

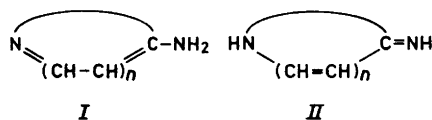
## Tautomerism, Acidity, and Electronic Spectra of 1,3,4-Thiadiazolylhydrazones. A Comparison with Amino-heterocycles

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The tautomerism of a series of 1,3,4-thiadiazolylhydrazones has been investigated by ultraviolet spectroscopy, and the compounds have been shown to exist as true hydrazones rather than as thiadiazolinone azines, in agreement with the results of LCAO-MO calculations. The acidity constants of the compounds show no direct relation to the calculated  $\pi$  electron distributions, but the correlation between calculated transition energies and experimental ultraviolet absorption maxima is satisfactory. A comparison is made with 2- and 4-aminopyridine and 2-aminothiazole. The results are discussed in relation to two atomic orbital models for the sulphur atom.

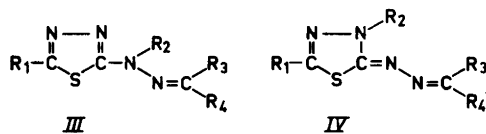
Heterocyclic amines capable of an amidine or vinylogous amidine type of tautomerism (I–II,  $n = 0$  or 1) have long been the subject of interest of organic chemists, and it has been quite common to ascribe to them the imine structure (II) when they show reactivities deviating from those of normal aromatic amines. However, Anderson and Seegar<sup>1</sup> have shown by



a comparison of ultraviolet spectra that the amino form (I) dominates in 2- and 4-aminopyridine in ether solution. Angyal and Angyal<sup>2</sup> were able to show, by measuring acidity constants of the conjugate acids of the amines and of their ring-substituted N-methyl derivatives, that the amino form dominates by a factor of  $2 \times 10^3 - 2 \times 10^5$  in water solution for 2- and 4-aminopyridine, 2-aminoquinoline, and 2-aminothiazole. X-Ray crystallography<sup>3</sup> and infrared spectroscopy<sup>4,5</sup> have also been used to establish the amino structure (I) for various six-membered heterocycles.

In a series of communications,<sup>6-10</sup> the preparation of various 1,3,4-thiadiazolylhydrazones (III,  $R_2 = \text{H}$ ) has been described. These are capable of the same kind of tautomerism, and it was regarded as a matter of interest to determine the position of the equilibrium, particularly as the extended con-

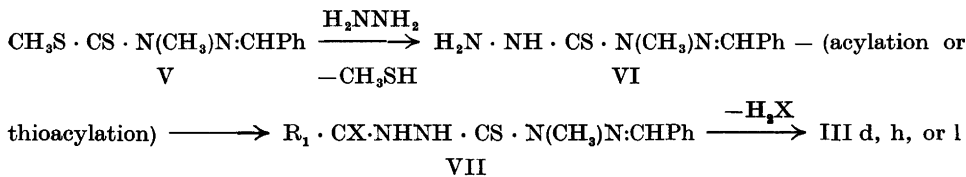
jugated system might tend to favour the thiadiazolinone azine structure (IV,  $R_2 = H$ ). Furthermore, it was hoped that these compounds would consti-



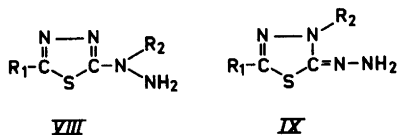
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|--|---|
| <p>a, <math>R_1 = R_2 = H, R_3 = R_4 = CH_3</math><br/>           b, <math>R_1 = H, R_2 = R_3 = R_4 = CH_3</math><br/>           c, <math>R_1 = R_2 = R_3 = H, R_4 = Ph</math><br/>           d, <math>R_1 = R_3 = H, R_2 = CH_3, R_4 = Ph</math><br/>           e, <math>R_1 = CH_3S, R_2 = H, R_3 = R_4 = CH_3</math><br/>           f, <math>R_1 = CH_3S, R_2 = R_3 = R_4 = CH_3</math><br/>           g, <math>R_1 = CH_3S, R_2 = R_3 = H, R_4 = Ph</math><br/>           h, <math>R_1 = CH_3S, R_2 = CH_3, R_3 = H,</math><br/> <math>R_4 = Ph</math></p> | <p>i, <math>R_1 = Ph, R_2 = H, R_3 = R_4 = CH_3</math><br/>           j, <math>R_1 = Ph, R_2 = R_3 = R_4 = CH_3</math><br/>           k, <math>R_1 = R_4 = Ph, R_2 = R_3 = H</math><br/>           l, <math>R_1 = R_4 = Ph, R_2 = CH_3, R_3 = H</math><br/>           m, <math>R_1 = R_3 = H, R_2 = CH_2Ph, R_4 = Ph</math><br/>           n, <math>R_1 = R_3 = H, R_2 = CH_2COOH, R_4 = Ph</math><br/>           o, <math>R_1 = H, R_2 = CH_2COOH, R_3 = CH_3,</math><br/> <math>R_4 = Ph</math></p> |
|--|---|

tute a suitable material for testing the validity of LCAO-MO calculations with different models for the sulphur atom in thiadiazole rings. Among observables, suitable for correlation with calculated quantities are tautomeric ratios, acidity constants, and positions of ultraviolet absorption bands.

For this investigation most of the methyl derivatives of the two possible tautomeric forms (III and IV,  $R_2 = CH_3$ ) have been prepared, with  $R_1 = H, CH_3S,$  and  $Ph,$  and  $R_3 = R_4 = CH_3$  or  $R_3 = H$  and  $R_4 = Ph.$  The methyl derivatives (III) were obtained as major products when methyl iodide was added to solutions of the hydrazones in sodium ethoxide, and the isomers (IV) when the hydrazones reacted with diazomethane. The assignment of the structures (III) or (IV) to the methyl derivatives was made by unambiguous synthesis of the methylated benzaldehyde hydrazones of structure (III) according to the following scheme:



The correlation of the methylated acetone hydrazones was made by hydrolysis to free hydrazines (VIII) or thiadiazolinone hydrazones (IX), followed by reaction with benzaldehyde to give (III,  $R_2 = CH_3, R_3 = H, R_4 = Ph$ ) or (IV,  $R_2 = CH_3, R_3 = H, R_4 = Ph$ ).



- |   |   |   |
|---|---|---|
| <p>a, <math>R_1 = R_2 = H</math><br/>           d, <math>R_1 = CH_3S, R_2 = CH_3</math></p> | <p>b, <math>R_1 = H, R_2 = CH_3</math><br/>           e, <math>R_1 = Ph, R_2 = H</math></p> | <p>c, <math>R_1 = CH_3S, R_2 = H</math><br/>           f, <math>R_1 = Ph, R_2 = CH_3</math></p> |
|---|---|---|

Hünig and Oette<sup>11</sup> have prepared the hydrazone (IX f) by hydrazinolysis of the corresponding methylthio-thiadiazole methiodide, and obtained a compound with the same melting point as the one prepared in the present work, which further confirms the assignments mentioned above.

Reaction between the free thiadiazolylhydrazones and benzyl chloride or sodium monobromoacetate in alkaline medium, in general produced compounds of the structure (III). However, acetophenone thiadiazolylhydrazone reacted with sodium monobromoacetate to give (IV o). This can probably be ascribed to a steric effect, since the corresponding benzaldehyde hydrazone under the same conditions gave (III n).

However, two of the acetone hydrazones, (III b) and (III f), could not be prepared since acetone was split off during the methylation process and the free thiadiazolylhydrazines (VIII b) and (VIII d) were obtained. The isomeric hydrazones (IX) could be prepared by acid hydrolysis of the acetone derivatives (IV b), (IV f), and (IV j), but the latter were considerably more resistant to hydrolysis than the isomers (III).

Unfortunately, all the thiadiazolylhydrazones treated in this investigation are too rapidly hydrolysed in aqueous acid solution to allow the acidity constants of their conjugate acids to be determined. Therefore, a quantitative determination of the tautomeric constants with the aid of the acidity constants is excluded. Instead, a qualitative estimation of the position of the tautomeric equilibrium with the aid of ultraviolet spectra was attempted. Fortunately, the spectra of the isomeric methyl derivatives (III,  $R_2 = CH_3$ ) and (IV,  $R_2 = CH_3$ ) are rather different. The spectra of the free thiadiazolylhydrazones are so similar to those of the methyl derivatives (III) that the presence of noticeable quantities of the isomers (IV,  $R_2 = H$ ) in the equilibrium mixtures is improbable. (Fig. 1 and Table 1).

#### METHOD OF CALCULATION AND CHOICE OF PARAMETERS

It is well known that the calculation of molecular quantities by the Hückel approximation can be improved by allowing the calculated charge densities to determine a new set of Coulomb integrals in an iterative procedure, which

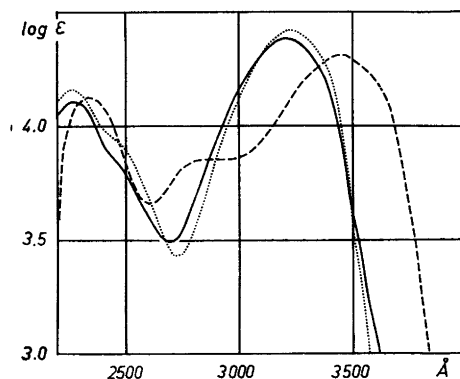


Fig. 1. Ultraviolet spectra in absolute ethanol of (III c, —), (III d, ...), and (IVd, ----).

Table 1. Ultraviolet spectra of thiadiazolyhydrazones (III) and thiadiazolinone azines (IV) in absolute ethanol

Compound	$\lambda_{\max}$ Å	$\epsilon$	$\lambda_{\max}$ Å	$\epsilon$	$\lambda_{\max}$ Å	$\epsilon$
IIIa	2790	13 600	2260	5 040	—	—
Anion <sup>a</sup>	3250	12 300	2460	7 800	—	—
IVb	3050	7 600	2570	8 600	—	—
IIIc	3210	24 400	2270	12 900	—	—
Anion <sup>a</sup>	3780	21 700	2820	5 450	2420	12 500
III d	3230	27 000	2260	14 500	—	—
IV d	3440	20 800	2860	7 250	2340	13 600
III e	2980	16 000	—	—	—	—
Anion <sup>a</sup>	3420	13 100	2160	5 450	—	—
IV f	3160	11 800	2620	9 600	—	—
III g	3350	25 000	2540	8 300	2260	13 700
Anion <sup>a</sup>	3890	27 000	—	—	—	—
III h	3360	25 000	2600	8 900	2270	13 500
IV h	3550	23 500	2900	7 900	2320	16 700
III i	3180	20 800	2370	8 400	—	—
Anion <sup>a</sup>	3750	17 700	—	—	—	—
III j	3190	16 400	—	—	—	—
IV j	3450	12 000	2410	12 700	—	—
III k	3470	27 000	2290	18 700	—	—
Anion <sup>a</sup>	4080	28 000	3250	8 000	—	—
III l	3490	30 700	2780	8 900	2280	19 200
IV l	3690	24 100	3160	11 000	2370	24 100
III m	3220	25 400	2270	15 200	—	—
III n	3210	24 200	2270	14 100	—	—
IV o	3470	15 900	2890	8 000	2330	12 000

is continued until convergent results are obtained. This  $\omega$ -technique in a way takes the repulsion between electrons on the same atom into account, and it has been used with some success by, among others, Wheland and Mann<sup>12</sup> for the calculation of the dipole moment of fulvene, by Nagakura<sup>13</sup> on simple carboxylic acid derivatives, by Streitwieser<sup>14</sup> for the calculation of ionization potentials, and by Janssen<sup>15</sup> for the calculation of transition energies of simple thioamides. A further improvement can be reached by including in the iterative procedure calculation of new sets of resonance integrals from the bond orders obtained in the previous Hückel calculation. Janssen's method of calculation,<sup>15</sup> neglecting overlap, has been used for the thiadiazolyhydrazones. In his work, both singly and doubly bonded sulphur atoms are treated, and reasonable results are obtained without the explicit inclusion of d orbitals. However, Longuet-Higgins<sup>16</sup> has proposed that the orbitals on the sulphur atom in thiophene should be treated as hybrids between 3p and 3d orbitals ( $pd^2$ ). This treatment has been extended to thiazole and thiadiazoles by Zahradnik and Koutecky,<sup>17</sup> and recently Vincent and Metzger<sup>18</sup> have published a more refined calculation on thiazole employing Longuet-Higgins sulphur model and including overlap. Both groups of authors conclude that the Longuet-Higgins model gives a correct order of reactivities for the carbon atoms in thiazole, whereas a sulphur model which utilizes only the  $3p_z$  orbital gives

the wrong order. For the thiadiazoles<sup>17</sup> no correlation with observables was made. Therefore, it was regarded as a matter of interest to test these two models on the thiadiazolyldhydrazones, for which three sets of observables, tautomeric ratios (qualitative), acidity constants, and ultraviolet spectra, are available. All calculations were performed with the Longuet-Higgins model, in the following referred to as the  $pd^2$  model ( $\beta_{C-S} = 0.8\beta$ ), and with the  $p_z$  model with  $\alpha_s = \alpha + \beta$ <sup>15</sup> and  $\beta_{C-S} = 0.8\beta$ . For the carbon atoms no auxiliary inductive parameters<sup>19</sup> were used. It is remarkable that the carbon-nitrogen bond lengths in aminopyrimidines<sup>20,21</sup> are rather similar, 1.30 – 1.33 Å, and also that the formal single bonds are somewhat shorter than bonds which should have more double bond character. The same apparent discrepancy is found in dicyandiamide.<sup>22</sup> It seems reasonable to assume that all the carbon-nitrogen bond lengths in the thiadiazolyldhydrazones are nearly equal and of about the same length as in the aminopyrimidines. If the resonance integral for a pure carbon-nitrogen double bond, 1.27 Å,<sup>23</sup> is given the value  $\beta$ ,<sup>24</sup> and assuming proportionality between resonance integrals and overlap integrals,<sup>25</sup> a value of  $0.9\beta$  for all the carbon-nitrogen bonds under consideration is arrived at. The length of the nitrogen-nitrogen bonds, between two  $sp^2$  hybridized atoms, was assumed to be 1.32 Å as in diformylhydrazine,<sup>26</sup> and from the overlap integral, calculated according to Mulliken *et al.*<sup>27</sup>, a value of  $0.8\beta$  was obtained for  $\beta_{NN}$ . For the exocyclic carbon-sulphur bond, a more arbitrary value of  $0.6\beta$  was used. This is justified by its relatively slight influence on the calculations. The parameters are summarized in Table 2.

#### THEORETICAL CALCULATION OF TAUTOMERIC RATIOS

The calculation of the tautomeric constant  $K_T$  (1) requires a knowledge of the change in free energy accompanying the tautomeric change. This energy change is made up of different terms, among which the one due to differences

$$K_T = \frac{C_{III}}{C_{IV}} = \exp(-\Delta G/RT) \quad (1)$$

in  $\pi$  electron stabilization,  $\Delta E_\pi$  is accessible by simple LCAO-MO calculations. Other terms arise from differences in  $\sigma$ -bond energy and entropy. The first

Table 2. Coulomb and resonance integrals

X	$\alpha_x$	X - Y	$\beta$
C	$\alpha$	C - C	$\beta$
$\dot{N}_{sp^2}$	$\alpha + 0.5\beta$	C - N	$0.9\beta$
$\ddot{N}_{sp^2}$	$\alpha + 1.5\beta$	$N_{sp^2} - N_{sp^2}$	$0.8\beta$
$\ddot{N}_{sp^3}$	$\alpha + 0.9\beta$	$N_{sp^2} - N_{sp^3}$	$0.5\beta$
$S_p$	$\alpha + \beta$	C - S (ring)	$0.8\beta$
$S_z$		C - S (subst)	$0.6\beta$
$S_{pd^2}$	$\alpha$ (two orbitals)	$pd^2 - pd^2$	$\beta$

Table 3. Calculated (in units of  $\beta$ ) and experimental energy quantities for 2-aminopyridine (Xa), 4-aminopyridine (XIa), 2-amino-thiazole (XIIa), and the corresponding isomeric imines (Xb–XIIb).

	Xa	Xb	XIa	XIb	XIIa, p <sub>z</sub>	XIIb, p <sub>z</sub>	XIIa, pd*	XIIb, pd*
Lowest antibonding orbital	-1.138	-0.883	-1.190	-0.982	-1.517	-1.607	-1.155	-1.011
Highest bonding orbital	0.904	0.388	0.917	0.407	0.574	0.293	0.810	0.505
Total $\pi$ electron energy	14.254	13.860	14.244	13.858	13.100	12.842	13.702	13.514
$\Delta E_{\pi \rightarrow \pi^*}$	-2.042	-1.271	-2.107	-1.389	-2.091	-1.900	-1.965	-1.516
$\Delta G_{\text{calc}}$	0.394		0.386		0.258		0.188	
$\Delta G_{\text{exp}}$ kcal/mole (Ref. <sup>2</sup> )	7.3		4.0		6.0			

Table 4. Calculated energy quantities (in units of  $\beta$ ) for thiaziazolyldiazones (III) and thiaziazolinone azines (IV).

	IIIa	IVa	IIIc	IVc	IIIe	IVe	IIIg	IVg	IIIi	IVi	IIIk	IVk
<i>p<sub>z</sub></i> Model												
Lowest antibonding orbital	-1.195	-1.068	-0.838	-0.789	-1.204	-1.071	-0.840	-0.791	-0.949	-0.940	-0.821	-0.786
Highest bonding orbital	0.595	0.298	0.529	0.258	0.439	0.257	0.416	0.226	0.504	0.286	0.471	0.249
Total $\pi$ electron energy	16.842	16.638	27.884	27.716	19.036	18.838	30.074	29.916	27.856	17.636	38.894	38.710
$\Delta E_{\pi \rightarrow \pi^*}$	-1.780	-1.366	-1.367	-1.047	-1.643	-1.328	-1.256	-1.017	-1.453	-1.226	-1.292	-1.035
$\Delta G$	0.204		0.168		0.198		0.168		0.220		0.184	
pd <sup>2</sup> Model												
Lowest antibonding orbital	-1.035	-0.765	-0.811	-0.648	-1.061	-0.780	-0.819	-0.653	-0.803	-0.733	-0.750	-0.649
Highest bonding orbital	0.747	0.464	0.635	0.399	0.591	0.397	0.542	0.350	0.656	0.437	0.587	0.381
Total $\pi$ electron energy	17.368	17.178	28.398	28.226	19.606	19.404	30.642	30.454	28.384	28.194	39.416	39.242
$\Delta E_{\pi \rightarrow \pi^*}$	-1.782	-1.239	-1.446	-1.047	-1.652	-1.177	-1.361	-1.003	-1.459	-1.170	-1.337	-1.030
$\Delta G$	0.190		0.172		0.202		0.188		0.190		0.174	

of these terms is probably not very important compared with  $\Delta E_\pi$ , since both tautomers contain the same number of bonds of each kind. The  $T\Delta S$  term is less readily estimated. Since the geometry of the molecule is not very much altered by the tautomeric change, it is probable that this term is small, and that  $\Delta G$  is mainly determined by  $\Delta E_\pi$ . It is also probable that the  $T\Delta S$  term is of the same order of magnitude for all the tautomeric systems under consideration here. Angyal and Angyal<sup>2</sup> have calculated  $\Delta G$  values for 2- and 4-aminopyridine and for 2-amino-thiazole. No real correlation is found between the  $\Delta E_\pi$  and  $\Delta G$  values (Table 3). If  $\beta$  is given values in the commonly accepted range  $-30$  to  $-50$  kcal,<sup>28</sup>  $\Delta G$  values between 6 and 20 kcal are obtained. It is obvious that these results are too uncertain to allow a decision regarding the correctness of the assumptions made above regarding the magnitude of the  $T\Delta S$  term. All that can be said is that the calculations give the greatest  $\pi$  electron stabilization to the tautomers which actually are the most stable ones. No decision can be made regarding the respective merits of the  $p_z$  and  $pd^2$  models in describing the aminothiazole. Apparently, the amine form (I) is always the more stable one as long as the amino group is attached to a ring system with reasonable resonance stabilization. On the contrary, in cyclic amides<sup>29</sup> and thioamides,<sup>30</sup> the tautomer with the substituent doubly bonded to the ring is the more stable one. This is probably due to superior resonance stabilization in the amide and thioamide groups.

The  $\Delta E_\pi$  values in Table 4 show that the thiadiazolylylhydrazones (III) are more stable than the tautomers (IV) by about  $-0.2\beta$ . The  $p_z$  and  $pd^2$  models give very similar results. Similarly, the amino- and hydrazinothiadiazoles are found to be more stable than the tautomers by  $-0.25\beta$  to  $-0.10\beta$ . In this case the  $pd^2$  model gives distinctly lower  $\Delta E_\pi$  values (Table 5).

#### ACIDITY CONSTANTS

It has previously been noticed<sup>6</sup> that the thiadiazolylylhydrazones show weakly acidic properties. This can be qualitatively explained by strong electron attraction of the  $\pi$ -deficient thiadiazole ring, and also by resonance stabilization of the anions. It was considered worthwhile to try to correlate the acidity constants with the calculated  $\pi$  electron charge,  $q_N$ , on the nitrogen atom carrying the acidic proton. The  $pK_a$  and  $q_N$  values are found in Table 6. Longuet-Higgins<sup>31</sup> has shown that a linear relation should exist between  $q_N$  and  $pK_a$  values, and reasonable correlations have also been found for several series of closely related cationic heterocyclic acids.<sup>31-33</sup> In the present investigation, however, the correlation obtained was rather unsatisfactory. In each pair of hydrazones with the same  $R_1$ , the benzaldehyde hydrazone is a stronger acid than the acetone hydrazone, in agreement with the  $q_N$  values. On the other hand, the effect of the substituent  $R_1$  is not correctly reproduced. The  $pK_a$  values of the acetone hydrazones increase in the order  $R_1 = CH_3S$ , Ph, H, and of the benzaldehyde hydrazones in the order  $CH_3S$ , H, Ph, whereas the  $q_N$  values increase in the order Ph, H,  $CH_3S$ . Both models for the sulphur atom give qualitatively similar results, and the correlation does not favour any of them. In his deduction, Longuet-Higgins<sup>31</sup> assumes that the entropies

Table 5. Calculated energy quantities (in units of  $\beta$ ) for thiaziazolyhydrazines (VIII), thiaziazolinone hydrazones (IX), thiaziazolyamine (XIII), and thiaziazolinone imine (XIV).

	VIIIa	IXa	VIIIc	IXc	VIIIe	IXe	XIII	XIV
$p_z$ Model								
Lowest antibonding orbital	-1.429	-1.439	-1.499	-1.527	-0.965	-0.946	-1.425	-1.436
Highest bonding orbital	0.467	0.194	0.370	0.161	0.421	0.186	0.632	0.357
Total $\pi$ electron energy	15.148	14.956	17.338	17.152	26.166	25.908	13.328	13.072
$\Delta E_{\pi \rightarrow \pi^*}$	-1.896	-1.633	-1.869	-1.688	-1.386	-1.132	-2.057	-1.793
$\Delta G$	0.192		0.186		0.258			0.256
$pd^2$ Model								
Lowest antibonding orbital	-1.041	-0.869	-1.073	-0.906	-0.825	-0.760	-1.038	-0.854
Highest bonding orbital	0.564	0.358	0.488	0.308	0.527	0.342	0.849	0.561
Total $\pi$ electron energy	15.696	15.598	17.928	17.814	26.718	26.618	13.866	13.676
$\Delta E_{\pi \rightarrow \pi^*}$	-1.605	-1.227	-1.561	-1.214	-1.352	-1.102	-1.887	-1.415
$\Delta G$	0.098		0.114		0.100			0.190



Table 6.  $pK_a$  values for thiadiazolyhydrazones (III,  $R_2 = H$ ) and  $q_N$  values for (III) and (IV)

Compound	$pK_a$	$q_N$	
		$p_z$	$pd^2$
IIIa	10.8	1.813	1.797
IVa		1.761	1.727
IIIc	10.0	1.799	1.784
IVc		1.750	1.729
IIIe	10.5	1.815	1.802
IVe		1.767	1.743
IIIg	9.6	1.800	1.789
IVg		1.756	1.735
IIIi	10.7	1.808	1.793
IVi		1.754	1.729
IIIk	10.2	1.794	1.780
IVk		1.743	1.722

of ionization are the same for all the rather similar conjugate acids of heterocyclic amines which are the subjects of his investigation. This assumption is more likely to be valid for cationic acids, which ionize without creating new charges, than for the neutral thiadiazolyhydrazones, which ionize with formation of differently charged species. Therefore, the failure to obtain a linear correlation may be ascribed to differences in entropy of ionization, caused by the substituents  $R_1$ , particularly as the differences between the individual  $pK_a$  and  $q_N$  values are small.

It is also of interest to study the  $q_N$  values for the isomeric azines (IV). The relation known as "the Gustafsson paradox"<sup>34,35</sup> (2) where  $x$  and  $y$  denote two tautomeric acids with a common anion, shows that the tautomer having the smallest weight has the highest static acidity. Therefore,  $q_N$  for the NH

$$K_T = \frac{C_x}{C_y} = \frac{K_{a,y}}{K_{a,x}} \quad (2)$$

group in the azines (IV) should be lower than in the hydrazones (III). This is also found to be the case, thus confirming the results of the calculations of  $\Delta E_{\pi}$  values.

#### ULTRAVIOLET SPECTRA

It can be seen from Table 1 that the hydrazones (III) generally absorb at shorter wavelengths than the corresponding azines (IV). This is correctly reproduced by the calculated transition energies (Table 4), though the differences are exaggerated, particularly in the calculations with the  $pd^2$  model. The same applies to the thiadiazolyhydrazines (VIII) and their isomers (IX), the spectra of which are recorded in Table 7. Their transition energies and other energy values are found in Table 8. The spectra of 2-aminothiazole and thiazolinone-2-imine have been recorded by Wilson and Woodger<sup>36</sup>

Table 7. Ultraviolet spectra of thiadiazolylhydrazines (VIII) and thiadiazolinone hydrazones (IX) in absolute ethanol

Compound	$\lambda_{\max}$ Å	$\epsilon$	$\lambda_{\max}$ Å	$\epsilon$
VIIIb	2650	5 600	—	—
VIIIc	2820	8 200	—	—
VIIIId	2870	10 600	—	—
IXd	2890	5 500	—	—
VIIIe	3060	14 400	—	—
VIIIIf	3110	15 200	2260	7 500
IXf	3330	7 400	2440	13 100

and found to show a similar relation ( $\lambda_{\max}$ : 2550 Å for the amine, 2600 Å for the imine). This is also qualitatively reproduced by the calculated transition energies, though much better by the  $p_z$  than by the  $pd^2$  model. The 2- and 4-aminopyridines also absorb at shorter wavelengths than the corresponding imines,<sup>1,37,38</sup> and that too is in agreement with the calculations (Table 3). The orders between the absorption maxima of 2- and 4-aminopyridine ( $\lambda_{\max}$ : 2950 Å and 2625 Å, respectively) and between those of their imines (3580 Å and 3120 Å) are also in accord with the calculations.

From Tables 1 and 7 it appears that for compounds with the same  $R_1$  the wavelengths of the first absorption maxima increase in the order hydrazone (VIII), acetone hydrazone (III) and benzaldehyde hydrazone (III), and also in the order hydrazone (IX), acetone azine (IV) and benzaldehyde azine (IV), *i.e.* with increasing conjugation. The calculated transition energies decrease in the same order.

The effect of the substituent  $R_1$  is also fairly correctly reproduced. It can be seen (Table 1) that the bathochromic effect increases in the series  $H < CH_3S < Ph$ . The transition energies for the hydrazines (VIII), hydrazones (IX), acetone hydrazones (III), and acetone azines (IV) decrease in the same order. However, for the benzaldehyde hydrazones (III), the order between  $CH_3S$  and  $Ph$  is reversed by the  $p_z$  model, and for the benzaldehyde azines this order is reversed by both models for the sulphur atom. The deviations are small, and on the whole the agreement between the calculated and experimental transition energies can be said to be satisfactory, particularly with regard to the rather naive method of calculation. A moderately close linear relation is fulfilled (Fig. 2). The best straight lines have been computed by the method of least squares, and spectroscopic  $\beta$  values of 11 400  $cm^{-1}$  for the  $p_z$  model and 16 900  $cm^{-1}$  for the  $pd^2$  model were obtained. The correlation, however, is far better for the  $p_z$  model than for the  $pd^2$  model, the correlation coefficients being 0.9960 and 0.8232, respectively.

The effect of the Coulomb integral for the sulphur atom on the transition energy calculated with the  $p_z$  model has also been investigated. As appears from Fig. 3, the energy levels show an obvious dependence on the  $\alpha_s$  values, whereas the difference between them is much less affected. If this is correct, triazolylhydrazones and oxadiazolylhydrazones should show spectra similar

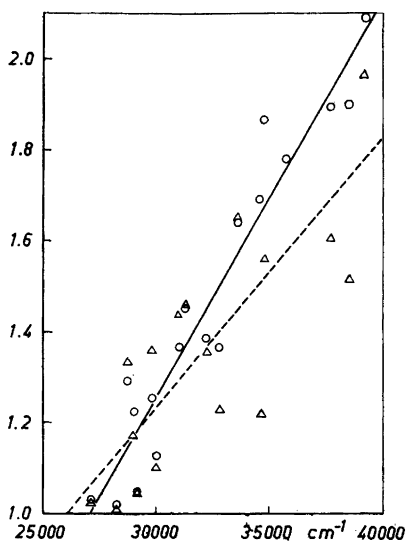


Fig. 2. Plot of calculated transition energies (in units of  $-\beta$ ) versus experimental wavenumbers for absorption maxima. The best straight lines have been computed by the method of least squares for the  $p_z$  model (O, —) and the  $pd^2$  model ( $\Delta$ , ----)

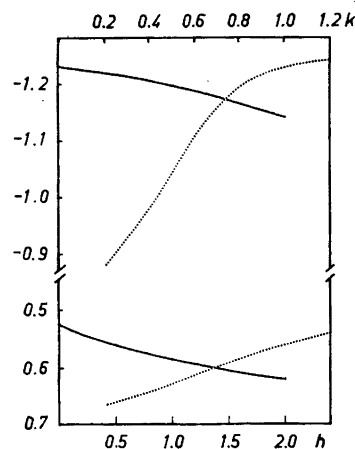
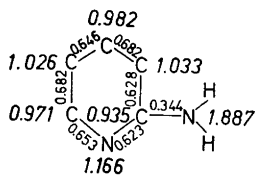


Fig. 3. Energy of the highest bonding and lowest antibonding orbital (in units of  $\beta$ ) of (IIIa) as function of  $k$  in  $\beta_{cs} = k\beta$  (upper abscissa, .....,  $a_s = a + \beta$ ) and as function of  $h$  in  $a_s = a + h\beta$  (lower abscissa, —,  $\beta_{cs} = 0.8\beta$ ).

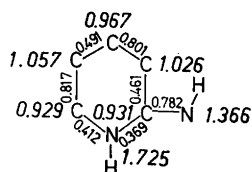
to those of the thiadiazolylhydrazones. It is possible that a similar dependence can explain the, at first sight, rather surprising observation of Bulka *et al.*<sup>39</sup> that exchange of sulphur for selenium in thiazolon-azines has only a very slight spectral effect. The influence of  $\beta_{cs}$  is much stronger both on the energy levels and the transition energy (Fig. 3) except in the neighbourhood of  $1.0\beta$  where the transition energy is nearly constant.

#### CHARGE DISTRIBUTIONS

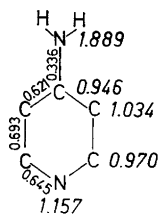
The calculated charge distributions for some representative systems are shown in Fig. 4. A considerable difference can be seen between the results with the  $p_z$  and  $pd^2$  models, the former giving rise to far greater separation of charges. Therefore, correlations with dipole moments might constitute a more promising way of comparing the merits of the two sulphur models for the LCAO-MO approximation used in this work. However, Vincent and Metzger<sup>18</sup> have shown that inclusion of overlap in the calculation with the  $pd^2$  model for thiazole increases the charge separation and gives a reasonable dipole moment if the  $\sigma$  polarisations of Smyth<sup>40</sup> are used. Summing up, both models for the sulphur atom can be said to give equivalent results for the tautomeric constants, since the calculations in all cases give the greatest  $\pi$  electron stabilization to the dominating tautomeric form. Neither of the models



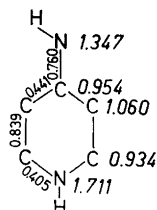
a



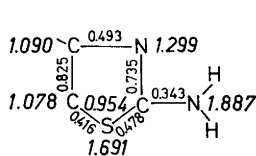
b



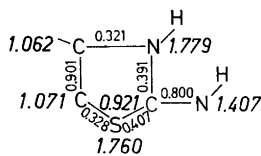
c



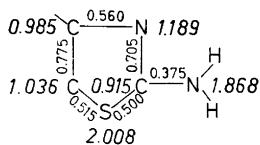
d



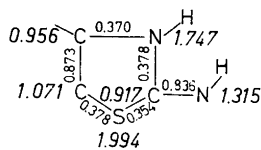
e



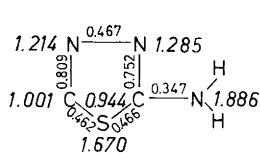
f



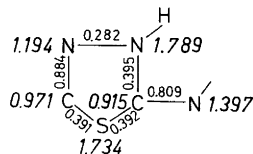
g



h



i



j

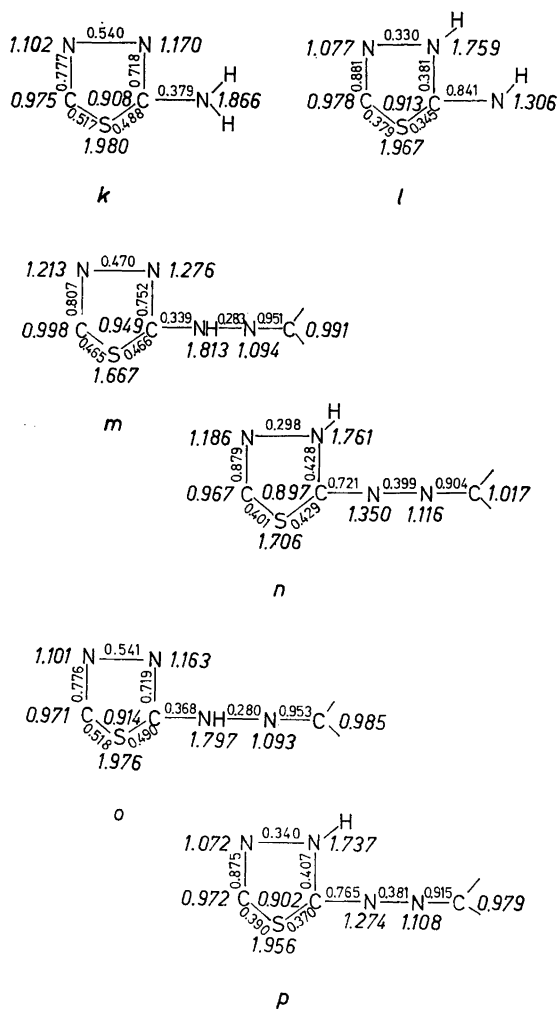


Fig. 4. Calculated  $\pi$  electron densities and mobile bond orders. The diagrams e, f, i, j, m, and n have been calculated with the  $p_z$  model g, h, k, l, o, and p with the  $pd^2$  model.

can correlate the  $q_N$  and  $pK_a$  values, but this must not mean that the calculated  $q_N$  values are without significance, since the lack of correlation may be due to other causes. The gross features of the ultraviolet spectra are reproduced by both models, but the numerical agreement is far better when the  $p_z$  model is used. However, it is possible that the systems used in this investigation are insensitive to the real differences between the two models, and therefore the superiority of the  $p_z$  model for the 1,3,4-thiadiazole system must await further confirmation.

## EXPERIMENTAL

*1-Benzylidene-2-methyl-thiocarbohydrazide (IV)*. Methyl 2-methyl-3-benzylidene-dithiocarbazate<sup>41</sup> (V) (11.2 g) and anhydrous hydrazine (3 ml) were refluxed in absolute ethanol for 20 min. On cooling a colourless precipitate was formed (8.8 g, 85 % yield), which crystallized from absolute ethanol as colourless needles, m.p. 150–151°. (Found: C 52.0; H 5.91; N 26.8; S 15.2.  $C_9H_{12}N_4S$  (208.28) requires C 51.9; H 5.81; N 26.9; S 15.4).

*Benzaldehyde N-methyl-N-thiadiazolyl-hydrazone (III d)*. The thiocarbohydrazide (VI) (0.65 g) was refluxed with triethyl orthoformate (2 ml) for 5 min, and then the mixture was refluxed with water (5 ml) for 2 h to destroy the remaining orthoester. The resulting oil was extracted with benzene (20 ml), and after drying with anhydrous calcium sulphate, 6 N hydrochloric acid in absolute ethanol (2 ml) was added to the benzene solution. A crystalline hydrochloride was formed. This was dissolved in ethanol (3 ml), and water (20 ml) was added. A precipitate of colourless hairs was formed (0.42 g, 60 % yield), m.p. 88–89°. The analytical figures are found in Table 8.

*1-Benzylidene-2-methyl-5-dithiocarbomethoxy-thiocarbohydrazide (VII,  $R_1 = CH_3S$ ,  $X = S$ )*. The thiocarbohydrazide (VI) (2.1 g) was dissolved in N sodium ethoxide (20 ml), and dimethyl trithiocarbonate (1.4 g) was added. On the following day the solution was poured into N acetic acid (50 ml), and a precipitate of pale yellow rods (2.9 g, 95 % yield) was obtained, m.p. 140–141° (decomp.) after recrystallization from toluene. (Found: C 44.2; H 4.71; N 18.9; S 32.0.  $C_{11}H_{14}N_4S_3$  (298.43) requires C 44.3; H 4.73; N 18.8; S 32.2).

*Benzaldehyde N-methyl-N-(methylthio-thiadiazolyl)-hydrazone (III h)*. The thiocarbohydrazide (VII,  $R_1 = CH_3S$ ,  $X = S$ ) (1.5 g) was kept at 150° until the evolution of gas had ceased. The semisolid residue was recrystallized twice from absolute ethanol and gave colourless prisms (0.95 g, 72 % yield), m.p. 133–134°. The analytical figures are found in Table 8.

*Benzaldehyde N-methyl-N-(phenylthiadiazolyl)-hydrazone (III l)*. The thiocarbohydrazide (VI) (1.1 g) was dissolved in hot ethanol (50 ml) and carboxymethyl dithiobenzoate<sup>42</sup> (1.1 g) in N NaOH (6 ml) was added. The red colour faded rapidly, and a precipitate was formed (1.0 g, 64 % yield), which crystallized from ethanol as pale yellow rods, m.p. 183–184°. The analytical figures are found in Table 8.

## Methylation of thiadiazolylhydrazones

a) *With methyl iodide in sodium ethoxide solution*. The thiadiazolylhydrazones were dissolved in 1.5 equivalents of N sodium ethoxide in absolute ethanol, and 2 equivalents of methyl iodide were added. After 24 h the solutions were evaporated, and the residues were extracted with hot toluene. The toluene solutions were subjected to chromatography on alumina. The behaviour of the isomers (III) and (IV) towards eluting agents is very uniform, which greatly facilitated the separation. Benzene eluted small to moderate amounts of the isomers (IV), and then the isomers (III) were eluted by ether with 10 % of ethanol. From the acetone derivative (III a) a non-crystalline product was obtained. This was dissolved in absolute ether, and a solution of hydrogen chloride in absolute ethanol was added. The crystalline product was found to consist of the hydrochloride of the hydrazine (VIII b), and probably the acetone residue had been split off during the chromatography. Similarly, the acetone hydrazone (III e) gave the crystalline hydrazine (VIII d) directly on chromatography after methylation.

b) *With diazomethane*. Several of the thiadiazolylhydrazones are only slightly soluble in the common solvents, but as a generally useful mixture, absolute ethanol, toluene, and dimethyl sulphoxide in the proportions 4:4:1 (v/v) was employed. To each hydrazone, an ether solution of 2 equivalents of diazomethane was added. The progress of the reaction was followed by chromatography on paper, impregnated with dimethyl sulphoxide,<sup>43</sup> and in all cases the starting material was consumed after 24 h. The solutions were evaporated and the isomeric methyl derivatives separated by chromatography as described above. Only in one case was a non-crystalline product obtained (IV b), but it was transformed into a crystalline hydrochloride as described for the hydrazine (VIII b). The yields, melting points, solvents for recrystallization, and analytical results for the methylated thiadiazolylhydrazones are summarized in Table 8.

Table 8. Solvents for recrystallization, yields, melting points, and analytical figures for thiazolylhydrazones (III) and thiazolinone azines (IV).

Compound	Solvent	Yield %		M.p.	Formula	C		H		N		S	
		RHals <sup>a</sup>	CH <sub>2</sub> N <sub>2</sub>			found	calc.	found	calc.	found	calc.	found	calc.
IVb	Ethanol-ether	—	43	152—153°	C <sub>6</sub> H <sub>11</sub> N <sub>4</sub> SOCl <sup>b</sup>	34.6	34.9	5.17	5.37	27.2	27.1	15.7	15.5
IIIId	Ethanol-water	91	19	88—89°	C <sub>10</sub> H <sub>10</sub> N <sub>4</sub> S	55.0	55.0	4.41	4.62	25.7	25.7	14.7	14.7
IVd	Ethanol	3	71	101—102°	C <sub>10</sub> H <sub>10</sub> N <sub>4</sub> S	55.0	55.0	4.89	4.62	25.7	25.7	14.8	14.7
IVf	Petroleum ether (40—60°)	13	58	46—47°	C <sub>8</sub> H <sub>12</sub> N <sub>4</sub> S <sub>2</sub>	38.8	38.9	5.48	5.59	25.9	25.9	29.8	29.6
IIIh	Ethanol	72	27	133—134°	C <sub>11</sub> H <sub>12</sub> N <sub>4</sub> S <sub>2</sub>	50.1	50.0	4.67	4.58	21.3	21.2	24.3	24.3
IVh	Ethanol	11	67	113—114°	C <sub>11</sub> H <sub>12</sub> N <sub>4</sub> S <sub>2</sub>	50.2	50.0	4.76	4.58	21.2	21.2	24.2	24.3
IIIj	Cyclohexane	63	21	81—82°	C <sub>13</sub> H <sub>14</sub> N <sub>4</sub> S	58.5	58.5	5.62	5.73	22.9	22.7	13.0	13.0
IVj	Ethanol	22	57	96—97°	C <sub>12</sub> H <sub>14</sub> N <sub>4</sub> S	58.6	58.5	5.82	5.73	22.8	22.7	12.9	13.0
IIIi	Ethanol	68	28	183—184°	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> S	65.0	65.3	4.83	4.79	19.1	19.0	10.8	10.9
IVl	Ethanol	17	69	122—123°	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> S	65.0	65.3	4.80	4.79	19.2	19.0	10.9	10.9
IIIIm	Ethanol	69	—	132—133°	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> S	65.4	65.3	4.72	4.79	19.1	19.0	10.9	10.9
IIIIn	Ethanol	55	—	242—243°	C <sub>11</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> S	50.4	50.4	3.77	3.84	21.4	21.4	12.1	12.2
IVo	Ethanol	36	—	191—192°	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S	51.9	52.2	4.33	4.38	20.1	20.3	11.5	11.6

<sup>a</sup> For compounds b-1 = CH<sub>3</sub>I, for III m = PhCH<sub>2</sub>Cl, for III n and IV o = BrCH<sub>2</sub>CO<sub>2</sub>.

<sup>b</sup> Hydrochloride.

Table 9. Solvents for recrystallization, melting points, and analytical figures for thiadiazolyhydrazines (VIII) and thiadiazolinone hydrazones (IX).

Compound	Solvent	M.p.	Formula	C		H		N		S	
				found	calc.	found	calc.	found	calc.	found	calc.
IXb	Ethanol	120–121°	$C_3H_6N_4S + 1.2 HCl^a$	20.8	20.7	4.14	4.17	31.8	32.2	18.5	18.4
VIIIId	Toluene	120–121°	$C_3H_6N_4S_2$	27.4	27.3	4.54	4.54	31.5	31.8	36.4	36.4
IXd	Heptane	82–83°	$C_3H_8N_4S_2$	27.5	27.3	4.62	4.54	31.9	31.8	36.3	36.4
VIIIIf	Toluene	148–149°	$C_3H_{10}N_4S$	52.6	52.4	5.02	4.89	27.0	27.2	15.6	15.5
IXf	Heptane	85–86°	$C_3H_{10}N_4S$	52.6	52.4	5.09	4.89	26.9	27.2	15.4	15.5

<sup>a</sup> Hüinig and Oette<sup>11</sup> also comment on the tendency of these bases to form hydrochlorides with between one and two molecules of hydrogen chloride.



## Other alkylations

*Benzaldehyde N-benzyl-N-thiadiazolyldiazone (III<sub>m</sub>)* was prepared by substituting benzyl chloride for methyl iodide in the reaction (a) above. It crystallized from ethanol as pale yellow rods, m.p. 132–133°. The analytical figures are found in Table 8.

*Benzaldehyde N-carboxymethyl-N-thiadiazolyldiazone (III<sub>n</sub>)* was obtained by reaction between sodium monobromoacetate and a solution of benzaldehyde thiadiazolyldiazone (III<sub>c</sub>) in 1.5 equivalents of N NaOH. On acidification after 24 h, the crude product separated, and it crystallized from ethanol as colourless hairs, m.p. 242–243° (Table 8).

*Acetophenone 3-carboxymethyl-thiadiazolin-2(3)-one azine (IV<sub>o</sub>)* was obtained by reaction between sodium monobromoacetate and acetophenone thiadiazolyldiazone as in the preceding experiment. It crystallized from ethanol as long, colourless plates, m.p. 191–192° (Table 8).

*Thiadiazolyldiazines (VIII) and thiadiazolinone hydrazones (IX)*. These were prepared by refluxing the corresponding acetone derivatives for a short time in hydrochloric acid solution. The water-insoluble bases were liberated by addition of sodium acetate, the others were isolated as hydrochlorides. The melting points, solvents for recrystallization, and analytical results are found in Table 9.

*The ultraviolet absorption spectra* were recorded in absolute ethanol solution with a Beckman DU spectrophotometer with photomultiplier attachment.

*The acid dissociation constants* (Table 6) were determined in water with 1 % of ethanol with standard spectrophotometric technique, utilizing the large bathochromic shifts on ionization.

*The numerical calculations* were performed with the electronic digital computer "SMIL" of the Department of Numerical Analysis of the University of Lund.

The financial support by *The Swedish Natural Science Research Council, Stiftelsen Lars Hiertas Minne, and Hierta-Retzius Stipendiefond* is gratefully acknowledged. The author is also grateful to Miss Karin Göransson and Miss Gunilla Isaksson for valuable experimental assistance, to Fil.Kand. Leif Robertsson for programming the calculations, and to Fil.Kand. Lars Adolfsson for performing part of the numerical calculations.

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Received January 28, 1964.

