmetrical thiazoline structure (Fig. 1).

As earlier suggested [3], the two possible thiazoline isomers in the reaction mixture are in equilibrium and interconvert via isothioureid **II** (Scheme 1). However, we found that the **III** : **IV** ratio depends on the content of base in the mixture, and most frequently in the ^{31}P NMR spectra of the reaction mixtures we observed signals of one isomer only (Fig. 1).

In the reaction mixtures in acetic acid, that we used for the synthesis of most compounds, signals of only one thiazoline isomer were observed. In basic mixtures (2.5–3 equiv of base per 1 mol of bisphosphonate), the result was dependent on the substituent at the N^3 atom of the thioureid. With bulky substituents (**If**, R = *t*-Bu), too, signals of only one isomer were observed. In the case of sterically unhindered substituents (**Ic**, R = Et), both possible thiazoline isomers were present (Fig. 2). At R = Ar in basic media, the spectra contained unresolved multiplets, which is, too, evidence for the appearance of the second thiazoline isomer under such conditions.

We conclude that the existence in acidic reaction mixtures of one of the two possible thiazoline isomers is explained by its stabilization by hydrogen bonding (Scheme 3). In basic media, the thiazoline ring is not protonated and no hydrogen bond is formed; as a result, the second isomer appears, provided substituent R does not prevent this sterically.

Scheme 3.



Change in the ratio of the intermediate thiazolines affects the final result of the reaction. It was found that addition of varied amounts of acid or water in the reaction mixtures of haloketones with arylthioureidobisphosphonates leads to significant changes in the ratio of the resulting isomeric thiazoles. As a rule, in a more acidic or more aqueous medium, cyclization

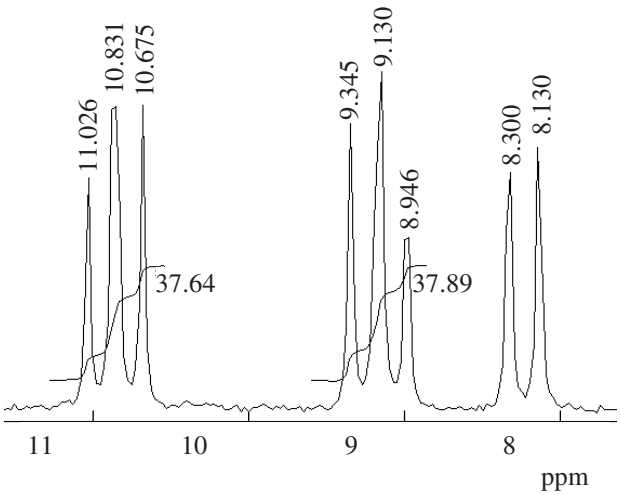


Fig. 1. ^{31}P NMR spectrum of the reaction mixture of thioureid **If** disodium salt (R = *t*-Bu) with bromoacetone in water. The doublet at 8.2 ppm belongs to thiazole **V** and two doublets of doublets at 9.1 and 10.8 ppm belong to two different P atoms of thiazoline **IV**. Operating frequency 121 MHz.

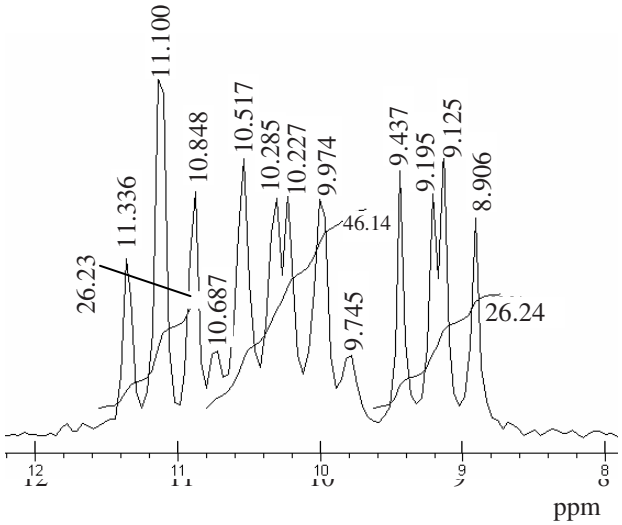
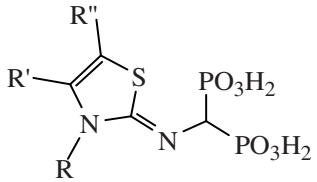


Fig. 2. ^{31}P NMR spectrum of the reaction mixture of thioureid **Ic** (R = Et) as a salt with 2.45 equiv of NEt_3 with bromoacetophenone in aqueous methanol. The two sets of two doublets of doublets belong to thiazolines **III** and **VI**. Operating frequency 81 MHz.

Table 3. [1]H NMR data for the synthesized thiazolylmethylenebisphosphonates of the general formula



Comp. no.	R	R', R"	P	δ(CHP_2, t), ppm ($^2J_{PH}$, Hz)	Other proton signals, δ, ppm
Va	CH_3	CH_3, CO_2Et	A	3.37 (19.0)	2.55 s (3H, CH_3), 1.23 t + 4.19 q (7.0 Hz, Et), 3.38 s (3H, CH_3)
Va	〃	〃	B	2.97 (15.9)	2.5 s (3H, CH_3), 1.21 t + 4.14 q (7.0 Hz, Et), 3.27 s (3H, CH_3)
Vb	C_2H_5	Ph, H	A	3.60 (19.4)	1.07 t + 4.02 q (7 Hz, Et), 7.55 m (5H, Ph), 6.91 s (1H, TzH)
Vb	〃	〃	B	3.00 (16.0)	0.98 t + 3.63 q (6.8 Hz, Et), 7.35–7.55 m (5H, Ph), 6.00 s (1H, TzH)
Vc	C_2H_5	*p*-Cl-C_6H_4, H	C	3.00 (17.6)	0.57 t + 3.32 q (diffuse, Et), 6.83 m + 6.90 (4H, C_6H_4), 6.17 s (1H, TzH)
Vd	C_2H_5	*p*-CH_3-C_6H_4, H	A	3.72 (20.0)	1.07 t + 4.11 q (7 Hz, Et), 7.38 m (4H, *n*-C_6H_4), 6.93 s (1H, TzH)
Vd	〃	〃	B	3.01 (16.0)	0.97 t + 3.62 q (diffuse, Et), 7.27 m (4H, *n*-C_6H_4), 5.94 s (1H, TzH)
Vd	〃	〃	C	3.14 (18.6)	0.58 t + 3.36 q (7.2 Hz, Et), 6.76 m (4H, *n*-C_6H_4), 6.16 s (1H, TzH)
Ve	C_2H_5	*p*-CH_3O-C_6H_4, H	A	3.7 (diffuse)	1.07 t + 3.6 m (Et), 7.09 m + 7.46 (4H, C_6H_4), 3.17 s (3H, CH_3), 6.84 s (1H, TzH)
Vf	C_2H_5	*m*-O_2N-C_6H_4, H	A	3.69 (20.2)	1.08 t + 4.11 m (Et), 7.09 m + 7.46 (4H, C_6H_4), 7.13 s (1H, TzH)
Vg	C_2H_5	2,4-$Cl_2C_6H_3$, H	A	3.68 (19.7)	diffuse 1.06 t + 3.62 m (Et), 7.63 m + 7.70 + 7.90 (3H, C_6H_3), 7.06 s (1H, TzH)
Vh	C_2H_5	CH_3, CO_2Et	A	3.33 (19.0)	1.17 t + 3.91 q (7 Hz, Et), 2.55 s (3H, CH_3), 1.23 t + 4.17 q (7.0 Hz, Et)
Vi	CH_2=$CHCH_2$	CH_3, H	B	2.98 (16.2)	2.01 s (3H, CH_3), 4.34 m (2H, CH_2), 5.13 m (4H, $2CH_2$), 5.92 m (1H, CH), 5.69 s (1H, TzH)
Vj	CH_2=$CHCH_2$	Ph, H	A	3.76 (19.8)	4.72 m (2H, CH_2), 4.80 d (17.2 Hz, 1H, CH_2), 5.07 d (10.5 Hz, 1H, CH_2), 5.76 m (1H, CH), 7.4–7.6 m (5H, Ph), 6.96 s (1H, TzH^5)
Vk	CH_2=$CHCH_2$	*p*-Cl-C_6H_4, H	A	3.65 (20.0)	4.67 m (2H, CH_2), 4.82 d (17.4 Hz, 1H, CH_2), 5.09 d (10.1 Hz, 1H, CH_2), 5.78 m (1H, CH), 7.51 m + 7.59 (4H, C_6H_4), 6.94 s (1H, TzH^5)
Vl	CH_2=$CHCH_2$	*p*-CH_3-C_6H_4, H	A	3.71 (19.4)	2.36 s (3H, Me), 4.70 m (2H, CH_2), 4.84 d (17.6 Hz, 1H, CH_2), 5.08 d (10.7 Hz, 1H, CH_2), 5.77 m (1H, CH), 7.33 m (4H, C_6H_4), 6.88 s (1H, TzH^5)
Vl	〃	〃	B	3.03 (16.0)	2.34 s (3H, Me), 4.21 m (2H, CH_2), 4.82 d (17.4 Hz, 1H, CH_2), 4.97 d (10.6 Hz, 1H, CH_2), 5.89 m (1H, CH), 7.25 m (4H, C_6H_4), 5.99 s (1H, TzH^5)
Vl	〃	〃	C	3.08 (17.7)	1.77 s (3H, Me), 3.98 m (2H, CH_2), 4.53 d (17.4 Hz, 1H, CH_2), 4.75 d (10.5 Hz, 1H, CH_2), 5.26 m (1H, CH), 6.77 m (4H, C_6H_4), 6.25 s (1H, TzH^5)
Vm	CH_2=$CHCH_2$	*m*-O_2N-C_6H_4, H	A	3.61 (19.5)	4.64 m (2H, CH_2), 4.87 d (17.2 Hz, 1H, CH_2), 5.10 d (10.4 Hz, 1H, CH_2), 5.83 m (1H, CH), 7.81 m + 7.95 + 8.37 + 8.32 s (4H, C_6H_4), 6.99 s (1H, TzH^5)
Vn	CH_2=$CHCH_2$	*p*-Ph-C_6H_4, H	A	3.57 (19.8)	4.66 m (2H, CH_2), 4.91 d (1H, CH_2), 5.15 d (1H, CH_2), 5.85 m(1H, CH), 7.37–7.86 m (9H, Ph + C_6H_4), 6.88 s (1H, TzH^5)

Table 3. (Contd.)

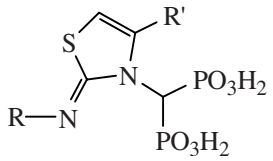
Comp. no.	R	R', R"	P	δ(CHP_2, t), ppm ($^2J_{PH}$, Hz)	Other proton signals, δ, ppm
Vn	CH_2=$CHCH_2$	*p*-Ph-C_6H_4, H	A	3.57 (19.8)	4.66 m (2H, CH_2), 4.91 d (1H, CH_2), 5.15 d (1H, CH_2), 5.85 m(1H, CH), 7.37–7.86 m (9H, Ph + C_6H_4), 6.88 s (1H, TzH^5)
Vo	CH_2=$CHCH_2$	3,4-$(OH)_2C_6H_3$, H	A	3.79 (20.0)	4.7–4.9 m (3H, CH + CH_2), 5.08 d (1H, CH_2), 5.75 m (1H, CH), 6.64–6.91 m (4H, Ar + CH)
Vp	CH_2=$CHCH_2$	β-naphtyl, H	A	3.71 (19.5)	4.69–4.9 m (3H, CH + CH_2), 5.07 d (1H, CH_2), 5.79 m (1H, CH), 7.01 s (1H, CH), 7.51–8.12 m (7H, naphtyl)
Vq	CH_2=$CHCH_2$	3,5-(*tert*-Bu)$_2$-4-OH-C_6H_2, H	A	3.79 (20.0)	1.37 s [18H, (*t*-Bu)$_2$], 4.67 m (2H, CH_2), 4.82 d (17 Hz, 1H, CH_2), 5.13 d (11 Hz, 1H, CH_2), 5.85 m (1H, CH), 7.14 s (2H, Ar), 6.93 s (1H, TzH^5)
Vr	CH_2=$CHCH_2$	CH_3, CH_3	A	3.81 (19.9)	2.15 s (3H, CH_3), 2.22 s (3H, CH_3), 4.91 m (2H, CH_2), 5.09 d (16.9 Hz, 1H, CH_2), 5.20 d (10.9 Hz, 1H, CH_2), 5.94 m (1H, CH)
Vs	CH_2=$CHCH_2$	Ph, CH_3	A	3.96 br.	2.05 s (3H, Me), 4.62 m (2H, CH_2), 4.75 d (17.1 Hz, 1H, CH_2), 5.02 d (10.7 Hz, 1H, CH_2), 5.67 d (1H, CH), 7.3–7.6 m (5H, Ph)
Vt	CH_2=$CHCH_2$	CH_3, $CON(CH_3)_2$	A	3.47 (19.4)	2.17 s (3H, Me), 2.96 s (6H, 2Me), 4.67 m (2H, CH_2), 5.18 m (2H, CH_2), 5.96 m (1H, CH)
Vu	CH_2=$CHCH_2$	CH_3, $COCH_3$	A	3.40 (18.8)	2.35 s (3H, Me), 2.50 s (3H, Me), 4.59 m (2H, CH_2), 5.22 m (4H, 2CH_2), 5.93 m (1H, CH)
Vv	Ph	CH_3, H	A	3.56 (17.8)	1.92 (3H, CH_3), 7.52–7.72 m (5H, Ph), 6.84 s (1H, TzH^5)
Vv	″	″	B	3.06 (16.9)	1.77 (3H, CH_3), 7.30–7.50 m (5H, Ph), 5.96 s (1H, TzH^5)
Vv	″	″	C	3.12 (18.0)	1.37 (3H, CH_3), 6.86–7.11 m (5H, Ph), 6.06 s (1H, TzH^5)

Table 4. ^{31}P NMR data for selected synthesized thiazolylmethylenebisphosphonates **V**

Comp. no.	R	R', R"	P	δ(P_2CH, d), ppm ($^2J_{PH}$, Hz)
Vb	C_2H_5	Ph, H	B	14.5 (16.2)
Vf	C_2H_5	*m*-O_2N-C_6H_4, H	A	10.1 (19.3)
Vh	C_2H_5	CH_3, CO_2Et	A	14.8 (18.7)
Vj	CH_2=$CHCH_2$	Ph, H	B	14.5 (16.5)
Vk	CH_2=$CHCH_2$	*p*-Cl-C_6H_4, H	B	14.3 (16.0)
Vl	CH_2=$CHCH_2$	*p*-CH_3-C_6H_4, H	C	11.0 (17.5)
Vq	CH_2=$CHCH_2$	3,5-(*tert*-Bu)$_2$-4-OH-C_6H_2, H	A	9.54 (19.8)
Vq	″	″	B	14.6 (16)
Vq	″	″	C	11.0 (19)
Vs	CH_2=$CHCH_2$	Ph, CH_3	A	9.5 (18.5)
Vs	″	″	0.66[a]	10.4 (diffuse)
Vs	″	″	B	13.8 (16.5)
Vu	CH_2=$CHCH_2$	CH_3, $COCH_3$	A	14.7 (19)
Vu	″	″	0.83[a]	13.8 (18.2)
Vu	″	″	2.1[a]	13.5 (15.6)
Vu	″	″	B	13.5 (15.5)

[a] Number of NEt_3,equivalents added to a DMSO-d_6.solution.

Table 5. ^{1}H NMR data for the synthesized thiazolylmethylenebisphosphonates of the general formula



Comp. no.	R	R'	P	δ(CHP_2, t), ppm ($^2J_{PH}$, Hz)	δ(TzH^5, s), ppm	Other proton signals, δ, ppm
VIa	*t*-Bu	CH_3	A	4.53 (23.0)	6.75	1.39 s (*t*-Bu), 2.25 s (CH_3)
VIb	Ad	CH_3	A	4.55 (23.1)	6.72	1.6–2.16 m (15H, Ad), 2.25 s (CH_3)
VIb	″	″	B	4.16 (21.8)	6.60	1.6–2.12 m (15H, Ad), 2.20 s (CH_3)
VIb	″	″	C	3.95 (22.8)	5.85	1.0–1.58 m (15H, Ad), 1.66 s (CH_3)
VIc	Cyclohexyl	CH_3	A	4.60 (22.9)	6.70	1.20–1.95 m + 3.25 m (10+1H, cyclohexyl), 2.26 s (CH_3)
VIc	″	″	C	3.96 (22.6)	5.87	0.60–1.45 m + 2.69 m (10+1H, cyclohexyl), 1.64 s (CH_3)
VId	Cyclohexyl	*p*-CH_3-C_6H_4	B	4.25 (21.4)	6.74	1.2–1.94 m + 3.18 m (10+1H, cyclohexyl), 2.37 s (3H, CH_3), 5.6 br.s (OH), 7.27 d + 7.53 d (*p*-C_6H_4)
VIe	Ph	CH_3	A	4.83 (22.5)	6.82	2.33 s (3H, CH_3), 7.34 m + 7.53 m (3H+2H, C_6H_5)
VIe	″	″	B	5.69 (23.5)	5.59	2.48 s (3H, CH_3), 6.93 m + 7.26 m (3H+2H, C_6H_5)
VIf	*p*-O_2N-C_6H_4	CH_3	B	5.82 (23.8)	6.00	2.6 s (3H, CH_3), 7.14 d + 8.15 d (*p*-C_6H_4)
VIg	*p*-O_2N-C_6H_4	*p*-CH_3-C_6H_4	A	4.53 (22.6)	6.99	2.39 s (3H, CH_3), 7.35 d + 7.45 d (*p*-C_6H_4), 7.48 d + 8.30 d (*p*-C_6H_4)
VIg	″	″	B	4.34 (22.1)	6.50	2.36 s (3H, CH_3), 7.28 d + 7.60 d (*p*-C_6H_4), 7.26 d + 8.22 d (*p*-C_6H_4)
VIh	*p*-Cl-C_6H_4	*p*-CH_3–C_6H_4	B	4.28 (22.7)	6.34	2.36 s (3H, CH_3), 7.12 d + 7.41 d (*p*-C_6H_4), 7.27 d + 7.61 d (*p*-C_6H_4)

preferentially involves the N^3 atom. By varying conditions of the reaction of ureid **Ia** with bromoacetone we could selectively synthesize both isomers. However, the effect of acid turned to be not fully unambiguous and should be studied additionally.

Thus, we established that the cyclization of thioureidobisphosphonates in their reaction with haloketones provides either sterically less hindered of the two possible thiazole isomers or a mixture of the isomers. In the last case, by varying reaction conditions one can control its result and synthesize one or the other isomer. The structure of the obtained products can be reliably established by NMR spectroscopy. A method of synthesis of previously unknown thiazolinobisphosphonic acids is developed.

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were registered on a Varian VXR-300 spectrometer at 300 (^{1}H) and 121 (^{31}P) MHz for resonance and a Varian Gemini-200 at 200 and 81 MHz, respectively

Solutions of thioureidobisphosphonates. Aminomethylenbisphosphonic acid, 1.91 g (10 mmol), was

Table 6. ^{31}P NMR data for selected synthesized thiazolylmethylenebisphosphonates **VIa–VIh**

Comp. no.	R	R'	P	δ(P_2CHP, d), ppm ($^2J_{PH}$, Hz)
VIa	*t*-Bu	CH_3	A	8.7 (22.2)
VIb	Ad	CH_3	C	9.1 (22.8)
VIc	Cyclohexyl	CH_3	A	8.7 (22.5)
VIc	″	″	C	8.8 (22.6)
VId	Cyclohexyl	4-CH_3-C_6H_4	B	8.2 (21.8)
VIk	Ph	CH_3	A	9.3 (22.8)
VIf	*p*-O_2N-C_6H_4	CH_3	B	9.4 (23.8)
VIg	*p*-O_2N-C_6H_4	4-CH_3-C_6H_4	A	9.6 (22.6)
VIg	″	″	B	9.8 (22.1)

Table 7. Yields and analytical data for the synthesized compounds

Comp. no.	Yield, %	Found, %			Formula	Calculated, %		
		C	H	N		C	H	N
IVa	57	39.72	5.34	6.73	$C_{14}H_{22}N_2O_7P_2S$	39.63	5.23	6.60
IVb	80	36.85	4.87	5.78	$C_{14}H_{21}ClN_2O_7P_2S·CH_3OH$	36.71	5.13	5.71
IVc	58	49.61	6.42	6.41	$C_{20}H_{28}N_2O_7P_2S·1/2\ NEt_3$	49.95	6.47	6.33
IVd	66	46.97	5.82	6.01	$C_{20}H_{27}ClN_2O_7P_2S·1/2\ NEt_3$	47.02	5.92	5.96
IVe	70	50.88	6.73	6.30	$C_{21}H_{30}N_2O_7P_2S·1/2\ NEt_3$	50.83	6.67	6.17
Va	88	28.76	4.60	7.58	$C_9H_{16}N_2O_8P_2S$	28.88	4.31	7.49
Vb	69	38.33	4.37	7.35	$C_{12}H_{16}N_2O_6P_2S$	38.10	4.26	7.41
Vc	78	34.71	3.74	6.80	$C_{12}H_{15}ClN_2O_6P_2S$	34.92	3.66	6.79
Vd	61	39.57	4.88	7.14	$C_{13}H_{18}N_2O_6P_2S$	39.80	4.63	7.14
Ve	67	38.42	4.61	6.74	$C_{13}H_{18}N_2O_7P_2S$	38.24	4.44	6.86
Vf	65	33.94	3.82	10.06	$C_{12}H_{15}N_3O_8P_2S$	34.05	3.57	9.93
Vg	44	32.11	3.43	6.32	$C_{12}H_{14}Cl_2N_2O_6P_2S$	32.23	3.16	6.26
Vh	92	30.75	4.79	7.16	$C_{10}H_{18}N_2O_8P_2S$	30.94	4.67	7.21
Vi	48	29.60	4.20	8.38	$C_8H_{14}N_2O_6P_2S$	29.27	4.30	8.54
Vj	67	40.28	4.20	7.27	$C_{13}H_{16}N_2O_6P_2S$	40.01	4.13	7.18
Vk	96	36.69	3.72	6.54	$C_{13}H_{15}ClN_2O_6P_2S$	36.76	3.56	6.60
Vl	66	41.25	4.35	6.61	$C_{14}H_{18}N_2O_6P_2S$	41.59	4.49	6.93
Vm	62	35.72	3.69	9.57	$C_{13}H_{15}N_3O_8P_2S$	35.87	3.47	9.65
Vn	79	49.17	4.58	6.21	$C_{19}H_{20}N_2O_6P_2S$	48.93	4.32	6.01
Vo	84	36.74	4.02	6.46	$C_{13}H_{16}N_2O_8P_2S$	36.98	3.86	6.63
Vp	91	46.25	4.33	6.30	$C_{17}H_{18}N_2O_6P_2S$	46.37	4.12	6.36
Vq	94	48.43	6.50	5.46	$C_{21}H_{32}N_2O_7P_2S$	48.64	6.22	5.40
Vr	60	31.62	4.87	8.11	$C_9H_{16}N_2O_6P_2S$	31.59	4.71	8.19
Vs	85	41.40	4.71	6.88	$C_{14}H_{18}N_2O_6P_2S$	41.59	4.49	6.93
Vt	21	32.90	5.14	10.47	$C_{11}H_{19}N_3O_7P_2S$	33.09	4.80	10.52
Vu	86	32.32	4.44	7.48	$C_{10}H_{16}N_2O_7P_2S$	32.44	4.36	7.57
Vv	82	36.01	3.52	7.61	$C_{11}H_{14}N_2O_6P_2S$	36.27	3.87	7.69
VIa	38	31.57	5.34	8.02	$C_9H_{18}N_2O_6P_2S$	31.40	5.27	8.14
VIb	52	42.74	5.67	6.71	$C_{15}H_{24}N_2O_6P_2S$	42.66	5.73	6.63
VIc	90	35.44	5.32	7.68	$C_{11}H_{20}N_2O_6P_2S$	35.68	5.44	7.56
VId	33	45.69	5.36	6.35	$C_{17}H_{24}N_2O_6P_2S$	45.74	5.42	6.28
VIe	72	36.13	3.92	7.80	$C_{11}H_{14}N_2O_6P_2S$	36.27	3.87	7.69
VIf	36	32.56	3.40	10.11	$C_{11}H_{13}N_3O_8P_2S$	32.28	3.20	10.27
VIg	21	41.96	3.67	8.54	$C_{17}H_{17}N_3O_8P_2S$	42.07	3.53	8.66
VIh	24	43.22	3.68	5.81	$C_{17}H_{17}ClN_2O_6P_2S$	43.01	3.61	5.90

dissolved in a mixture of 16 ml of MeOH, 4 ml of water, and 8 ml of triethylamine. Isothiocyanate, 12 mmol, was then added, and the mixture was heated for 10 h at 60°C (with AdNCS or *t*-BuNCS, the mixture was kept for two weeks at 40°C) and then evaporated at 40°C in a water-jet-pump vacuum to obtain a viscous oily residue. The residue was dissolved in 30 ml of water, and the solution was treated with activated charcoal, filtered, and by-products were extracted with ether (3×15 ml). The ethereal solution was evaporated at 40°C to obtain a viscous oily residue. According to ^{1}H NMR data, the residue contained thioureidomethylenebisphosphonic acid and 2.1–2.5 equiv of triethylamine. It was dissolved in 20 ml of MeOH, and the solution was used in the synthesis of thiazsoles and thiazolines.

(2-R-Imino-4-Ar-4-hydroxythiazolin-3-yl)methylenebisphosphonic acids IVa–IVe. A solution of 10 mmol of N^3-(Ad or *t*-Bu)thioureidomethylenebisphosphonic acid, prepared as described above, was acidified with 50 mmol of AsOH, after which 1.1 equiv of haloketone was added, and the mixture was stirred for 6 h at room temperature (according to the ^{31}P NMR spectrum, the mixture consisted almost exclusively of thiazoline). Water, 5 ml, was then added, and the mixture was acidified with 2 ml (~20 mmol) of concentrated HBr. Crystals formed and were filtered off, washed with methanol and acetone, and dried in air.

Product **IVb** precipitated as a solvate with one molecule of MeOH, and Ad-substituted compounds **IVc**–**IVe,** as complexes with 1/2 NEt_3.

(3-R-4-R'-5-R"-2,3-dihydro-1,3-thiazol-2-ylimino)methylenebisphosphonic acids Va–Vu. Water, 3 ml, was added to the thoureid solution, and it was acidified with HCl to pH 1–2. Haloketone, 1 equiv, was then added, and the mixture was refluxed for 30 min. After cooling, the product was filtered off, washed with methanol and acetone, and dried in air.

(3-Phenyl-4-methyl-2,3-dihydro-1,3-thiazol-2-ylimino)methylenebisphosphonic acid (Vc). Phenylthioureidomethylenebisphosphonic acid trisodium salt trihydrate, 4.96 g, was dissolved in a mixture of 30 ml of water, 10 ml of MeOH, and 22 mmol of HCl, after which 1.05 ml (13 mmol) of bromoacetone was added. The mixture was stirred until homogeneous and left at room temperature. After 8 h the product began to precipitate. After 5 days the precipitate was filtered off, washed in succession with aqueous methanol, methanol, and acetone, and dried in air.

(2-R-Imino-4-methylthiazol-2,3-dihydro-1,3-thiazol-3-yl)methylenebisphosphonic acids VIa–VIc. Concentrated HBr, 4 ml (~40 mmol), and 11 mmol of bromoacetone were added to a solution of 10 mmol of N^3-R-thioureidomethylenebisphosphonic acid, prepared as described above. The mixture was refluxed for 10 min, cooled, and the product was filtered off.

[2-Cyclohexylimino-4-(4-methylphenyl)-2,3-dihydro-1,3-thiazol-3-yl]methylenebisphosphonic acid (VId). Acetic acid, 5 ml, and 11 mmol of 4-methylphenyl bromomethyl ketone were asses to a solution of 10 mmol of (N^3-cyclohexyl)thioureidomethylenebisphosphonic acid, prepared as described above. The mixture was refluxed for 40 h. During this period, the product precipitated. It was filtered off, washed with MeOH and acetone, and dried in air.

According to the ^{31}P NMR spectrum of the reaction mixture, two isomeric thiazoles, **VI** (56 %) and **V** (44%), formed during reaction, but the product that crystallized was a pure compound **VId**.

(4-Methyl-2-phenylimino-2,3-dihydro-1,3-thiazol-3-yl]methylenebisphosphonic acid (VIe). Phenyl isothiocyanate, 11 mmol, was added to 10 mmol of aminomethylenebisphosphonic acid in a mixture of 16 ml of MeOH, 4 ml of water, and 6.2 ml (45 mmol) of triethylamine. The mixture was heated for 3 h at 60°C, cooled, and acidified with 0.3 ml (5.3 mmol) of acetic acid. Bromoacetone, 11 mmol, was added, the mixture was stirred and left for 24 h at room temperature, after which it was acidified with 4 ml of conc. HCl. The product crystallized after rubbing with a glass rod. It was filtered off, washed with MeOH and acetone, and dried in air.

[2-(4-Nitrophenyl)imino-4-R-2,3-dihydro-1,3-thiazol-3-yl]methylenebisphosphonic acids VIf and **VIg** were prepared like **VId**, refluxed for 3 h, and the products precipitated after cooling and acidifying with 4 ml of conc. HBr. The product was filtered off, washed with MeOH and acetone, and dried in air.

[2-(4-Chlorophenyl)imino-4-(4-methylphenyl)-2,3-dihydro-1,3-thiazol-3-yl]methylenebisphosphonic acid (VIh) was prepared like **VId** and refluxed for 6 h. After cooling, the product gradually precipitated. It was filtered off, washed with MeOH and acetone, and dried in air.

By ^{31}P NMR data, the reaction mixture contained two isomeric thiazoles, **VI** and **V,** in a ca. 1:1 ratio, but

the product that crystallized was a pure compound **VIh**.

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