RING-CHAIN ISOMERISM (TAUTOMERISM) OF FUNCTIONALLY SUBSTITUTED HYDRAZONES (REVIEW)

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The known data on the ring-chain tautomerism (isomerism) of hydrazones with functional substitutents in the alkylidene or hydrazine fragment of the molecules are systematized. The structural factors and conditions that determine the reversible conversion of the corresponding linear derivatives to representatives of heterocycles – isoindole, tetrahydrofuran, pyrazole, isoxazole, 1,2,4-triazole, 1,3,4-thiadiazole, 1,3,4-oxadiazine, 1,2,4-triazine, 1,3,4-thiadiazine, 1,2,4,5-tetrazine, etc. – are correlated.

Ring-chain isomerism (and tautomerism) is one of the fundamental problems of heterocyclic chemistry. Bordering upon it, in addition to other problems (the thermodynamic stabilities of linear and ring structures, the possibilities of the synthesis of rings from linear derivatives or, vice versa, the synthetic aspects of opening of the heteroring, etc.), is the problem of interconversions of heterocycles [1-3], which are generally realized through an intermediate linear form, which is fixed in individual cases. Monographs [4, 5] have been specially devoted to the problems of ring-chain tautomerism, and its individual aspects have been reflected in numerous studies (for example, see [6, 7]).

The range of subjects that have been involved in ring-chain transformations is extremely wide and diversified, and the principles observed are often contradictory, which hinders correlations. The further accumulation of information for particular variants of ring-chain isomerism (and tautomerism) and its systematization are therefore necessary.

An attempt of this sort is made in this review. The selection of derivatives of hydrazones as the subject is due in many respects to the peculiarities of the structure of the C=N–NH functional grouping. A C=N bond, which is active in reactions involving the addition (including intramolecular) of polar XH groupings, and an NH group, which in turn may attack polar multiple bonds, including those found within the confines of the same molecule, are simultaneously present in it. As a consequence of this, the ring-chain transformations of functionally substituted hydrazones are represented quite extensively. It is not surprising that the problems of the ring-chain transformations of derivatives of hydrazones have already been examined in part in monographs [8, 9].

In principle, hydrazones themselves without additional functional groupings are also capable of ring-chain transformations to aziridine derivatives. The problems of diaziridine–hydrazone interrelationships have been illuminated in detail (see [10]) and are not examined here.

In the discussion of the material in this review we will be guided by the generally accepted sense embodied in the concept of "tautomerism" and "isomerism" [6, 11]. We have examined only those data that can be regarded as reliably proved using as our basis the principles of the correctness of evidence indicated in a monograph [5].

The ring-chain transformations of functionally substituted hydrazones can be divided into two groups: 1) transformations due to reaction of the C=N bond of the hydrazone fragment, to which a polar group in the alkylidene (type 1a) or hydrazone (type 1b) fragment of the molecule adds; 2) transformations via reaction of the NH group of the hydrazone, which attacks a multiple bond in the alkylidene (type 2a) or hydrazone (type 2b) fragment. The material of the review is arranged in accordance with this scheme.

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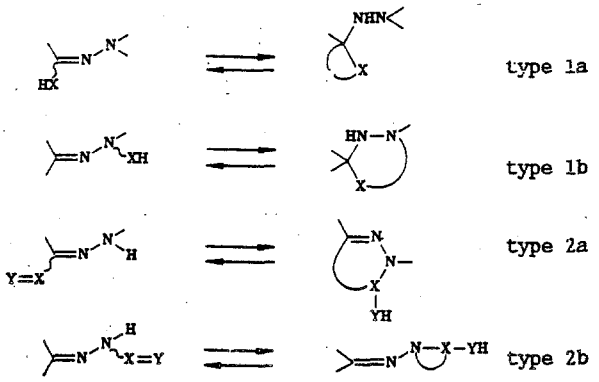
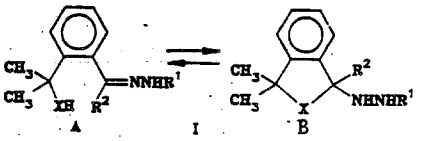


Let us point out that isomerism (or tautomerism) with the participation of three- and four-membered rings was not observed in this series, probably because of the steric strain in them. Instances of reversible cyclizations with the formation of seven-membered rings or rings with more than seven members are extremely rare.

1. RING-CHAIN TAUTOMERISM DUE TO THE HYDRAZONE C=N BOND

1.1 With the Participation of the XH Group in the Alkylidene Fragment (Type 1a)

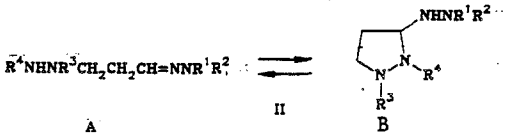
Isomeric ring-chain transformations of this type have been noted for phthalane derivatives (X = O, S) [12]. When X = O, I generally exist in linear form IA, and the formation of cyclic compounds IB has been observed only in the case of 2,4-dinitrophenylhydrazones; both isomers were isolated when R^2 = 3-$CH_3C_6H_4$. All of the described thiophthalanes (X = S) have a cyclic structure.



A I B

R^1=C_6H_5, 2,4-$(NO_2)_2C_6H_3$, $CONH_2$; R^2=Ar

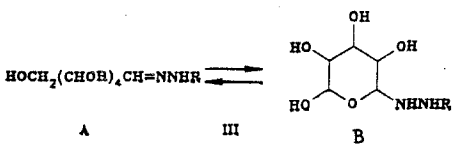
Depending on the nature of substituents R^1 and R^2, II exist in linear β-hydrazinohydrazone form IIA (R^1 = R^2 = CH_3; R^1 = H, R^2 = 4-$NO_2C_6H_4$, $COCH_3$) or in the form of cyclic isomer IIB – a hydrazinopyrazolidine (R^1 = H, R^2 = CSC_6H_5) [13]. Tautomerism of the IIA ⇄ IIB type has been noted only for benzoylhydrazones (R^2 = COC_6H_5); the percentage of the linear form increases with an increase in the polarity of the solvent.



A II B

R^1=H, CH_3; R^2=CH_3, 4-$NO_2C_6H_4$, $COCH_3$, COC_6H_5, CSC_6H_5; R^3=$COCH_3$; R^4=$CH(CH_3)_2$, C_6H_5

Arylhydrazones of the simplest γ- and δ-hydroxy carbonyl compounds have a linear structure [14, 15], and the cyclic structure assigned to 4-hydroxy-5α-cholestan-3α-ol 2,4-dinitrophenylhydrazone on the basis of the IR spectra therefore should most likely be rejected. In this series ring-chain tautomerism has been reliably observed only for glucose arylhydrazones with electron-acceptor substituents attached to the amino nitrogen atom [III, R = $NO_2C_6H_4$, 2,4-$(NO_2)2C_6H_3$]. The destabilization of hydrazone form IIIA by electron-acceptor substituents is probably explained by disruption of the chain of π, p, π conjugation in it and stabilization of the ring due to more effective p, π conjugation [15].



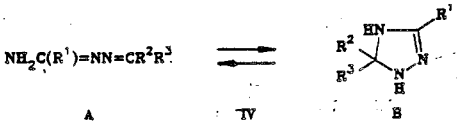
A III B

1.2. With the Participation of the XH Group in the Hydrazone Fragment (Type 1b)

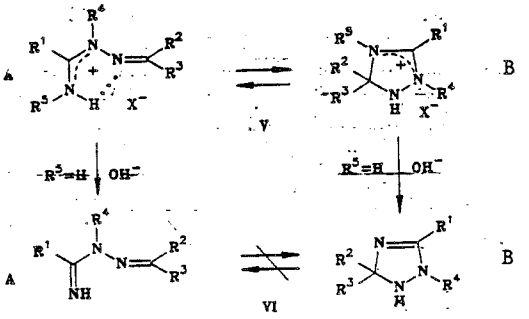
Hydrazones that have polar C=X groups that are bonded directly to the amino nitrogen atom are capable of tautomerism. These include the numerous and practically important classes of hydrazones — acyl- and thioacylhydrazones, alkylidene derivatives of amidrazones, semi- and thiosemicarbazones, etc. Due to a 1,3-prototropic shift within the fragment —NH—C=X ⇄ —N=C—XH they can undergo conversion to a tautomeric form, which acquires the ability to undergo type 1b cyclization.

Acylhydrazones [8, p. 49] exist only in the linear form and do not display a tendency to undergo conversion to the cyclic 1,3,4-oxadiazoline form.

Both linear (A) [17] and cyclic (B) [18] structures have been assigned to 1-alkylidene derivatives. However, according to the data in [19], these derivatives (R^1 = CH_3, C_6H_5) exist only in the linear form.



In an acidic medium or in the form of quaternary salts (R^4 = H, alkyl) amidrazone derivatives are actually capable of undergoing tautomeric transformations [20-23]. In the case of N-unsubstituted salts V (R^4 = H) tautomerism is observed when R^1 = C_6H_5; the percentage of 1,2,4-triazoline tautomer VB does not exceed 10%. Acetamidrazonium iodide derivatives (R^1 = CH_3) exist in various solvents only in linear form VA [20-22]; this is explained by the unfavorable (for intramolecular cyclization) spatial orientation of the C=N bond and the NH_2 group.

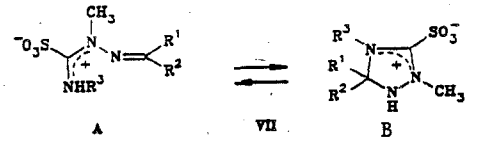


R^1=CH_3, C_6H_5; R^2=R^3=H, Alk, Ar; R^4=R^5=H, CH_3

Replacement of H by an alkyl substitutent (R^4 = alkyl) promotes a shift of the equilibrium to favor cyclic form B; an increase in the volume of R^4 increases its percentage [22]. On passing from acetamidrazonium to benzamidrazonium derivatives (R^1 = C_6H_5) the linear form, as in the case of unsubstituted salts, is destabilized; this is most likely explained by an increase in it of steric interaction between R^1 and R^4 attached to the C=N bond. The opposite dependence is observed in the case of variation of the substituents in the alkylidene fragment: on passing from an aliphatic radical (R^2 = CH_3) to an aromatic radical (R^2 = Ar) the percentage of the linear form increases. This also occurs when the volume of the substituents in the alkylidene fragment is decreased (4% ring when R^3 = tert-C_4H_9, and 18% when R^3 = CH_3; R^1 = C_6H_5, R^2 = CH_3 [23]). Electron-donor substituents in the benzene ring of radical R^2, which increase the negative charge on the N^1 atom, also shift the equilibrium to favor linear tautomer VA; this should be associated with strengthening of the intramolecular hydrogen bond (IHB) that exists in it.

The corresponding acyclic derivatives VIA are formed in the neutralization of salts V, which have a linear structure in the crystalline state; however, the salts, which exist in the form of substituted 1,2,4-triazolium iodides, give 1,2,4-triazolines VIB. The two isomers of the free bases do not display a tendency to undergo the tautomeric transformation VIA ⇄ VIB [23].

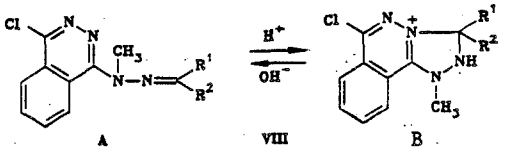
Distinct tendencies of the effect of electronic and steric factors on the constant of the equilibrium VIIA ⇄ VIIB could not be ascertained for the related ring-chain tautomerism of 2-methylthiosemicarbazone S,S,S-trioxides VII [24].



A VII B

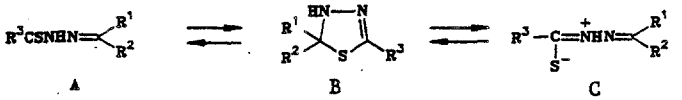
R^1=H, CH_3; R^2=alkyl; R^3=H, CH_3, $CH_2C_6H_5$, 2,6-$(CH_3)_2C_6H_3$

The acid–base isomerization VIIIA ⇄ VIIIB was observed for hydrazones of the phthalazine series [25].



A VIII B

Thioacylhydrazones IX display a greater tendency for existence in the cyclic form and thereby to undergo ring-chain transformations as compared with the oxygen and nitrogen analogs. Linear structure A (R^1 = H, CH_3; R^2 = CH_3, aryl; R^3 = $CH_2C_6H_5$, aryl) was assigned to these compounds in early studies (for example, see [26]). Mayer and Lauerer [27], however, showed that alkylidene derivatives of aromatic thioacylhydrazones IX (R^3 = aryl) have cyclic structure B, and the tautomerism IXA ⇄ IXB was proposed in two cases (R^1 = H, R^2 = aryl, R^3 = $CH_2C_6H_5$, C_6H_5) for solutions in DMSO.



A B C

IX

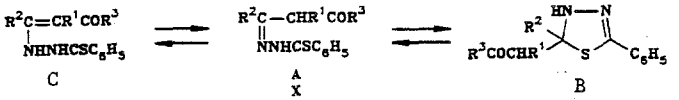
Thioacylhydrazones IX of the aliphatic (R^3 = H, alkyl, $CH_2C_6H_5$) and aromatic (R^3 = aryl) series [28-33], of isatin and N-isatins [34-36], and of α- and β-dicarbonyl compounds [37-41] have been studied. Alkylidene derivatives of thioaroyl- and thiopivaloylhydrazines generally exist only in cyclic form IXB [28, 30-33]. Tautomerism here is observed only for thiobenzoylhydrazones of benzaldehyde, anisaldehyde, and acetone in polar media [30, 31]. Aliphatic thioacylhydrazones in solutions usually form tautomeric mixtures IXA ⇄ IXB, the compositions of which in deuterochloroform vary over wide ranges and are determined by the character of substituents R^1-R^3. The following principles can be noted: an increase in the volume of substituent R^3 in the thioamide fragment or in its electron-acceptor character stabilizes thiadiazoline form IXB; donor and bulky substituents R^1 and R^2, which decrease the electrophilicity or steric accessibility of the carbon atom of the C=N bond, favor hydrazone structure IXA.

The development of yet another linear form – betaine IXC – the percentage of which depends in a complex manner on the nature of the substituents, was noted on passing to polar aprotic solvents (DMSO, DMF) in individual cases [31].

Adamantane thioformylhydrazone exists in cyclic form [42]. Mloston and Huisgen [42] assume that the primary product of protonation of the corresponding anion C, the ring–chain equilibrium for which is shifted to favor the open form, is the linear thioformylhydrazone, which is converted to the thermodynamically more favorable form of the IXB type.

As in the case of thiobenzhydrazones of monocarbonyl compounds, 1,3,4-thiadiazoline form B is also preferred for thiobenzhydrazones of γ-hydroxybutyraldehyde and α-dicarbonyl compounds – diacetyl and benzil [37, 43]. Equilibrium A ⇄ B occurs on passing to thiophenylacetylhydrazine derivatives in polar media.

The products of condensation of thiobenzhydrazide with methyl acetoacetate and its α-alkyl-substituted homologs [39] also have the structure of the corresponding 1,3,4-thiadiazolines XB, and only a derivative of α-isopropylacetoacetic acid ester (R^1 = iso-C_3H_7, R^2 = CH_3, R_3 = OCH_3) in polar media (DMSO, DMF) exists partially in open hydrazone form XA. Thiobenzoylhydrazones of cyclic β-keto esters are mixtures of enehydrazine C and thiadiazoline B form; the percentage of the latter decreases in polar solvents [39].



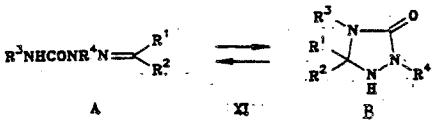
C A X B

R^1=H, alkyl, R^2=CH_3; R^1–R^2=–$(CH_2)_3$–, –$(CH_2)_4$–

A tendency for existence in cyclic form B is also manifested in the case of derivatives of β-dicarbonyl compounds. In the case of thiobenzoylhydrazones of aroylacetaldehydes X ($R^1 = R^2 = H$, $R^3 = Ar$) equilibrium A ⇄ B ⇄ C is shifted completely to favor 1,3,4-thiadiazoline form XB [40].

A complex tautomeric equilibrium with the participation of several cyclic forms [40, 41], the principles of which are examined below, is established on passing to derivatives of aroylacetones ($R^1 = H$, $R^2 = CH_3$, $R^3 = Ar$) and aliphatic β-dicarbonyl compounds in solutions.

The tendencies noted above for 1-alkylideneamidrazones are also manifested to a certain extent in series of semicarbazones XI.



A XI B

Tautomeric (or isomeric) transformations are observed here only for salts or for solutions of these substances in acids. Thus unsubstituted semicarbazones generally exist in the form of linear isomer XIA; however, depending on the method used to obtain them, the products of the reaction of semicarbazide (R^3, $R^4 = H$) with some 5'-acetylbenzofurans exist in linear or cyclic forms; the latter are formed in an acidic medium [44].

2-Methyl- and 4-methylsemicarbazones (R^3, $R^4 = CH_3$) of aldehydes ($R^1 = H$) exist in DMSO and CF_3COOH in the form of linear tautomers XIA [45]. 2,4-Substitution evidently increases steric interaction between the aromatic ($R^2 = Ar$) substituent and radical R^4 in linear form A, which may explain the existence in CF_3COOH of tautomeric equilibrium A ⇄ B. The percentage of the cyclic tautomer decreases with an increase in both the electron-donor and electron-acceptor effects of the para substituents of the aromatic ring ($R^2 = Ar$). Uda and Kubota [45] explain this by primary protonation of the nitrogen atom of the C=N bond of the linear tautomer.

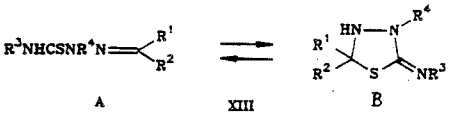
The steric effect of a phenyl ring attached to the $N_{(2)}$ atom ($R^4 = C_6H_5$) is similar to the effect of two methyl groups in the 2 and 4 position; this explains the ring-chain isomerization of acetone and acetophenone 2-phenylsemicarbazones (XI, $R^2 = CH_3$; $R^2 = CH_3$, C_6H_5; $R_3 = H$) [46, 47]. Depending on the method of preparation, linear A or cyclic B isomers are formed. Isomerization XIA ⇄ XIB is observed under acid-catalysis conditions.

On the whole, the principles of the change in ring-chain equilibrium A ⇄ B [48] that are characteristic for alkylidene derivatives of 2-methylamidrazonium salts V [23] are retained for derivatives of 2-methyl-2-aminoguanidinium iodide and carbonyl compounds XII. As expected, the position of the equilibrium in this case is shifted somewhat to favor linear form XIIA as compared with derivatives V.

A XII B

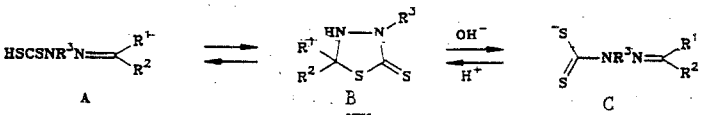
$R^1 = H, CH_3$; $R^2 = Alk, Ar$

Unsubstituted ($R^4 = H$) [27, 49]and 2- ($R^4 = CH_3$) or 4-substituted ($R^3 = CH_3$) [50] thiosemicarbazones in DMSO are linear tautomers XIIIA, which undergo cyclization in trifluoroacetic acid [27, 50], in contrast to their oxygen analogs [45].



A XIII B

In contrast to the 2,4-dimethylsemicarbazone [44], acetone 2,4-dimethylthiosemicarbazone ($R^1 = R^2 = R^3 = R^4 = CH_3$) is cyclic tautomer XIIIB in both DMSO and an acidic medium [50].

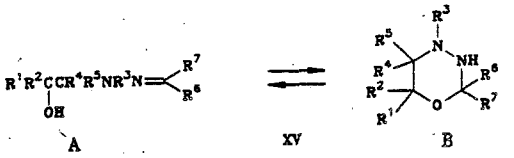


A B XIV C

$R^3 = H, Alk$; $R^1 = R^2 = H, Alk, Ar, Het$

Ring-chain tautomerism has been proved for the products of condensation of dithiocarbazinic acids with aldehydes and ketones [27]. In solutions they form XIVA ⇄ XIVB mixtures; upon alkalization the equilibrium is shifted to favor linear anion XIVC.

The tautomerism of hydrazones with the participation of six-membered heterocycles was observed for the first time in the case of N-alkyl-N-(2-hydroxyalkyl)hydrazones XV [51-53].



A XV B

This form of tautomerism was subsequently investigated in detail in a series of studies [54-66]. It was shown that $N_{(2)}$-unsubstituted hydrazones (R^3 = H), as well as derivatives of lactic acid hydrazide, have completely linear structure XVA and are not capable of undergoing cyclization [52, 53, 55, 57, 61]; the reason for this is evidently stabilization of the linear form by an IHB.

The products of the reaction of carbonyl compounds with N-alkyl-substituted β-hydrazino alcohols (XVB, R^3 = alkyl) form A ⇄ B equilibrium mixtures. With an increase in branching of R^3 the percentage of the ring form in the equilibrium mixture increases substantially, sometimes reaching 100% [53-56, 60, 61].

$N_{(2)}$-Aryl-substituted hydrazones (R^1 = R^2 = R^5 = R^6 = H, R^3 = Ar) also exist in solution in the form of tautomeric mixtures [65]. In the case of pinacolone derivatives it was shown that the concentration of cyclic form XVB increases with an increase in the electron-acceptor character of the substituent in the para position of the benzene ring; this is associated with disruption of the p,π conjugation in the system of C=N–N bonds and weakening of the IHB in hydrazone XVA.

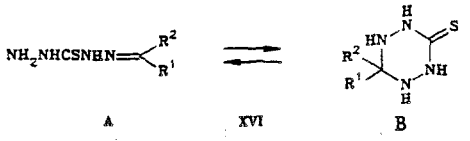
Substituents in the 2 position (R^6, R^7) have the opposite effect. In the products of the condensation of N-methyl-N-(1-hydroxy-1-phenyl-2-propyl)hydrazine with aliphatic aldehydes an increase in the volume of alkyl substituent R^7 shifts the equilibrium to favor form A [51]. This is probably associated with intensification of the 1,3-diaxial interactions in the chair conformer, which is preferred for 1,3,4-oxadiazines. Hydrazones of aromatic aldehydes (R^3 = H, R^7 = Ar) exist only in the linear form [64, 66] as a consequence of its stabilization by p,π,π conjugation.

The introduction of a second substituent into the 2 position, i.e., transition to derivatives of ketones, leads to marked destabilization of the ring [54, 55, 61, 65]. However, cyclohexanone derivatives exist only in ring form XVB [63]. The opposite dependence is observed in the case of derivatives of aromatic ketones. The percentage of the ring form increases on passing from derivatives of aromatic aldehydes to acetophenone derivatives (R^6 = CH_3, R^7 = Ar). The percentage of acyclic isomer XVA decreases with intensification of the electron-acceptor character of the para substituent in the aryl ring of the hydrazone fragment [66].

Substitution in the 6 position of the ring also has a substantial effect on the position of the equilibrium [55, 58-61, 66]. The introduction of a methyl group (R^1 = H, R^2 = CH_3) substantially increases the percentage of the cyclic tautomer [55, 59]. syn-Axial interactions in the ring develop when a second alkyl substituent is introduced into the 6 position; this leads to an increase in the percentage of the open tautomer (for example, when R^1 = R^6 = R^7 = CH_3 and R^2 = H, the percentage of the linear tautomer is 24% [55], as compared with 95% when R^2 = CH_3 [61]). However, when two methyl groups are present in the 6 position and only one is present in the 2 position (R^6 = H), the equilibrium concentration of the ring form remains virtually unchanged as compared with 1-(N-methyl-hydrazino)-2-propanol derivatives (R^1 = H, R^2 = CH_3) [55] and even increases as compared with hydrazones from 2-(N-methyl-hydrazino)ethanol (R^1 = R^2 = H) [53].

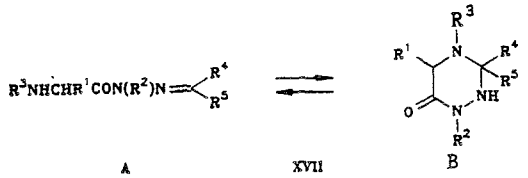
Replacement of the hydroxy group by an amino group promotes a shift of the equilibrium to favor the cyclic form, as in the case of five-membered derivatives. Thiocarbohydrazide monohydrazones XVI (R^1 = H, Alk; R^2 = H, alkyl, aryl) [67, 68] in solutions form tautomeric mixtures, the compositions of which depend markedly on the nature of the alkylidene fragment. The benzylidene derivative exists only in linear form A, while the products of condensation with sterically hindered aliphatic aldehydes and cyclohexanone exist only in cyclic

form B. An increase in steric strain (R = H, R^1 = iso-C_3H_7, tert-C_4H_9) increases the percentage of hydrazone XVIA (70% linear tautomer for R^1 = tert-C_4H_9). A similar phenomenon is also observed for derivatives of ketones with an increase in branching of R^1 ($R^2 \neq H$).



A XVI B

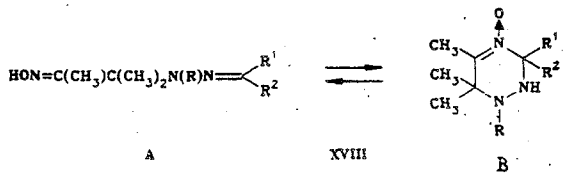
Acyclic $N_{(2)}$-unsubstituted 2-aminoacylhydrazones (R^2 = H) XVII exist only in linear form A (R^1 = R^3 = alkyl, R^5 = R^4 = CH_3) [69]. When the amino group is included in an aziridine ring (XVII, R^1–R^3 - $-CH_2-$), the formation of both isomers of XVII is observed. Derivatives of aromatic aldehydes also exist in the form of linear isomer XVIIA, while derivatives of ketones exist in ring form B [70].



A XVII B

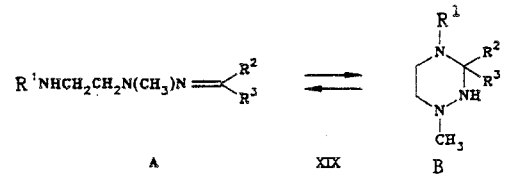
$N_{(2)}$-Substituted ($R^2 \neq H$) 2-aminoacylhydrazones generally form tautomeric mixtures; the percentage of the cyclic form increases with an increase in the volume of substituent R^2. Branching of radicals R^1 and R^3 leads to destabilization of the cyclic tautomer. With an increase in the temperature and the polarity of the solvent the equilibrium is shifted to favor hydrazone XVIIA [71].

In the case of α-(alkylidenehydrazine) oximes the changes in the position of the equilibrium XVIIIA ⇄ XVIIIB as a function of the structure are similar to those noted above [72].



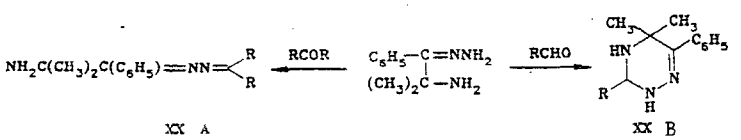
A XVIII B

Replacement of the carbonyl group in 2-aminoacylhydrazones by a methylene group leads to a shift in the equilibrium to favor cyclic tautomer XIXB; this was demonstrated for the products of the reaction of N-alkyl-2-(1-methylhydrazino)ethylamine with aldehydes and ketones [73, 74]. An increase in the volume of substituent R^1 usually shifts the equilibrium to favor hydrazone A, but on passing from R^1 = H to R^1 = CH_3 the equilibrium is shifted to favor cyclic form B; in the opinion of Lobanov and co-workers [74] this is due to the additional possibility of stabilization of the linear tautomer when R^1 = H due to an IHB. An increase in the substitution in the 3 position of the ring of XIXB leads to an increase in form A [74].



A XIX B

The products of condensation of hydrazones of α-amino ketones with aldehydes exist in cyclic form XXB (R^1 = CH_3, C_6H_5), while the products of condensation with ketones exist in linear form XXA [R = CH_3, $-(CH_2)_5-$] [75].



XX A XX B

The principles of the tautomerism of hydrazones that are derivatives of 2-hydrazino thiols XXI have been studied [76-80]. In contrast to the corresponding oxygen and nitrogen analogs, a cyclic tautomer develops for compounds that are not substituted at the amino nitrogen atom (R^4 = H). In the case of derivatives of ketones (R^4 = alkyl) tautomerism occurs

only for pinacolone hydrazones ($R^5 = CH_3$, R^6 = tert-C_4H_9) [78], and the remaining compounds have cyclic formula B.

A XXI B

Hydrazones of aliphatic aldehydes exist in the cyclic form ($R^4 = CH_3$, $R^5 = R^6 = H$). Hydrazone XXIA develops in the tautomeric mixture in the case of derivatives of other carbonyl compounds [77, 79]. In [80, 81] it was shown that the reaction of 1-(1-methylhydrazino)-2-propanethiol with benzaldehyde and nicotinaldehyde leads to hydrazone A and perhydro-1,3,4-thiadiazine B, respectively. Ring-chain tautomerism was observed for the hydrochloride of a benazldehyde derivative [80]. However, Potekhin and co-workers [77] demonstrated that arylidene derivatives generally form tautomeric mixtures and that the equilibrium constant in solution depends only slightly on the character of the substituent in the benzene ring ($R^6 = Ar$). In the opinion of Potekhin and co-workers [77], a possible reason for this is the closeness of the temperatures at which the equilibrium constants were determined to the isoequilibrium temperatures. An increase in the volume of the substituent attached to the nitrogen atom (R^4) leads to a shift of the equilibrium to favor ring B.

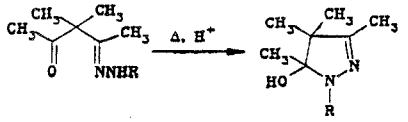
When $R^4 = H$, the introduction of a methyl substituent into the mercaptoethyl group gives rise to an increase in the enthalpy of the acyclic form as compared with the ring form, probably because of an increase in the skew interactions ($R^1 = R^5 = R^6 = CH_3$). However, the appearance of yet another methyl group in this position shifts the equilibrium completely to favor acyclic tautomer XXIA ($R^1 = R^2 = R^5 = R^6 = CH_3$) [76]. An increase in the volume of substituents R^5 and R^6 has a similar effect, and ring form XXIB cannot be detected in the case of pinacolone derivatives.

2. TAUTOMERISM DUE TO THE AMINO ATOM OF THE C=N–NH GROUP

2.1. With the Participation of the Functional Group in the Alkylidene Fragment (Type 2a)

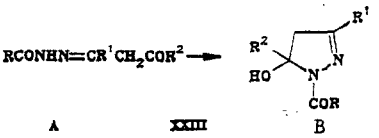
The reaction between β-dicarbonyl compounds and monoalkyl(aryl)hydrazines is used in the synthesis of pyrazoles [82]. However, if structural factors exclude aromatization of the initially formed addition product or do not favor it, the corresponding mono- and bishydrazones can be synthesized.

Thus stable monoalkyl- and monoarylhydrazones of α,α-dimethylacetylacetone, as well as the isomeric 5-hydroxy-2-pyrazolines XXII [83-85] and 5-hydroxy-1-phenyl-3,4,4-trimethyl-2-pyrazoline [86], are known; however, tautomerism between them is not observed. The cyclic isomers are more stable, since the hydrazones are converted to them irreversibly upon heating in the presence of acidic catalysts. 4a-Hydroxy-4a,7a-dihydro-5H-pyrazolo[5,4-b]quinuclidine proved to be stable because of the steric strain that should be present in the dehydration product [87].



A XXII B

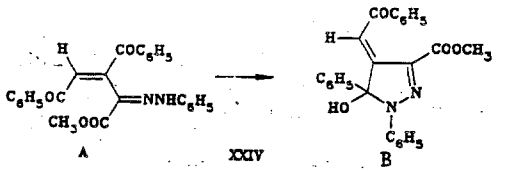
Monoacylhydrazones of the simplest β-dicarbonyl compounds, which are not inclined to undergo aromatization under mild conditions because of the electron-acceptor effect of the acyl group, also exist in the form of 5-hydroxy-2-pyrazoline tautomers XXIIIB [88-90]. 5-Hydroxy-2-pyrazolines are also products of condensation of benzoylacetone and dibenzoylmethane with semicarbazide [91], thiosemicarbazide, and 3-alkylsemicarbazides [92, 93], as well as of salts of N-aminoguanidine with β-dicarbonyl compounds in a ratio of 1:1 [92].



A XXIII B

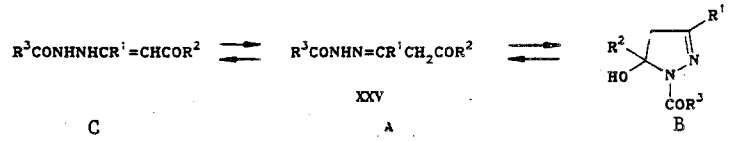
R=CH_3, CH_2CN, C_2H_5, $CH(CH_3)_2$, YC_6H_4, nicotinoyl, $CONH_2$; $R^1=R^2=CH_3$, C_6H_5; $R^1=CH_3$, $R^2=C_6H_5$

According to the results of x-ray diffraction analysis, the product of condensation of phenylhydrazonochloroacetate with N-phenacylpyridinium bromide in the crystalline state has 5-hydroxy-2-pyrazoline structure XXIVB [94].



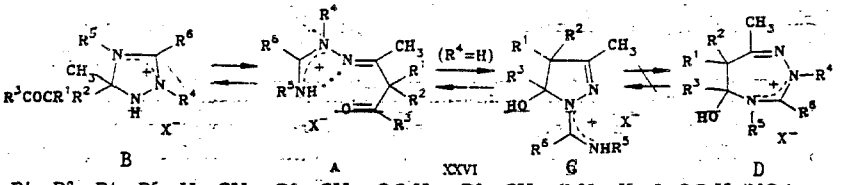
A comparison of the spectral characteristics of the products of condensation of some conjugated acetylenic ketones with aroylhydrazines [95, 96], to which hydrazone structure A was assigned, with the data in [88, 89] also provides evidence in favor of their existence in the 5-hydroxy-2-pyrazoline form.

Compounds for which in solutions equilibrium between 5-hydroxy-2-pyrazoline form B and one of the linear (A and C) forms is observed can be obtained by varying the electronic and steric properties of the dicarbonyl or hydrazide component. The products of the reaction of acetylpinacolone with acylhydrazines (XXV, $R^1 = CH_3$, R^2 = tert-C_4H_9, R^3 = Alk, Ar) in solutions are mixtures of three tautomeric forms [97, 98]; this is evidently due to the substantial increase in the steric strain in the cyclic form due to the tert-butyl group. The introduction of electron-acceptor substituents into the aromatic ring of the N-aroyl radical (R^3 = Ar) shifts the equilibrium to favor the 5-hydroxy-2-pyrazoline form. Branching of the radical of the N-acyl part in the case of hydrazides of aliphatic acids (R^3 = Alk), on the other hand, promotes an increase in the percentages of linear tautomers A and C. A similar pattern is also observed in the case of stable hydrazones of aroylacetaldehydes ($R^1 = H$, $R^2 = C_6H_5$, R^3 = Ar) [99] and aliphatic β-dicarbonyl compounds [100], where the stability of the linear forms is achieved through effective conjugation in them, and an increase in the volume of substituent R^1 leads to stabilization of cyclic tautomer XXVB. Linear (XXVA) and cyclic (XXVB) isomers can be isolated in pure form in the case of the products of condensation of benzoylacetaldehyde with aroylhydrazines ($R^1 = H$; R^2 = Ar, $R^3 = CH_2Ar$, Ar) [101]. The product of condensation of 1-hydrazinophthalazine with benzoylacetone is represented in solutions by a tautomeric mixture in which the enehydrazine, hydrazone, and 5-hydroxy-2-pyrazoline forms are present in comparable amounts [102].



The introduction of an ester group ($R^1 = COOCH_3$) into the β position leads to appreciable stabilization of hydrazone form A (R^2 = tert-C_4H_9, Ar; R^3 = Alk, C_6H_5) [97, 103, 104]. An increase in the electron-acceptor properties of the substituents in aromatic ring R^2 shifts the equilibrium to favor ring B. In series of derivatives of hydrazides of aliphatic acids an increase in the volume of substituent R^3 favors open hydrazine form A [104]. The products of condensation of aroylacetones with aroylhydrazines ($R^1 = CH_3$, $R^2 = R^3$ = Ar) are represented in solutions by mixtures of the enehydrazine (C) and 5-hydroxy-2-pyrazoline (B) forms [105]. Satisfactory correlation of the equilibrium constants with the Hammett σ constants of the para substituents in the aromatic ring is observed in this series; an increase in the donor character favors the cyclic tautomer.

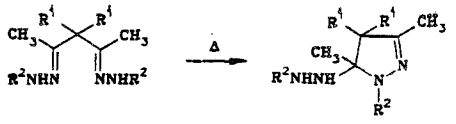
The fundamental possibility of tautomerism with the participation of derivatives of three different heterocycles XXVIB-D exists for the products of condensation of amidrazones (or their salts) with β-dicarbonyl compounds. In the free-base form such compounds exist in solutions only in linear forms XXVIA (tautomeric mixtures of the hydrazone and enehydrazone). Ring-chain tautomerism A ⇄ C is observed in the case of hydriodides or picrates of amidrazones; seven-membered heterocycle XXVID is not formed in any case [106, 107]. The introduction of a substituent into the α position of the β-dicarbonyl component ($R^2 = CH_3$) shifts the equilibrium to favor the hydrazone form, which becomes the only form for α,α-dimethylacetylacetone derivatives. Replacement of phenyl radical R^6 by a methyl group shifts the equilibrium completely to favor the 5-hydroxy-2-pyrazoline tautomer. Only a salt of 1,2,4-triazoline XXVIB, which does not display a tendency to undergo ring opening, is formed when the hydrogen atom attached to the $N_{(2)}$ atom is replaced by a methyl group.



B A XXVI G D

$R^1=R^2=R^4=R^5=H$, CH_3; $R^3=CH_3$, OC_2H_5; $R^6=CH_3$, C_6H_5; X=I, $OC_6H_2(NO_2)_3$

Stable bis(arylhydrazones) [83] and bis(acetylhydrazones) of α,α-dimethylacetylacetone [85], as well as the isomeric 5-hydrazino-2-pyrazolines XXVIIB, have been described. As in the case of mono derivatives XXII, the linear isomers undergo irreversible cyclization on heating [83, 85].



A XXVII B

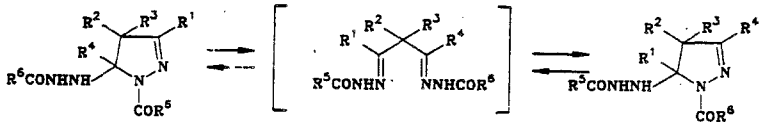
$R^1=H$, CH_3; $R^2=C_6H_5$, 2,4-$(NO_2)_2C_6H_5$, CH_3CO

Bis(acylhydrazones) of β-diketones also have a cyclic hydrazinopyrazoline structure [108], although a linear structure was previously erroneously assigned to them [109, 110].

Acetylacetone bis(4-phenylsemicarbazone) and its cyclic isomer XXVIIB (R^1 = H, R^2 = $CONHC_6H_5$) were isolated independently [92, 93]. As in the cases described above, this bis(semicarbazone) A is converted to the cyclic form B. Malondialdehyde bis(semicarbazone) and its thiosemicarbazone [111], as well as acetylacetone bis(thiosemicarbazone) and its N-alkyl homologs [92, 93], have only cyclic structures, although they were previously considered to be linear tautomers [112, 113].

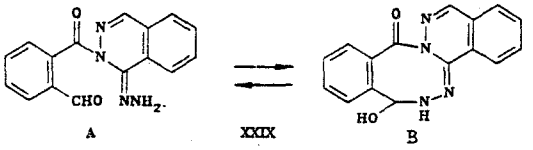
Ring-chain tautomerism XXVIIA ⇄ XXVIIB was observed for bis(benzamidrazonium) and bis(guanylhydrazonium) salts of acetylacetone [92]. The free bases have a completely linear structure and are represented by mixtures of stereoisomers of the hydrazone and enehydrazine forms.

The fact of the existence of bis(acylhydrazones) of 1,3-dioxo compounds in the form of the corresponding 1-acyl-5-acylhydrazino-2-pyrazolines [108] suggested the fundamental possibility of the existence of the ring-ring tautomerism XXVIIIB ⇄ XXVIIIC. This tautomeric transformation was demonstrated in [114] when R^1, R^4 = alkyl, R^5 = C_6H_5, and R^6 = 4-ClC_6H_4. Irreversible isomerization to one of the forms occurs in individual cases (R^1 = R^2 = R^3 = R^4 = R^6 = CH_3) [84].



B A XXVIII C

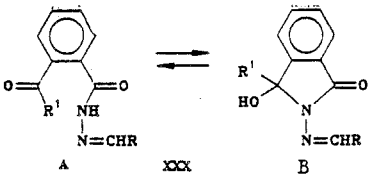
The ring-chain tautomerism XXIXA ⇄ XXIXB in aqueous solution is assumed [115] for the products of condensation of 1-hydrazinophthalazine with phthalaldehyde:



A XXIX B

2.2. With the Participation of the Functional Substituent in the Hydrazone Fragment (Type 2b)

Examples of ring-chain tautomerism of this type are unknown, and the only instance of isomeric transformation was observed for arylhydrazones (R = Ar) in series of derivatives of phthalic acid (XXX, R^2 = Ar). Cyclic structure XXXB was assigned to such compounds when R^1 = Ar, whereas these derivatives have linear structure A when R^1 = $N(CH_2)_4Z$ (Z = CH_2, O) [116].

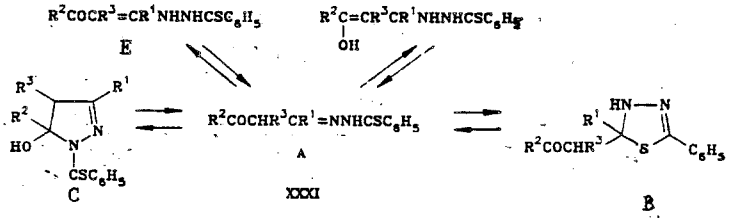


A XXX B

3. RING–RING TAUTOMERISM WITH THE PARTICIPATION OF DERIVATIVES OF TWO DIFFERENT HETEROCYCLES

The presence in hydrazones of no less than two functional groups that are capable of participating in ring–chain transformations creates the fundamental possibility of the existence of no less than two cyclic forms and, thereby, the possibility for their interconversions, particularly the development of tautomerism with the participation of two heterocyclic derivatives.

Ring–ring tautomerism for derivatives of two different heterocycles was first observed in the case of products of the condensation of thiobenzoylhydrazine with β-dicarbonyl compounds XXXI [38, 41]. Here there is a possibility for the existence of a complex tautomeric equilibrium that includes five forms A-E. It was found that existence only in ring tautomeric forms B or C is characteristic in nonpolar media for all of the investigated derivatives (R^1 = H, alkyl, CF_3, $COOCH_3$; R^2 = alkyl). An increase in the volume of substituents R^1 and R^2 in the case of symmetrical diketones (R^3 = H) gives rise to a peculiar effect: the percentage of 5-hydroxy-2-pyrazoline C initially increases, whereas it decreases sharply on passing to the dipivaloylmethane derivative (R^1 = R^2 = tert-C_4H_9). As expected [5, p. 172], the introduction of an α substituent into the β-dicarbonyl component (R^3 = alkyl) stabilizes the ring into the composition of which this substituent enters, viz., 5-hydroxy-2-pyrazoline C.



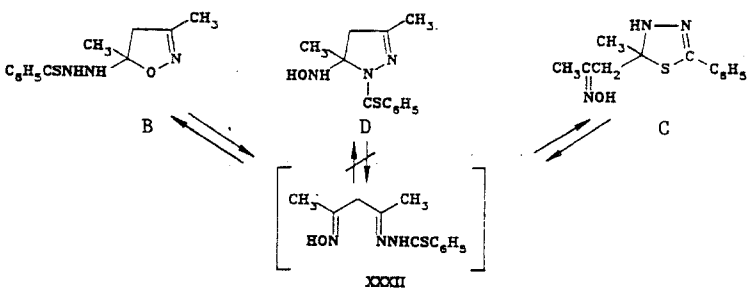
E A XXXI C B

The same tendencies in the change in the equilibrium are also manifested in solutions in DMSO. However, linear tautomers – enehydrazine E and hydrazone A (for acylpinacolone derivatives) – also develop here in individual cases.

The introduction of acceptor substituents into the aromatic ring of the β-dicarbonyl component (R^2 = Ar) shifts the equilibrium to favor the linear forms; the reason for this is the more rapid disappearance of thiadiazoline tautomer XXXIB as compared with the simultaneously occurring increase in the percentage of the other cyclic 5-hydroxy-2-pyrazoline form C [40]. However, the equilibrium is shifted to favor 1,3,4-thiadiazoline B on passing to derivatives of aroylacetaldehydes (R^1 = H, R^2 = Ar); this is probably explained by significant facilitation of nucleophilic attack by the sulfur atom at the C=N bond [40].

Acetylacetone thiophenylacetylhydrazone exists only in 5-hydroxy-2-pyrazoline form XXXIC [41].

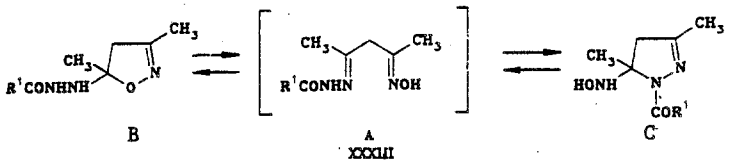
Another variant of ring–ring tautomerism is observed for acetylacetone thiobenzoylhydrazone monooxime XXXII [117], where there is a fundamental possibility for tautomerism of three different heterocycles B-D. In nonpolar media the equilibrium is shifted completely to favor isoxazoline B, whereas ring–ring 5-hydrazine-2-isoxazoline–1,3,4-thiadiazoline (B ⇄ C)



B D C XXXII

equilibrium is observed in strongly polar solvents (DMSO, DMF). The development of a linear (A) or yet another cyclic (D) form was not observed in any solvent.

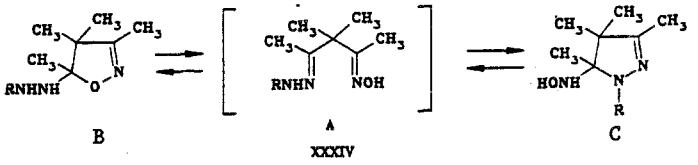
The ring-ring tautomerism XXXIIIB ⇄ XXXIIIC is possible for the products of the reaction of hydrazides with 5-hydroxy-3,5-dimethyl-2-isoxazoline. It was found that these compounds exist only in 5-hydrazido-2-isoxazoline form B and do not display a tendency to undergo conversion to ring C or linear form A (R^1 = C_6H_5, 4-$NO_2C_6H_5$) [118].



B A C

XXXIII

The ring-ring tautomerism XXXIVB ⇄ XXXIVC was observed for α,α-dimethylacetylacetone oxime acylhydrazones [119].

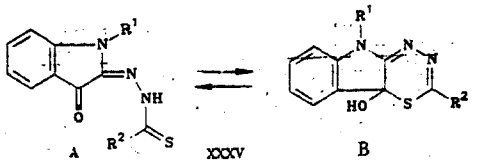


B A C

XXXIV

The percentage of 2-isoxazoline form B increases with an increase in the volume of substituent R (in DMSO from 5% to 95% on passing from R = CH_3 to R = iso-C_3H_7). An increase in the polarity of the solvent stabilizes tautomer C; however, a linear dependence on the E_T value of the solvent is not observed. As in the case of acyl derivatives [118], on passing from an alkyl substituent to a phenyl substituent (R = C_6H_5) the equilibrium is shifted completely to favor hydrazinoisoxazoline B. The isomerization B → C is observed for derivatives of isopropyl- and benzylhydrazine upon dissolving in $CDCl_3$; it is reversible in DMSO in the case of benzylhydrazine and irreversible for isopropylhydrazine.

In conclusion, let us present the only example of ring-chain isomerism in which the hydrazone grouping is not involved in the reaction but acts as a connecting link [120]. This reversible cyclization is characteristic for isatin thioacylhydrazones, which undergo isomerization to compounds of the XXXVB type in an acidic medium.



A XXXV B

We should also mention individual examples of electrovalent tautomerism with the participation of compounds related to hydrazones. Thus, in the opinion of Khalikova [121] and Fahr and co-workers [122-123], this is characteristic for 1,3,4-oxadiazolines XXXVI; this was concluded on the basis of the IR spectra, but the expected doubling of the signals is not observed in the PMR spectra [123].

A XXXVI B

R=alkyl, $R^1=R^2=C_6H_5$; $R^1—R^2$= 2,2'-biphenylene 2,2'-thiodiphenylene

The tautomerism XXXVIIA ⇄ XXXVIIB (R = tert-C_4H_9) in solutions was observed in [124]. In $CDCl_3$ the equilibrium is shifted almost completely to favor ring B, whereas A:B = 2:1 in CD_3OD. When the tert-butyl substituent is replaced by a 3,4-$(CH_3O)_2C_6H_3$ or C_2H_5O group the equilibrium is shifted to favor linear tautomer A.

A XXXVII B

Thus the information presented above indicates the necessity of thoroughly taking into account all of the fundamentally possible isomeric or tautomeric variants in the given series. Ignoring this circumstance frequently led to incorrect interpretation of the structure. The necessity of such refinements is particularly important when one is dealing with the structures of physiologically active compounds such as 1,3-diketone bis(thiosemicarbazones) [92, 93], which have pronounced antitumor activity. This in turn is important in structure–activity correlation and, thereby, for the purposeful synthesis of compounds of this series.

The synthetic significance of the problem is illustrated by examples of the development of methods for the synthesis of compounds such as 5-hydroxy- and 5-hydrazino-2-pyrazolines and new derivatives of 1,2,4-triazoline, 1,3,4-thiadiazoline, 1,3,4-oxadiazine, 1,3,4-thiadiazine, 1,2,4-triazine, etc. The observed facts and principles of tautomerism or isomerism in series of functionally substituted hydrazones will undoubtedly be useful for subsequent correlations and predictions of ring-chain tautomeric systems as a whole. The above-noted variants of the rare phenomenon ring-ring tautomerism of heterocyclic derivatives of various types, for example, serve as a confirmation of this.

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SYNTHESIS OF SOME 4-(HETARYL)METHYL-γ-LACTONES

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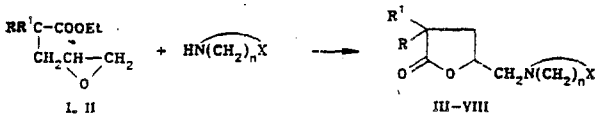
The reaction of alkylglycidylmalonate and alkylglycidylacetoacetate esters with pyrrolidine, piperidine, and morpholine has given butanolides in which these heterocycles are attached to the 4-position of the lactone ring.

Continuing work on the synthesis of functionally-substituted lactones, we have now developed a method for the synthesis of novel butanolides bearing a saturated nitrogen heterocycle at the 4-position of the lactone ring. Accessible starting materials for compounds of this type are alkylglycidylmalonate (I) and alkylglycidylacetoacetate esters (II) [1-4].

Reaction of the oxides (I) with pyrrolidine and piperidine with equimolar amounts of the reactants proceeds with fission of the α-carbon–oxygen bond of the oxide to give the 2-alkyl-2-ethoxycarbonyl-4-pyrrolidinomethyl-4-butanolides (III) or the 2-alkyl-2-ethoxycarbonyl-4-piperidinomethyl-4-butanolides (IV) (Table 1).

Analogously, the interaction of oxides II with pyrrolidine and piperidine leads to the formation of 2-alkyl-4-pyrrolidinomethyl-4-butanolides (V) and 2-alkyl-4-piperidinomethyl-4-butanolides (VI) (Table 1). High yields of the latter are obtained when the oxide–amine ratio is 1:2.

Condensation of the oxides (I) and (II) with morpholine was examined with various ratios of starting materials, to give the 2-alkyl-4-morpholinomethyl-2-ethoxycarbonyl-4-butanolides (VII) and 2-alkyl-4-morpholinomethyl-4-butanolides (VIII) (Table 1).



I, II III–VIII

R=C_4H_9, C_5H_{11}, C_6H_{13}; I, III, V, VII R^1=COOEt; II R^1=$COCH_3$; IV, VI, VII R^1=H; III, V n=3, IV, VI n=4; X=CH_2; VII, VIII n=4, X=O

Butanolides (V), (VI), and (VIII) were also obtained by alkaline hydrolysis of butanolides (III), (IV), and (VII).

The addition of heterocyclic amines to oxides (I) and (II) follows Krasuskii's rule, to give the above butanolides.

The hydrochlorides of butanolides (III-VIII) display moderate hypotensive and antiallergic activity. Reduction of the arterial pressure in animals requires near-toxic doses of the hydrochloride of butanolide (IIIa). The hydrochloride of (IVa) has a moderate antidepressant effect.

EXPERIMENTAL

IR spectra were obtained on IKS-14 and IKS-22 spectrometers, in thin films or in vaseline oil. PMR spectra were obtained on Varian T-60 (60 MHz) and Hitachi-Perkin-Elmer R-208 (60 MHz) spectrometers, internal standard tetramethylsilane.

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