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ISOMERISM OF HYDRAZONES OF (2-BENZOTHIAZOLYLTHIO)- AND (2-BENZOXAZOLYLTHIO)ACETIC ACIDS

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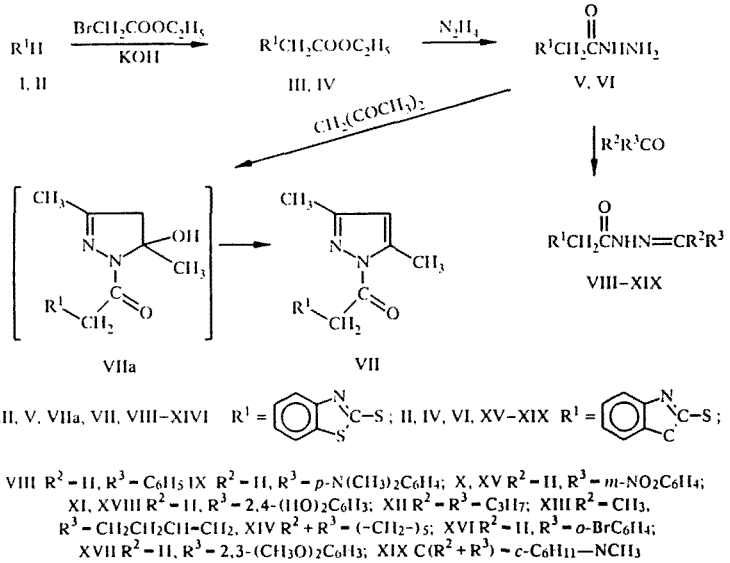
PMR spectroscopy was used to show that the hydrazones of (2-benzothiazolyl) and (2-benzoxazolyl)acetic acids exist in solution as equilibrium mixtures of stereoisomeric forms due to conformational and geometric isomerism.

The *Z',E'* isomerism of hydrazides [1] and hydrazones [2] of aliphatic acids as well as of benzoylhydrazones [3] due to hindered rotation about the C—N amide bond has been studied in considerable detail. However, such isomerism has not been observed in the hydrazones of (2-benzimidazolylthio)acetic acids obtained in our previous work [4].

In the present study, we found that 2-mercaptobenzothiazole (I) and 2-mercaptobenzoxazole (II) react with ethyl bromoacetate upon heating in 2-propanol in the presence of KOH to give the corresponding ethyl esters III and IV, which readily react without isolation with hydrazine hydrate to form hydrazides V and VI, which condense with aldehydes and ketones to yield acylhydrazones VIII-XIX.



I, III, V, VIIa, VII, VIII–XIVI R^1 = ; II, IV, VI, XV–XIX R^1 = ;

VIII R^2 = H, R^3 = C_6H_5 IX R^2 = H, R^3 = *p*-$N(CH_3)_2C_6H_4$; X, XV R^2 = H, R^3 = *m*-$NO_2C_6H_4$; XI, XVIII R^2 = H, R^3 = 2,4-$(HO)_2C_6H_3$; XII R^2 = R^3 = C_3H_7; XIII R^2 = CH_3, R^3 = $CH_2CH_2CH{=}CH_2$, XIV $R^2 + R^3$ = $(-CH_2-)_5$; XVI R^2 = H, R^3 = *o*-BrC_6H_4; XVII R^2 = H, R^3 = 2,3-$(CH_3O)_2C_6H_3$; XIX $C(R^2 + R^3)$ = *c*-C_6H_{11}—NCH_3

Hydrazones VIII-XIX may exist as four stereoisomeric forms due to geometrical syn-, anti isomerism relative to the C=N bond (*E, Z*) and conformational (or rotational) isomerism due to hindered rotation about the N—CO amide bond (*E'*, *Z'*).

Acylhydrazones VIII-XIX exist in DMSO solution as mixtures of two stereoisomers as indicated by doubling of the =CH, CH_2CO, and NH proton signals in the PMR spectrum, which coalesce upon heating to 120°C. The signal doubling, in principle, may result from hindered rotation not only about the N—CO bond but also about the N—N bond, especially since the rotational barrier in several hydrazones is rather high [2]. In order to elucidate this phenomenon, cyclic hydrazone VII, in which geometrical isomerism and rotation about the N—N bond are excluded, was obtained as a model compound.

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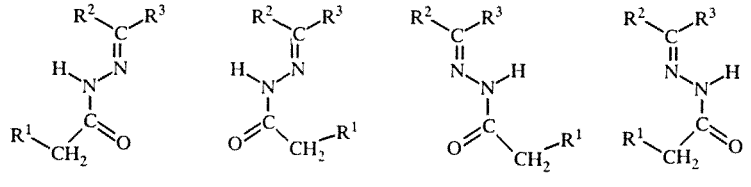
TABLE 1. Characteristics of Hydrazones VII-XIX

Compound	Chemical formula	mp, °C	Yield, %
VII	$C_{14}H_{13}N_3OS_2$	107...108	83
VIII	$C_{16}H_{13}N_3OS_2$	156...157	85
IX	$C_{18}H_{18}N_4OS_2$	173...174	54
X	$C_{16}H_{12}N_4O_3S_2$	179	58
XI	$C_{16}H_{13}N_3O_3S_2$	210	67
XII	$C_{16}H_{21}N_3OS_2$	91...92	78
XIII	$C_{15}H_{17}N_3OS_2$	88...90	59
XIV	$C_{15}H_{17}N_3OS_2$	148...150	56
XV	$C_{16}H_{12}N_4O_4S$	153...154	65
XVI	$C_{16}H_{12}BrN_3O_2S$	183...186	71
XVII	$C_{18}H_{17}N_3O_4S$	173...175	70
XVIII	$C_{16}H_{13}N_3O_4S$	>170 (decomp.)	78
XIX	$C_{15}H_{18}N_4O_2S$	129...131	59

The reaction of β-diketones with acylhydrazides leads to hydrazones with 1-acyl-5-hydroxypyrazolidine structure (VIIa) [5]. A PMR study of the product of the condensation of the hydrazide of (2-benzothiazolyl)acetic acid with acetylacetone showed that the reaction does not terminate with the formation of 1-acyl-5-hydroxypyrazolidine (VIIa), but rather pyrazole VII is formed due to the loss of water. The signals of the protons of the methyl group at the C=N and C=C bonds are found at 2.38 and 2.15 ppm, respectively. The signals of the CH_2CO group protons appear as two singlets at 4.16 and 4.78 ppm, while the signal for the =CH group protons is found at 6.16 ppm. The carbonyl group band for pyrazole VII is shifted in the IR spectrum to 1720 cm^{-1}, while the carbonyl group band for hydrazones VIII-XVIII is found at 1670-1680 cm^{-1}. Heating pyrazole VII in DMSO solution to 120°C does not lead to coalescence of the CH_2CO group signals. This failure indicates that the N—CO amide bond in pyrazole VII, which is conjugated with the pyrazole ring, has a higher rotational barrier than hydrazones VIII-XIX.

By analogy with the literature data [1, 2], the chemical shift of the CH_2CO and NH group proton signals of the *Z'*-conformer in hydrazones VIII-XIX lies upfield, while the =CH— group proton signal lies downfield relative to the corresponding signal of the *E'*-conformer.



EZ' *EE'* *ZZ'* *ZE'*

Table 2 shows that the equilibrium among the hydrazones obtained in highly polar DMSO solution is shifted toward the *E'* isomer with the exception of hydrazones XI and XVIII. Acylhydrazones are capable of forming intermolecular hydrogen bonds [1]. Solvents capable of forming intermolecular hydrogen bonds with a solute lead to the predominance of the isomer with diminished capacity for self-association. The capacity for self-association in DMSO solution is clearly greater for the *Z'* isomer. An exception is found for hydrazones XI and XVIII, in which the *Z'* isomer predominates in solution. This finding indicates that the capacity for self-association in this case is greater for the *E'* isomer, probably due to the 2,4-dihydroxyphenyl fragment found in XI and XVIII. The greater fraction of the *Z'* isomer in solutions in chloroform, which has low polarity, indicates its greater capacity for self-association in comparison with the *E'* isomer. However, in nonpolar solvents such as benzene and CCl_4, hydrazones VIII, XII, XIII, and XIX exist only in the *E'* form. On the basis of the data given by Zelenin et al. [2], we may assume that there is π—*p*—π conjugation for the coplanar C=N—N··—C=O fragment in nonpolar solvents. The alternative *Z'* isomer is destabilized by dipole—dipole repulsion of the oxygen and imine nitrogen atoms.

TABLE 2. PMR Spectral Data for V-XIX

Compound	Solvent	Chemical shifts, δ, ppm				E′ isomer, %
		$CH_2C=O$, s	=CH, s	NH, s	Other signals	
V	DMFA-d_7	4,11	—	—	—	—
VI	DMFA-d_7	4,07	—	—	—	—
VII	DMSO-d_6	4,16 (*Z′*) 4,78 (*E′*)	6,16	—	2,15 (3H, s, $CH_3C=O$) 2,38 (3H, s, $CH_3C=N$)	55
VIII	DMSO-d_6	4,22 (*Z′*) 4,62 (*E′*)	7,93 (*E′*) 8,13 (*Z′*)	11,53 (*Z′*) 11,67 (*E′*)	— —	65
	$CDCl_3$	3,98 (*Z′*) 4,58 (*E′*)	7,69 (*E′*) 7,93 (*Z′*)	9,93 (*Z′*) 11,04 (*E′*)	— —	57
	C_6D_6	4,40 (*E′*)	—	—	—	100
IX	DMSO-d_6	4,20 (*Z′*) 4,59 (*E′*)	—	11,33 (*Z′*) 11,44 (*E′*)	2,91 (6H, s, CH_3)	55
X	DMSO-d_6	4,29 (*Z′*) 4,67 (*E′*)	— —	11,89 (*Z′*) 12,02 (*E′*)	—	65
XI	DMSO-d_6	4,22 (*Z′*) 4,58 (*E′*)	8,13 (*E′*) 8,27 (*Z′*)	11,33 (*Z′*) 11,71 (*E′*)	—	43
XII	DMSO-d_6	4,22 (*Z′*) 4,49 (*E′*)	—	10,29 (*Z′*) 10,51 (*E′*)	0,82 (6H, t, CH_3)	62
	$CDCl_3$	3,98 (*Z′*) 4,49 (*E′*)	—	9,36 (br)	—	43
	CCl_4	4,47 (*E′*)	—	10,67 (*E′*)	0,81 (6H, t, CH_3)	100
	C_6D_6	4,51 (*E′*)	—	10,62 (*E′*)	—	100
XIII	DMSO-d_6	4,18 (*Z′*) 4,47 (*E′*)	—	10,22 (*Z′*) 10,40 (*E′*)	—	53
	CCl_4	4,44 (*E′*)	—	10,53 (*E′*)	—	100
XIV	DMSO-d_6	4,14 (*Z′*) 4,47 (*E*)	—	10,49 (*Z′*) 10,60 (*E*)	—	52
	$CDCl_3$	3,91 (*Z′*) 4,51 (*E′*)	—	—	—	27
XV	DMSO-d_6	4,18 (*Z′*) 4,60 (*E′*)	—	11,67 (*Z′*) 11,80 (*E′*)	—	68
XVI	DMSO-d_6	4,16 (*Z′*) 4,58 (*E′*)	—	11,71 (*Z′*) 11,87 (*E′*)	—	68
XVII	DMSO-d_6	4,11 (*Z′*) 4,51 (*E′*)	8,13 (*E′*) 8,29 (*Z′*)	—	3,67 (6H, d, CH_3)	62
XVIII	DMSO-d_6	4,18 (*Z′*) 4,56 (*E′*)	8,16 (*E′*) 8,24 (*Z′*)	—	—	44
XIX	DMSO-d_6	4,16 (*Z′*) 4,51 (*E′*)	—	10,49 (*Z′*) 10,60 (*E′*)	2,15 (3H, s, CH_3)	54
	C_6D_6	4,44 (*E′*)	—	—	1,82 (3H, s, CH_3)	100

EXPERIMENTAL

The IR spectra were taken for KBr pellets on a UR-10 spectrometer. The PMR spectra were taken on a Hitachi R-22 spectrometer at 90 MHz with HMDS as the internal standard. The quantitative PMR determinations were carried out by five-fold integration of the CH_2CO group.

The elemental analysis data of V-XIX for C, H, and S corresponded to the calculated values.

Hydrazide of (2-Benzothiazolylthio)acetic Acid (V). A solution of 14 g (0.25 mole) KOH in 10 ml water and 42 g (0.25 mole) 2-mercaptobenzothiazole was added to a mixture of 150 ml 2-propanol and 100 ml dioxane and, then, 40.2 g (0.25 mole) ethyl bromoacetate was added dropwise with stirring. The mixture was stirred for an additional 1.5 h at 70°C. The KBr precipitate was filtered off. Then, 75 ml hydrazine hydrate was added to the solution obtained at 35°C. The crystalline precipitate was filtered and washed with 2-propanol to give V in 78% yield, mp 163-165°C.

Hydrazide of (2-Benzoxazolylthio)acetic Acid (VI) was obtained in 92% yield by analogy to the above synthesis from 37.8 g (0.25 mole) 2-mercaptobenzoxazole, mp 139-140°C.

1-(2-Benzothiazolylthio)acetyl-3,5-dimethylpyrazole (VII). A mixture of 2.4 g (10 mmoles) hydrazide V and 40 ml acetylacetone was heated for 1.5 h at 80°C. Acetylacetone was partially distilled off. The crystalline precipitate was filtered off and washed with water.

TABLE 3. Analytical Data for Products V-XIX

Compound	Found, %			Chemical formula	Calculated, %		
	C	H	S		C	H	S
V	45,0	3,9	26,6	$C_9H_9N_3OS_2$	45,2	3,8	26,8
VI	48,5	4,0	14,5	$C_9H_9N_3O_2S$	48,4	4,1	14,4
VII	55,6	4,2	21,3	$C_{14}H_{13}N_3OS_2$	55,4	4,3	21,1
VIII	58,6	3,9	19,4	$C_{16}H_{13}N_3OS_2$	58,7	4,0	19,6
IX	58,5	4,8	17,4	$C_{18}H_{18}N_4OS_2$	58,4	4,9	17,3
X	51,6	3,2	17,5	$C_{16}H_{12}N_4O_3S_2$	51,6	3,2	17,2
XI	53,6	3,6	17,7	$C_{16}H_{13}N_3O_3S_2$	53,5	3,6	17,8
XII	57,5	6,2	19,3	$C_{16}H_{21}N_3OS_2$	57,3	6,3	19,1
XIII	56,3	5,5	20,2	$C_{15}H_{17}N_3OS_2$	56,4	5,4	20,1
XIV	56,3	5,3	20,1	$C_{15}H_{17}N_3OS_2$	56,4	5,4	20,1
XV	53,7	3,6	9,3	$C_{16}H_{12}N_4O_4S$	53,9	3,4	9,0
XVI	49,2	3,2	8,0	$C_{16}H_{12}BrN_3O_2S$	49,2	3,1	8,2
XVII	58,3	4,5	8,5	$C_{18}H_{17}N_3O_4S$	58,2	4,6	8,6
XVIII	56,1	3,7	9,4	$C_{16}H_{13}N_3O_4S$	56,0	3,8	9,3
XIX	56,4	5,5	10,0	$C_{15}H_{18}N_4O_2S$	56,6	5,7	10,1

(2-Benzothiazolyl)acetylhydrazone of Benzaldehyde (VIII). A mixture of 2.4 g (10 mmoles) hydrazide V, 40 ml dioxane, and 1.06 g (10 mmoles) benzaldehyde was heated to 45°C and stirred for an additional 2 h at room temperature. Dioxane was partially distilled off. The crystalline precipitate was filtered off and washed with ether.

(2-Benzothiazolylthio)acetylhydrazone of *p*-Dimethylaminobenzaldehyde (IX). A mixture of 2.4 g (10 mmoles) hydrazide V, 40 ml dioxane, and 1.49 g (10 mmoles) *p*-dimethylaminobenzaldehyde was heated for 1.5 h at 50°C and then cooled. The crystalline precipitate was filtered off and washed with ether.

(2-Benzothiazolylthio)acetylhydrazone of *m*-Nitrobenzaldehyde (X). A mixture of 2.4 g (10 mmoles) hydrazide V, 40 ml dioxane, and 1.51 g (10 mmoles) *m*-nitrobenzaldehyde was heated for 1.5 h at 50°C. Dioxane was partially distilled off and the mixture was diluted with petroleum ether. The crystalline precipitate was filtered off and washed with ether.

(2-Benzothiazolylthio)acetylhydrazone of 2,4-Dihydroxybenzaldehyde (XI) was obtained from 2.4 g (10 mmoles) hydrazide V, 40 ml dioxane, and 1.38 g (10 mmoles) 2,4-dihydroxybenzaldehyde according to the procedure described for hydrazone X.

(2-Benzothiazolylthio)acetylhydrazone of 4-Heptanone (XII). A mixture of 2.4 g (10 mmoles) hydrazide V, 40 ml dioxane, and 1.14 g (10 mmoles) 4-heptanone was stirred for 1 h at 40°C and 2 h at room temperature. Dioxane was partially distilled off. The crystalline precipitate was filtered off and washed with ether.

(2-Benzothiazolylthio)acetylhydrazone of 5-Hexen-2-one (XIII) was obtained from 2.4 g (10 mmoles) hydrazide V, 40 ml dioxane, and 0.98 g (10 mmoles) 5-hexen-2-one according to the procedure described for hydrazone X.

(2-Benzothiazolylthio)acetylhydrazone of Cyclohexanone (XIV) was obtained from 2.4 g (10 mmoles) hydrazide V, 40 ml dioxane, and 0.98 g (10 mmoles) cyclohexanone according to the procedure described for hydrazone X.

(2-Benzoxazolylthio)acetylhydrazone of *m*-Nitrobenzaldehyde (XV) was obtained from 4.46 g (20 mmoles) hydrazide VI, 80 ml dioxane, and 3.02 g (20 mmoles) *m*-nitrobenzaldehyde according to the procedure described for hydrazone X.

(2-Benzoxazolylthio)acetylhydrazone of *o*-Bromobenzaldehyde (XVI). A mixture of 6.69 g (30 mmoles) hydrazide VI, 100 ml dioxane, and 5.55 g (30 mmoles) *o*-bromobenzaldehyde was heated to 30°C and stirred for an additional 2 h at room temperature. The crystalline precipitate was filtered off and washed with ether.

(2-Benzoxazolylthio)acetylhydrazone of 2,3-Dimethoxybenzaldehyde (XVII). A mixture of 4.46 g (20 mmoles) hydrazide VI, 100 ml dioxane, and 3.3 g (20 mmoles) 2,3-dimethoxybenzaldehyde was stirred for 2 h at 30°C and then diluted with petroleum ether. The crystalline precipitate was filtered off and washed with ether.

(2-Benzoxazolylthio)acetylhydrazone of 2,4-Dihydroxybenzaldehyde (XVIII) was obtained from 4.46 g (20 mmoles) hydrazide VI, 80 ml dioxane, and 2.76 g (20 mmoles) 2,4-dihydroxybenzaldehyde according to the procedure described for hydrazone XVII.

(2-Benzoxazolylthio)acetylhydrazone of N-Methylpiperidone (XIX). A mixture of 4.46 g (20 mmoles) hydrazide VI, 80 ml dioxane, and 2.23 g (20 mmoles) N-methylpiperidone was heated to 60°C and stirred at room temperature for 2 h. Dioxane was partially distilled off and the mixture was diluted with petroleum ether. The crystalline precipitate was filtered off and washed with a small amount of acetone and, then, ether.

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