STRUCTURE OF 4,4,6-TRIMETHYL-2-ARYLAMINO-5,6-DIHYDRO-4H-1,3-THIAZINES AND -OXAZINES

E. M. Peresleni, A. P. Engoyan,
T. D. Zotova, Yu. N. Sheinker,
L. A. Ignatova, and B. V. Unkovskii

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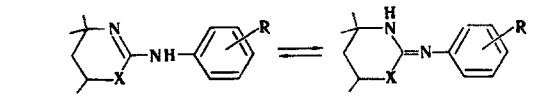
It is shown by means of IR, PMR, and UV spectra that 4,4,6-trimethyl-2-arylamino-5,6-dihydro-4H-1,3-thiazines and 4,4,6-trimethyl-2-arylamino-5,6-dihydro-4H-1,3-oxazines in the crystalline state and in solution exist primarily in the amino form. It was found that ionization to give cations proceeds more readily in the case of 1,3-oxazines than in the case of 1,3-thiazines. In addition, a decrease in the ability to undergo intermolecular association and a decrease in the energy barrier to rotation about the N-heteroring bond are observed for 1,3-oxazines.

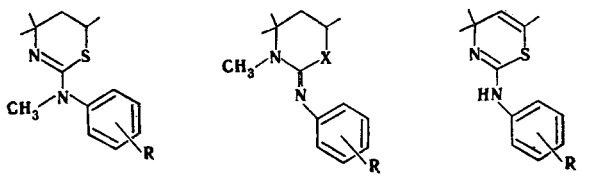
In one of our previous communications we demonstrated the amino structure of 2-phenylamino derivatives of 4,4,6-trimethyl-4H-1,3-thiazine (VII) [1].

In the present research we studied the hydrogenated analogs of these compounds — 2-phenylamine derivatives of 4,4,6-trimethyl-5,6-dihydro-4H-1,3-thiazine (I) and -oxazine (II).

The aim of the study was an examination of the effect of the degree of unsaturation of the ring and the character of the heteroatom in it on the tautomerism and physicochemical characteristics of the investigated compounds, since, as we have already reported for heterocyclic-ring unsubstituted hydrogenated compounds of this class [2], the literature contains contradictory data on their structures.



A B



III, IV V, VI VII

I, III, V X=S; II, IV, VI X=O

The structures of the investigated compounds were determined by comparison of the spectral characteristics of I and II with the corresponding data for model compounds with fixed amino (III and IV) and imino (V and VI) structures.

It follows from the data in Tables 1 and 2 that the differences in the $\nu_{C=N}$ frequencies in the IR spectra of the model compounds with fixed amino and imino structures are not very

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. M. V. Lomonosov Moscow Institute of Fine Chemical Technology, Moscow 119453.
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TABLE 1. Spectral Data for 4,4,6-Trimethyl-2-arylamino-5,6-dihydro-4H-1,3-thiazines

Compound	R	IR spectra, cm^{-1} in crystals: $\nu_{C=N}$ and $\nu_{C=C}$ of the phenyl ring	IR spectra in crystals: ν_{NH}	IR spectra in chloroform: $\nu_{C=N}$ and $\nu_{C=C}$ of the phenyl ring	IR spectra in chloroform: ν_{NH}	UV spectra in dioxane: λ_{max}, nm	UV spectra in dioxane: ε	PMR spectra in d_6-acetone, δ CH_3(4), ppm
Ia	*p*-OCH_3	1610s* 1595s	3120 m 3200 m	1580 s 1630 sh	3380 m 3420 w	265 287 sh	15900 4200	1,27 and 1,15
Ib	*p*-CH_3	1620 s 1604 m	3130 m 3210 m	1580 s 1638 sh	3380 m 3420 w	263	16820	1,25 and 1,13
Ic	*m*-CH_3	1612 s 1590 s 1574 m	3110—3140 m 3210 m	1575—1587 s 1605 sh 1640 w	3380 m 3420 w	264	15800	1,27 and 1,17
Id	H	1612 s 1582 s	3120—3130 m 3200 w	1580 s 1635 sh	3380 m 3420 w	264	15600	1,25 and 1,15
Ie	*p*-Br	1608 s 1576 m	3100—3140 m 3190—3208 m	1590 m 1572 m 1638 w	3380 m 3420 w	271	19800	1,30 and 1,17
If	*m*-Cl	1609 s 1575 s	3100—3120 m 3190—3210 w	1575 s 1595 m 1640 w		266	14800	
IIIa	*p*-OCH_3	1612 s		1590 s 1610 s		261	7100	1,25 and 1,12
IIIb	*p*-CH_3	1615 s 1595 s		1590 s 1615 sh		267	6600	1,23 and 1,07
IIIc	*m*-CH_3	1609 sh 1596 s 1583 s		1580 s 1595 s 1610 sh		269	6300	
IIId	H	1601 m 1582 s		1585 s 1605 m		270	6220	1,23 and 1,12
IIIe	*p*-Br	1597 s 1575 s		1608 s 1583 m		277	8500	1,25 and 1,12
IIIf	*m*-Cl	1610 s 1583 s		1582 s 1610 s		278	6660	
Va	*p*-OCH_3	1602 m 1555 s 1498 m		1560 sb 1502 m		246 290 s sh	13100 5800	
Vb	*p*-CH_3	1555 sb		1560 sb 1504 m		245 280 s sh	12600 6700	1,50 and 1,45
Vd	H	1570 sb		1560 sb		240 275 sh	11760 7000	1,47 and 1,40

*Abbreviations: s is strong, m is medium, w is weak, sh is shoulder, s sh is strong shoulder, vb is very broad, b is broad, and sb is strong and broad.

large. However, a lower $\nu_{C=N}$ value is observed systematically in the imino models than in the amino models during a detailed examination of the spectra. Similarly, in the PMR spectra the chemical shifts of the 4-methyl groups are somewhat higher for the imino models than for the amino models.

Closeness in the $\nu_{C=N}$ frequencies in the IR spectra of the crystalline compounds and solutions of them, in the chemical shifts of the 4-methyl groups of the heterorings in the PMR spectra of deuteroacetone solutions, and in the λ_{max} values in the UV spectra to the corresponding characteristics for amino models III and IV, in contrast to the characteristics for imino models V and VI, is observed for the investigated thiazines I and oxazines II. These data constitute evidence in favor of the primary existence of thiazines I and oxazines II in the crystalline state and in solution in amino form IA, as was previously demonstrated for VII.

In addition to the band of a free NH group (3420 cm^{-1}, a low-frequency band ($\sim$3370 cm^{-1}) corresponding to associated NH groups is retained in the IR spectra in the low-frequency region for substituted thiazines I as well as for 2-arylamino-4H-1,3-thiazines VII in dilute solution (0.02%) in CCl_4 even when the solutions are heated to 70°. In the case of the PMR

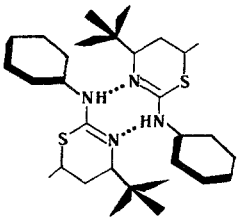
TABLE 2. Spectra Data for 4,4,6-Trimethyl-2-arylamino-5,6-dihydro-4H-1,3-oxazines

Compound	R	IR spectra, cm^{-1} in crystals: $\nu_{C=N}$ and $\nu_{C=C}$ of the phenyl ring	IR spectra, cm^{-1} in crystals: ν_{NH}	IR spectra, cm^{-1} in chloroform: $\nu_{C=N}$ and $\nu_{C=C}$ of the phenyl ring	IR spectra, cm^{-1} in chloroform: ν_{NH}	UV spectra in dioxane: λ_{max}	UV spectra in dioxane: ε	PMR spectra in d_6-acetone δ CH_3(4), ppm
IIa	*p*-OC_2H_5	1675 s 1600 w 1577 w	3070 m 3150 m 3215 w	1640 s	3400 w 3270 w	255 277 sh	18600 6600	1,18
IIb	*p*-OCH_3	1665 s 1600 w	3140 m 3200 w 3270 w	1640 s	3435 w	254 302	19900 1760	
IIc	*p*-CH_3	1663 s 1610 m	3140 br	1640 s 1608 w	3430 s	255 280 s sh	20760 2000	1,15
IId	*m*-CH_3	1660 s 1600 m 1580 w	3160 br	1645 s 1592 m	3435 m	254 280 sh	19400 2000	1,17
IIe	H	1664 s 1590 m	3150 w 3200 sh 3280 sh	1640 s 1588 m	3435 m	250 277 sh	20000 2000	1,17
IIf	*p*-Br	1670 s 1580 m	3150 m 3200 w 3280 w	1638 s 1580 m	3430 w	261	24300	1,20
IIg	*m*-Cl	1660 s 1590 m	3145 mb 3190 w	1640 s 1580 m	3425 w	256 280 sh	20000 3400	1,18
IVa	*p*-OC_2H_5	1690—1650 sb		1630 s		254 285 s sh	12800 1940	1,13
IVb	*p*-OCH_3	1630 s 1580 sh		1630 s		255 285 s sh	12680 2200	
IVc	*p*-CH_3	1640 s 1612 m		1630 s 1610 w		258 285 sh	14000 1500	1,13
IVd	*m*-CH_3	1648 sb 1590 s 1570 w				260 285 sh	13400 2000	1,13
IVe	H	1650 s 1594 s		1645 s 1595 s		259	13000	1,15
IVf	*p*-Br	1650 s 1590 w		1632 s 1587 m		268	16360	1,15
IVg	*m*-Cl	1645 s 1590 s 1570 w				264	13660	
VIa	*p*-OC_2H_5	1615 s				265 300 sh	17400 4000	1,32 and 1,29
VIb	*p*-OCH_3			1612 1575				
VIc	*p*-CH_3	1620 s 1600 s		1610 1580		265	15600	1,33 and 1,30
VId	*m*-CH_3	1628 s 1595 m 1578 w				264	14400	1,32 and 1,29
VIe	H	1615 1583				263	15200	
VIf	*p*-Br	1618 s 1575 s		1610		271	19160	
VIg	*m*-Cl	1610 s 1575 s				267	16000	1,33 and 1,30

spectra of the compounds in CS_2, $CDCl_3$, and tetrachlorethylene the signal of the NH proton at 4-5 ppm is markedly broadened, shifted to weak field (to 8.5-9.0 ppm), and converted to a narrow singlet as the temperature is lowered from 115 to −80°. A strong-field shift of the signals of the methyl group in the 4 position of the heteroring and of the ortho protons of the phenyl ring is observed over the same temperature range. Changes of this sort in the PMR spectra also occur as the concentration of I in nonpolar solvents increases.

In analogy with the previously studied thiazines VII, these data can be explained by the

formation of dimeric structures [3] due to hydrogen bonds. In these dimers the methyl groups of one molecule fall into the region of anisotropic shielding of the phenyl ring by another molecule,* and this has a substantial effect on their chemical shifts. Moreover, in contrast to VII, the chemical shifts of the signals of the two methyl groups in the 4 position of I are different and the strong-field shift of one of the signals is expressed more markedly as the temperature rises. This indicates nonequivalence of the groups due to their different spatial orientations in the half-chain form of the ring and different degrees of shielding by the benzene ring of the adjacent molecule in the dimeric structures.



Only one band of the free NH group at 3445 cm^{-1} is observed in the IR spectra of 0.02% solutions of 1,3-oxazines II in CCl_4. In the PMR spectra one does not observe a relationship between the chemical shifts of the signals of the 4-methyl groups and the ortho protons of the phenyl ring and the temperature; the signal of the NH group becomes broader as the temperature is lowered, but one does not observe a weak-field shift of the signal. These data indicate the absence of strong associates in solutions of II.

A systematic decrease in the absorption intensity and a shift of the maximum to the shorter-wave region are observed in the UV spectra on passing from dioxane to alcohol and mixtures of alcohol and water (as the water content increases) in the case of I and II as well as for 1,3-thiazine derivatives VII [1]. It follows from the pK_a data that these changes are due to ionization of the molecules to give the corresponding cations; this process occurs to a greater extent in the case of oxazines II, for which the pK_a values are 1-5 units higher, than for thiazines.

An approximate evaluation of the degree of ionization from the pK_a and pH data of solutions† of oxazines II showed that even in 90% alcohol partial ionization to give 10% of the cation occurs for oxazine IIf; the corresponding thiazine Ie is a neutral molecule under these conditions and ∿20% of the cation is contained only in a 50% aqueous alcohol solution. Azine IIe and its amino model IVe are practically completely converted to the cations (95 and 99%, respectively) in 50% aqueous alcohol, whereas the analogous thiazines Id and IIId contain 88 and 94% of the cation. All of the investigated compounds are ionized practically completely in 5% alcohol.

Conjugation between the phenyl ring and the amidine system of bonds is disrupted in N-methyl derivatives of azines III-VI because of steric hindrance arising because of the presence of a methyl group. This follows from the UV spectral data and the ionization constants in much the same way as previously observed for 2-arylamino-4H-1,3-thiazines [1]. Thus a substantial decrease in the extinction ($\Delta\varepsilon$ = 9380) is observed in N-methyl derivatives of thiazine IIId in dioxane as compared with Id, and the difference in the extinction ($\Delta\varepsilon$) for oxazine derivatives is 7000. The ionization constants also change in conformity with expectations. For the 2-phenylaminothiazine derivatives, $\Delta pK_a = pK_a^{IIId} - pK_a^{Id} = 7.79 - 6.88 = 0.91$, whereas this value decreases to 0.64 ($\Delta pK_a = pK_a^{IVe} - pK_a^{IIe} = 8.94 - 8.30$) for the corresponding oxazine IIe (all in methanol).

*For this reason, in the determination of the structures of azines I and II the comparison of the chemical shifts of the 4-methyl groups was made in a polar solvent (deuteroacetone), in which the formation of associates with the solvent hinders dimerization of the molecules.

†The percentages of the cations were found on the basis of the pK_a and pH values of the solutions (from the tables in [4]). The pK_a values were determined potentiometrically in alcohol and in 50% aqueous ethanol. The pH values of solutions of the same concentrations used for recording of the UV spectra were measured.

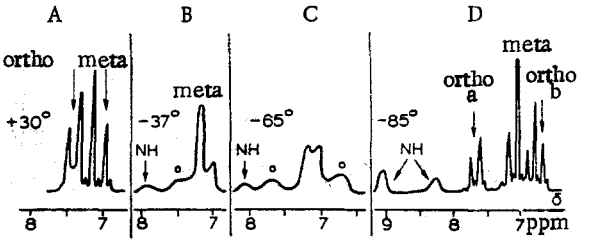


Fig. 1. Signals of the protons of the phenyl ring and the NH group in the PMR spectra of 4,4,6-trimethyl-2-tolylamino-5,6-dihydro-4H-1,3-thiazine (Ib) at various temperatures.

TABLE 3. Kinetic Parameters of Rotational Isomerism about the C–N bond in Molecules of Thiazines and Oxazines in Deuteroacetone (0.2 mole)

X	R	$\Delta\nu^*$, Hz	$K^\dagger$ (a/b)	T_c, °C	$\Delta G_{b\to a}^{\#}$, kcal/mole	$\Delta G_{a\to b}^{\#}$, kcal/mole
S	$-OCH_3$	55	0,5	−45	11,1	11,4
S	$-CH_3$	56	0,8	−37	11,4	11,6
S	−Br	57	1,1	−22	12,3	12,3
O	−OEt	57	8,0	−76	10,3	9,5
O	$-CH_3$	42	7,0	−70	10,7	9,9
O	−Br	55	5,0	−53	11,3	10,6

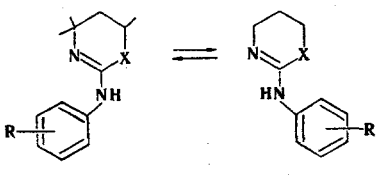
*This is the distance in Hertz between the center of the doublets of the ortho protons of the phenyl ring of rotational isomers a and b.

†The equilibrium constant of the rotational isomers was determined from the intensity of the signals of the ortho protons of each isomer at −85°C.

It should be noted that the basicities of 2-phenylaminodihydrothiazines are almost two orders of magnitude higher than for the analogous thiazine derivatives (thus pK_α of Id = 6.88, as compared with 5.1 for the analogous thiazine derivative [1]). It follows from these data that the double bond in the thiazine ring in the α position to the sulfur atom has an appreciable effect on the proton-acceptor capacity of the amidine system and that this effect is evidently transmitted through the sulfur atom.

The pattern of splitting of the signals of the protons of the phenyl ring in the PMR spectra of acetone solutions of I and II, which have para substituents in the phenyl ring, at ∿30° corresponds to the AA^1BB^1 four-spin system characteristic for p-disubstituted benzenes (Fig. 1, spectrum A). As the temperature is raised, the signal of the ortho protons of the phenyl ring broadens, passes through a coalescence stage (Fig. 1, spectrum B), and is split into two doublets with different intensities (Fig. 1, spectra C and D). The nonequivalence of the meta protons of the benzene ring shows up over the same temperature range. Thus superimposition of CC^1DD^1 and EE^1FF^1 system is observed at low temperatures (< −70°) for the phenyl protons. The signal of the NH proton also broadens as the temperature is lowered and is split into two singlets; the intensity ratio of the signals is the same as in the case of the phenyl ring ortho protons.

As in the case of 2-arylamino-4H-1,3-thiazines VII [3], the indicated dependence of the form of the spectrum on the temperature is associated with retarded rotation about the N-heteroring bond.



a b

The free energies of activation (ΔG) of this process at the coalescence temperature (T_c) were determined from the Eyring equation by the method in [5].

The data in Table 3 indicate an increase in the barrier to rotation as the electron-acceptor properties of substituents of the phenyl ring. In addition, on the basis of the literature data one should have expected a decrease $\Delta G^{\#}$ in this series of substituents. This anomalous dependence is evidently associated with the substantial effect of association of the investigated substances with the solvent molecules. The experimental value of the barrier to activation ($\Delta G^{\#}$) is equal to the sum of the characteristic barrier to a rotation about the C–N bonds ($\Delta G_C^{\#}$) and the energy of formation of hydrogen bonds with the solvent molecules (ΔG_H). When electron-acceptor substituents are introduced in the phenyl ring, in addition to a decrease in the characteristic barrier to rotation, one observes an increase in the energy of the hydrogen bonds in the associates with the solvent due to an increase in the acid character of the NH group, and in some cases the change in ΔG_H may be greater than the change in $\Delta G_C^{\#}$. It is evidently precisely this that may explain the increase in the experimental value of the activation barrier on passing to compounds with electron-acceptor substituents in the phenyl ring.

No changes in the character of the spectrum as the temperature changes are observed in the case of III and IV. This indicates the very low barrier to rotation in the amino models and confirms our assumption that the effect of association with the solvent is the determining factor during changes of the barriers to rotation about the C–N bond.

An examination of the data obtained in this study shows that replacement of the sulfur atom in the ring by an oxygen atom leads to a number of differences in the physicochemical properties of the investigated compounds. Thus an increase in the $\nu_{C=N}$ and ν_{NH} frequencies in the IR spectra, the extinctions of the absorption maxima in the UV spectra, and the ionization constants is observed on passing from 1,3-thiazines I to the corresponding 1,3-oxazines II.

In addition, in the case of the oxazines, as compared with the thiazines, there is a decrease in the capacity for intermolecular association, a reduction in the energy barriers to rotation, and, in the case of the N-methyl derivatives, weakening of the steric effect of the N-methyl group.

The observed differences are evidently associated with the difference in the electronegativities and effective volumes of the oxygen and sulfur atoms and with the presence in the latter of vacant d orbitals. However, it is not yet possible to clearly delimit the effect of each of these factors.

Moreover, replacement of the sulfur atom by an oxygen atom did not lead to an appreciable change in the tautomeric properties of the investigated compounds, since both the 1,3-thiazines and the 1,3-oxazines exist in the amino form.

EXPERIMENTAL

The synthesis of the investigated compounds is described in [6-8].

The IR spectra of mineral oil pastes and solutions ($CHCl_3$, CCl_4, and dioxane) of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The UV spectra of solutions of the compounds were recorded with an EPS-3 spectrophotometer. The PMR spectra of $(CD_3)_2CO$, CS_2, $CDCl_3$, and tetrachloroethylene solutions of the compounds were recorded with a JNM-C-60GL spectrometer. The chemical shifts were measured on the δ scale with tetramethylsilane as the internal standard.

The dioxane, $CHCl_3$, and CS_2 were specially purified by known methods [9]. Commercial chemically pure-grade CCl_4, $(CD_3)_2CO$, and $CDCl_3$ were used. The purity of the solvents was monitored from their spectra.

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REARRANGEMENT OF THE SEMIDINE TYPE IN THE INDOLE SERIES. SYNTHESIS OF 2-ARYLAMINO-3-ACETAMIDOINDOLES

G. N. Kurilo, N. I. Rostova, A. A. Cherkasova, and A. N. Grinev

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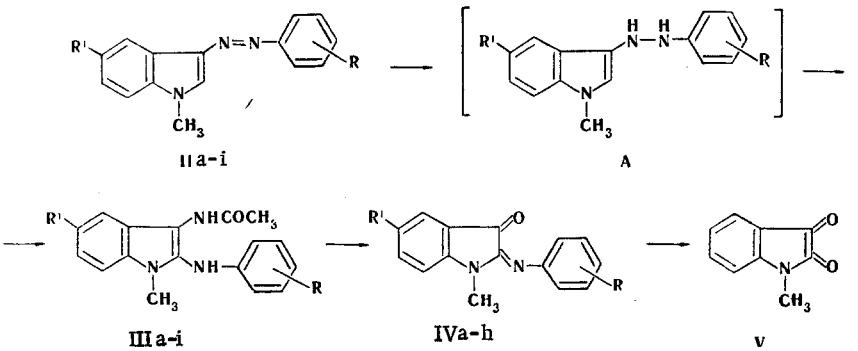
A previously unknown (in the indole series) rearrangement of the semidine type leading leading to the formation of 1-methyl-2-arylamino-3-acetamidoindoles, the oxidation of which gives 1-methylisatin α-anils, occurs when 1-methyl-3-arylazoindoles are treated with zinc in acetic acid in the presence of acetic anhydride and sodium acetate. Data from the UV, IR, and PMR spectra are presented.

We have found that 3-arylazoindoles (I) without a substituent attached to the nitrogen atom of the indole ring form indolo[1,2-c]quinazolines when they are reduced with zinc in acetic acid in the presence of acetic anhydride and sodium acetate [1]. The intermediates in this reaction are hydrazo derivatives, which undergo a rearrangement of the benzidine type during the reaction. In the present research we have established that compounds III, with a methyl group attached to the nitrogen atom of the indole ring of the 3-arylazoindoles, evidently also initially form hydrazo derivatives A; however, this is followed by a previously unknown (in the indole series) rearrangement of the semidine type to give 1-methyl-2-arylamino-3-acetamidoindoles (IIIa-i). The structures of IIIa-i were proved by their IR, UV, and PMR spectra and by oxidation to 1-methylisatin α-anils (IVa-h), of which IVa is identical to the known 1-methylisatin α-anil [2]. In addition, IVa was converted to the known 1-methylisatin (V) [3] by acid hydrolysis.

Rearrangements of the benzidine and semidine type have been previously observed in the case of the action of zinc in acetic acid on arylazo derivatives of imidazole [4].



IIa-i A IIIa-i IVa-h V

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