3. R. C. Dougherty, Top. Curr. Chem., 45, 93 (1974).
4. K. G. Häusler, Master's Dissertation, Merseburg (1979).
5. D. A. Hickman and I. Jane, Analyst, 104, 334 (1979).
6. G. Wagner and L. Rothe, Pharmazie, 22, 611 (1967).
7. S. Leistner, Master's Dissertation, Leipzig (1979).

---

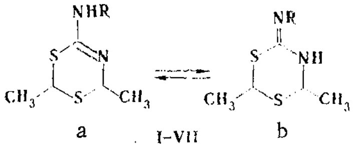
# BASICITIES AND STRUCTURES OF 2H,6H-2,6-DIMETHYL-4-AMINO-1,3,5-DITHIAZINE AND ITS N-ACYL DERIVATIVES

T. V. Kashik, G. V. Rassolova,
G. M. Gavrilova, V. I. Gostevskaya,
S. V. Amosova, and B. A. Trofimov

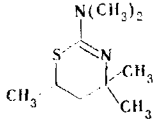
UDC 543.257.1:547.876'869.1:541.623

On the basis of a study of the basic properties of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine and its N-acyl derivatives it was concluded that N-acyldithiazines exist primarily in the amino form in methanol and acetone, regardless of the type of substituent (donor or acceptor) in the acyl fragment of these molecules. The intramolecular interrelationships between the exocyclic substituent and the protonation center in the investigated compounds correspond to the criteria of the ortho effect of nitrogen-containing heteroaromatic compounds.

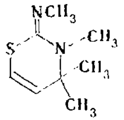
A study of N-acyl derivatives of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine (II-VII) in solution in chloroform, diethyl ether, and ethanol by IR and UV spectroscopy [1] showed that electron-acceptor substituents R' in the acyl fragment of these molecules (COR', where R' = $C_6H_5$, $CH_2Cl$, and $SO_2C_6H_4Me$-4) shift the tautomeric equilibrium to favor imino form b:



I-VII



VIII



IX

Ia R=H; IIa,b R=$COCH_3$; IIIa,b R=$COC_3H_7$; IVa,b R=$COC_4H_9$; Va,b R=$COC(CH_3)_3$; VIa,b R=COPh; VIIa,b R=$COCH_2Cl$

The existence of the indicated compounds in solutions in the form of a mixture of two tautomeric forms a and b may evidently be reflected in their reactivities. Thus, for example, a study by PMR spectroscopy of the direction of protonation in substituted 2-amino-4H-1,3-thiazines [2] with fixed amino (VIII) and imino (IX) forms that exclude tautomeric conversion indicates transfer of the protonation center in the imino form from the ring nitrogen atom (as in the case of VIII) to the exocyclic nitrogen atom. The higher basicity of IX as compared with VIII is the result of transfer of the protonation center. It is apparent from structures VIII and IX that 2-amino-4H-1,3-thiazine derivatives have a structure that is similar to that of the N-acyl derivatives of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine (a, b) that we previously investigated. It might therefore be expected that in the protonation of I-VII, which, according to the IR and UV spectroscopic data, are equilibrium mixtures of the a and b forms, the ratios of the basic strengths of their imino and amino forms would be retained in the same way as for the above-indicated VIII and IX, i.e., the basicity of the imino tautomer will be higher than that of the amino form. In this case the experimentally determined dissociation constants ($pK_a$) of the investigated N-acyl derivatives in solutions will be the effective dissociation constants of the equilibrium mixtures, which reflect the overall basicities of the imino and amino forms of these compounds. In conformity with the theory of acid-base protolytic tautomeric equilibria [3, 4] this fact may lead to disruption of the linearity be-

---

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk 664033. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 333-337, March, 1983. Original article submitted July 14, 1982.

0009-3122/83/1903-0268$07.50

TABLE 1. $pK_a$ of I-VII in Water, Methane, and Acetone

| Compound | $pK_a$ | | | $\sigma_m$ for NHR |
|---|---|---|---|---|
| | $H_2O$* | $CH_3OH$ | $CH_3COCH_3$ | |
| I | 7,00 | 8,30 | 8,32 | −0,16 |
| II | — | 4,37 | 4,46 | 0,21 |
| III | — | 4,41 | 4,47 | |
| IV | — | 4,40 | 4,66 | |
| V | — | 4,67 | 4,70 | |
| VI | — | 3,89 | 3,93 | 0,22 |
| VII | — | 3,20 | 3,22 | 0,30† |

---

*The $pK_a$ values in water were determined for compounds that display basicities in this solvent during potentiometric titration.

†The $\sigma_I$ value calculated from the equation [7] $\sigma_I(NR_1R_2) = 0.11 + 0.46[\sigma_I(R_1) + \sigma_I(R_2)]$, where $\sigma_I(COCH_2Cl) = 0.4$ [8], was used for the $NHCOCH_2Cl$ group.

tween the measured basicities of the investigated compounds and the polar constants of the corresponding substituents in them. In this case the dependence of the effective basicity constants of $\sigma_I$ is expressed by a curve, the asymptotes to which will be straight lines for compounds with electron-donor and electron-acceptor substituents.

In the hope of detecting these disruptions we determined the basicity constants of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine and its N-acyl derivatives I-VII in methanol and acetone (see Table 1) and thoroughly analyzed their dependence on the polar effects of the corresponding substituents. In selecting such different solvents as the media for studying the basicities we were guided not only by their definite analytical advantages over aqueous solutions (acyl derivatives are usually weak bases, and media with higher autoprotolysis constants than that of water are therefore necessary to study their basicities [5]) but also proceeded from the fact that the position of the tautomeric equilibrium of the investigated bases may depend on the properties of the solvent [6]. If such a dependence exists, it may be manifested in the nonidentical character of the change in the $pK_a$ values on passing from methanol to acetone for potentially tautomeric bases VI and VII (which have an electron-acceptor substituent in the acyl fragment of the molecules) and bases that exist primarily in the amino form (I-V). However, the data in Table 1 constitute evidence that on passing from methanol to acetone the basicities of compounds with both donor (I-V) and acceptor (VI, VII) substituents in the acyl fragment of the molecules are subject to the same principle — the $pK_a$ values for each of the compounds presented in Table 1 remain virtually unchanged in both solvents. For this reason, it is sufficient to examine the data obtained in any one solvent in order to ascertain the quantitative expressions that relate the basicities of the investigated series of compounds to their structures. Acetone was selected as the solvent to fulfill this role.

It follows from the data presented above that replacement of one of the hydrogen atoms of the amino group in I by an acetyl substituent (II, III) decreases the basicity of this compound by 3.86 $pK_a$ units. The successive change in the $pK_a$ values in the examined IV-VII series indicates the primarily inductive character of the effect of substituent R' on the basicities of these compounds. Thus for III-V the $pK_a$ value increases as the electron-donor character of the alkyl groups increases and decreases as the electron-acceptor properties of substituent R' increase on passing from VI to VII. On the basis of this, as the structural parameters that characterize the polar effect of R', we used inductive constants $\sigma_I$ in establishing the quantitative expression that relates the basicities of the investigated series of N-acyl-substituted II-VII to their structures.

Figure 1 (line 1) illustrates the linear relationship between the $pK_a$ values of the indicated compounds and inductive constants $\sigma_I$. The correlation equation for this case has the form

$$pK_{a\,CH_3COCH_3} = (4{,}35 \pm 0{,}04) - (6{,}47 \pm 0{,}49)\sigma_I, \quad r = 0{,}991, \ s_0 = 0{,}09, \ n = 6 \qquad (1)$$

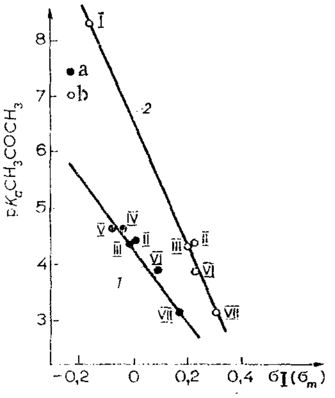


Fig. 1. Correlation of the $pK_a$ values ($CH_3COCH_3$) of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine derivatives with the polar constants of the substituents: 1) $pK_a = f(\sigma_I)$ (a); 2) $pK_a = f(\sigma_m)$ (b) (the numbers of the points correspond to the numbers of the compounds in Table 1).

In accordance with the existing concepts [4, 9], the existence of this sort of correlation dependence [the linear character of the function $pK_a = f(\sigma_I)$] for potentially tautomeric systems constitutes evidence that the tautomeric equilibrium is shifted to favor one of the forms or is totally absent.

Hence it may be concluded that the acyldithiazines that we investigated (regardless of the type of R' substituent in the acyl fragment of the molecules) exist virtually only in one tautomeric form under the experimental conditions. The PMR [10] and IR [1] spectroscopic data consistently indicate that the acyldithiazines with donor substituents exist primarily in amino form *a* in the crystalline state and in solutions. Consequently, the established possibility of the simultaneous description of the basic properties of acyldithiazines with donor (which exist in the amino form) and acceptor substituents within the framework of a single $pK_a = f(\sigma_I)$ dependence can be regarded as evidence that acyldithiazines with acceptor substituents exist in the same tautomeric form as the compounds with donor substituents, viz., in the amino form. This conclusion regarding the structure of the acyldithiazans finds confirmation in the elucidation of their protonation centers.

It is known that the protonation of amino derivatives of nitrogen-containing heteroaromatic compounds takes place at the ring nitrogen atom [11]. 2-Amino-4H,1,3-thiazines (VIII), the structure of which is similar to that of the investigated dithiazines, are also no exception to this rule. Their protonation in the fixed amino form also takes place at the endocyclic nitrogen atoms [2]. On the basis of these data it may be assumed that in the investigated series of acyldithiazines (if they exist primarily in the amino form) the protonation center is also the "pyridine" ring nitrogen atom. In this case aminodithiazine I and its acyl derivatives II-VII should constitute a single reaction series, viz., compounds of the o-substituted nitrogen-containing heterocyclic type, and in protonation should display those features of the "anomalous" ortho effect that are peculiar to nitrogen-containing heterocyclic compounds, the center of basicity in which is separated from the variable substituent by only one bond in addition to the bond between the substituent and the ring [12]. The ortho effect in the indicated compounds essentially reduces to the following principles.

1) The ortho substituent has primarily an inductive effect on the basicity of the "pyridine" nitrogen atom. The dependence of the $pK_a$ values on the structural parameters of the substituent is satisfied when these values are compared with the $\sigma_m$ ($\sigma_I$) constants.

2) The sensitivity of the center of basicity to the electronic effect of the ortho substituent is characterized by high numerical values ($\rho_m$ ranges from 10 to 12 $pK_a$ units) and is only slightly dependent on the type of heteroring. For example, the numerical values of

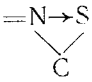
the $\rho_m$ parameter for 2-substituted pyridine ($\rho_m$ = 11.8) and 2-substituted imidazoles ($\rho_m$ = 11.1) are very close to one another [12]. The numerical value of this parameter increases somewhat on passing from water to nonaqueous media [12, 13].

Turning to the problem of the protonation center in the dithiazine molecules and taking into account the information set forth above we examined the dependence of the $pK_a$ values of these compounds (I-III, VI, and VII) on the $\sigma_m$ constants of the NHR substituents $pK_a = f(\sigma_m)$, which is represented by Eq. (2)

$$pK_{a\,CH_3COCH_3} = (6{,}56 \pm 0{,}13) - (11{,}07 \pm 0{,}59)\sigma_m,$$

$$r = 0{,}997,\ s_0 = 0{,}21,\ n = 5 \qquad (2)$$

It is apparent from the parameters of Eq. (2) and line 2 in Fig. 1 that the character of the $pK_a = f(\sigma_m)$ dependence corresponds completely to the above-indicated criteria of the ortho effect in nitrogen-containing heterocyclic compounds. Thus the basicities of the dithiazines in acetone (the same also pertains to the basic properties in methanol) are described by the $\sigma_m$ constants with high correlation quality ($r > 0.99$). The basicity of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine (I) also is subject to this dependence (calculated $pK_a$ = 8.33). Finally, the reaction constant of the investigated series of compounds ($\rho_m$ = 11.07) fits into the range of numerical values of this parameter established in the case of traditional series of 2-substituted nitrogen-containing heteroaromatic compounds. The display by dithiazines I-VII of the ortho effect peculiar to 2-substituted nitrogen-containing heterocyclic compounds constitutes unambiguous evidence that the investigated compounds upon protonation exist primarily in the amino form and that their protonation center is the "pyridine" ring nitrogen atom.

Having established the character of the intramolecular interrelationships between the center of basicity and the exocyclic substituent in the dithiazine molecules we also made an attempt to ascertain how the structure of the heteroring itself affects the basicity of the "pyridine" nitrogen atom. For this, we compared the basicities in water of 4-amino-1,3,5-dithiazine (I) ($pK_a$ = 7.00) and S-methylisothiourea (X) ($pK_a$ = 9.83) [14]. In selecting X as a model compound we were guided by the fact that 4-amino-1,3,5-dithiazine can be regarded as a cyclic derivative of S-methylisothiourea, the hydrogen atom of the imino group in which is replaced by the heteroatomic $-CH(CH_3)SCH(CH_3)-$ fragment, which closes to form a six-membered ring. A comparison of the indicated $pK_a$ values shows that the basicity of the heterocyclic derivative of S-methylisothiourea is much lower than the basicity of S-methylisothiourea ($\Delta pK_a$ = 2.83). The observed difference in the basicities of I and X is most likely associated with the fact that the cyclic thioalkyl group in I displays the electron-acceptor effect that is peculiar to it with respect to the center of basicity. One can evaluate the magnitude of this effect under the assumption that an identical orientation of the substituents (the exocyclic and heteroatomic groupings included in a ring) with respect to the reaction center (in this case ortho substitution) should cause additivity of the contributions of the effects of the indicated substituents to the electronic density of the nitrogen atom undergoing protonation. In this case using the value $\rho_m$ = 11.08 obtained above and the $\sigma_m$ = 0.15 constant of the $CH_3S$ group, which models the cyclic thioalkyl fragment of the dithiazine molecule, we obtain the contribution of the electron-acceptor effect ($\Delta' pK_a$) of the indicated fragment. The contribution of this effect to the basicity of 4-amino-1,3,5-dithiazine is $\Delta' pK_a = 11.08 \cdot 0.15 = 1.66$ $pK_a$ units. It is apparent that the $\Delta' pK_a$ values obtained does not compensate the established difference between the basicities of 4-amino-1,3,5-dithiazine and S-methylisothiourea ($\Delta pK_a$ = 2.83). This fact constitutes evidence that an additional structural effect, which we did not take into account and which plays a definite role in the formation of the basicity of dithiazine I and is responsible for its decreased basicity (by 1.17 $pK_a$ units) as compared with the hypothetical value (8.17 $pK_a$ units), is operative in dithiazine I molecules. Intramolecular electron interaction between the nitrogen and sulfur atoms in the 5 and 1 positions of the heteroring may be a structural effect of this sort in 4-amino-1,3,5-dithiazine molecules. If the incompensable difference between the $\Delta pK_a$ and $\Delta' pK_a$ values, which is 1.17 $pK_a$ units, is ascribed only to the effect of the intramolecular electron interaction in the  cyclic system, the energy of this interaction is 1.5 kcal/mole [(2.83 − 1.66)2.3RT].

## EXPERIMENTAL

The N-acyl derivatives of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine were obtained by the method in [1].

The ionization constants of I-VII were determined potentiometrically in absolute acetone and methanol by the method in [15, 16]. Codeine, the $pK_a$ of which is 9.62 in acetone [17] and 8.6 in methanol [16], was used as the standard.

## LITERATURE CITED

1. G. M. Gavrilova, É. I. Kositsyna, B. A. Trofimov, V. I. Gostevskaya, and S. V. Amosova, Khim. Geterotsikl. Soedin., No. 5, 622 (1982).
2. P. L. Ovechkin, L. A. Ignatova, and B. V. Unkovskii, Khim. Geterotsik. Soedin., No. 7, 946 (1971).
3. M. I. Kabachnik, The Chemistry and Application of Organophosphorus Compounds [in Russian], Izd. Akad. Nauk SSSR, Moscow (1957), p. 18.
4. Yu. A. Zhdanov and V. I. Minkin, Correlation Analysis in Organic Chemistry [in Russian], Izd. RGU (1966), p. 51.
5. L. N. Bykova, and S. I. Petrov, Usp. Khim., 39, 1631 (1970).
6. S. T. Ioffe, The Chemistry and Application of Organophosphorus Compounds [in Russian], Izd. Akad. Nauk SSSR, Moscow (1957), p. 76.
7. V. E. Bel'skii, Zh. Obshch. Khim., 40, 1374 (1970).
8. T. V. Kashik, B. V. Prokop'ev, A. S. Atavin, A. N. Mirskova, M. L. Al'pert, S. G. Pil'kevich, and S. M. Ponomareva, Zh. Org. Khim., 7, 1582 (1971).
9. T. A. Mastryukova, Yu. A. Sheinker, I. K. Kuznetsova, I. M. Peresleni, T. B. Sakharova, and M. I. Kabachkin, Zh. Obshch., Khim., 33, 3326, 3329 (1963).
10. V. K. Voronov, B. A. Trofimov, G. M. Gavrilova, S. V. Amosova, and V. I. Gostevskaya, Khim. Geterotsikl. Soedin., No. 4, 485 (1981).
11. G. Clark and D. D. Perren, Usp. Khim., 36, 288 (1967).
12. M. Chearton, J. Org. Chem., 30, 336 (1965).
13. M. G. Voronkov, T. V. Kashik, S. M. Ponomareva, and N. D. Abramova, Dokl. Akad. Nauk SSSR, 222, 350 (1975).
14. A. Albert, R. Goldacre, and J. Phillips, J. Chem. Soc., No. 12, 2240 (1948).
15. A. M. Shkodin and L. M. Sadovnichaya, Izv. Vyssh. Uchebn. Zaved., Ser. Khim. Khim. Tekhnol., No. 7, 4 (1964).
16. T. V. Kashik, B. V. Prokop'ev, G. V. Rassolova, and S. M. Ponomareva, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 1960 (1971).
17. N. A. Izmailov and T. V. Mozharova, Zh. Fiz. Khim., 34, 1543 (1960).