SYNTHESIS OF SUBSTITUTED 2-AMINO-5,6-DIHYDRO-4H-1,3-OXAZINES

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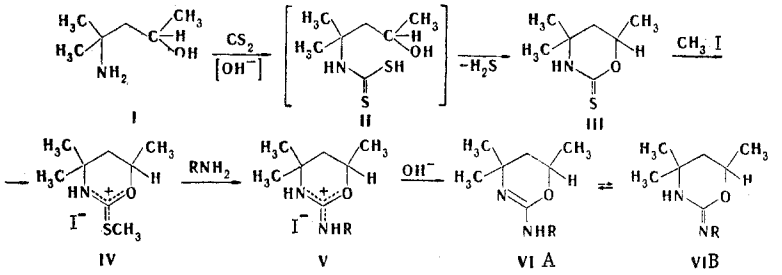
4,4,6-Trimethyl-2-alkyl(aryl)amino-5,6-dihydro-4H-1,3-oxazines were synthesized via two methods: amination of 4,4,6-trimethyl-2-methylthio-5,6-dihydro-4H-1,3-oxazine and cyclization of N-aryl-N'-(2-methyl-4-hydroxy-2-amyl)-S-methylisothiourea.

Within our plan to investigate the structures, tautomerism, reactivities, and pharmacological activity of N-heterocyclic amines [1,2], we turned to a study of 2-amino-5,6-dihydro-4H-1,3-oxazines. The literature contains only scanty information regarding individual representatives of this class of compounds [3-7], but as yet there has been no systematic investigation of the structures and reactivities of these compounds. In the present paper we describe the synthesis of 4,4,6-trimethyl-2-alkyl(aryl)amino-5,6-dihydro-4H-1,3-oxazines (VI), which we accomplished by two methods.



In the first method (method A), 2-amino-2-methyl-4-pentanol (I) on reaction with carbon disulfide in alkaline media is converted through the unstable N-(2-methyl-4-hydroxy-2-amyl)dithiocarbamic acid (II), which is in equilibrium with its sodium salt, to 4,4,6-trimethyl-5,6-dihydro-4H-1,3-oxazine-2-thione (III), the methylation of which in acetone gives 4,4,6-trimethyl-2-methylthio-5,6-dihydro-4H-1,3-oxazine hydriodide (IV). Aminolysis of IV with aliphatic and aromatic amines in methanol at 25°C gave 4,4,6-trimethyl-2-alkyl(aryl)amino-5,6-dihydro-4H-1,3-oxazine hydriodides (V) in 80-85% yields. Free bases VI (Table 1) were isolated from the corresponding hydriodides by the action of aqueous potassium carbonate or alkali.

In the second method (method B), I on reaction with p- and m-substituted aryl isothiocyanates is initially converted to N-aryl-N'-(2-methyl-4-hydroxy-2-amyl)thioureas (VII, Table 2).

Methylation of VII in acetone gives hydriodides of the corresponding S-methylisothioureas (VIII), which are readily cyclized by the action of alcoholic potassium hydroxide with splitting out of methyl mercaptan and conversion to aminooxazines (VI). The conversion of VIII to VI also occurs on heating aqueous or alcohol solutions of VIII in the absence of alkali, but the reaction proceeds at a lower rate in this case.

Cyclization also occurs successfully in one step by methylation of VII in alkaline media. It is precisely in this way, without isolation of the intermediately formed S-methyl derivatives (VIII), that we obtained most of the VI synthesized by method B. However, the formation of S-methylisothioureas in this one-

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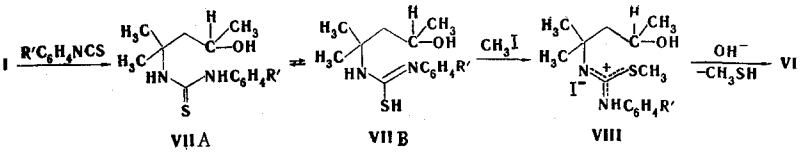

VIIA VIIB VIII

step process is clearly recorded by means of thin-layer chromatography (TLC) on aluminum oxide. An advantage of method B over method A is the exclusion of carbon disulfide, the simplicity of the preparative design of the process, the practically complete absence of side reactions, and the high degree of conversion of VIII, which makes it possible to obtain aminooxazines VI in yields up to 93%.

The cyclization ov VIII to VI apparently occurs via intramolecular nucleophilic attack of the carbon atom bonded to the heteroatoms by the oxygen of the OH group. This is promoted by acid catalysis, which is conducive to detachment of a proton from the hydroxyl group of VIII. We have repudiated the assumption of the possibility of nucleophilic substitution of the methylthio group by OH^- ions in the reaction medium to form N-aryl-N'-(2-methyl-4-hydroxy-2-amyl)ureas (IX) with subsequent cyclization of IX to VI with splitting out of water, since a genuine sample of IXa (aryl = phenyl) does not cyclize under these conditions, and the presence of IXa was not detected in the reaction mixture during the conversion of VIIIa to VIa.

We also demonstrated that aminooxazines VI are not formed from thioureas VII without prior methylation of them, although one might have assumed an analogous reaction for the thiol form (VIIB) with hydrogen sulfide evolution. This is apparently associated with the small percentage of the thiol form in the tautomeric mixture (VIIA ⇌ VIIB), which is characteristic for compounds with a thioamide group [8-10] and is confirmed in our case by the IR spectra of VII in the crystalline state and in solutions. The absorption bands characteristic for the thiol form (VIIB) at 2500-2600 cm^{-1}, which are affiliated with the stretching vibrations of the SH group, and the bands at 1600-1670 cm^{-1}, which correspond to the stretching vibrations of the C=N bond, are absent in the IR spectra of VII. In addition, intense bands at 1530-1560 cm^{-1}, which are characteristic for the thioamide group [11, 12], are observed in the IR specra of VII.

The aminooxazines (VI, Table 1) are crystalline substances that are stable on storage, are resistant to alkaline hydrolysis, and are titrated by perchloric acid in methanol as bases with pK_a 7.3-8.8. The IR spectra of VI in the crystalline state contain a band at 1660-1680 cm^{-1}, which is related to the stretching vibrations of the C=N bond, bands at 1500 and 1600 cm^{-1}, which characterize the stretching vibrations of the aromatic ring, and a band at 3150-3250 cm^{-1}, which is affiliated with the stretching vibrations of the NH group tied up in intermolecular hydrogen bonds. Intense absorption at 250-260 nm (log ε 4.35) is observed in the UV spectra of VI.

The amine–imine tautomerism (VIA ⇌ VIB) possible for this class of compounds will be discussed in a separate communication.

TABLE 1. 4,4,6-Trimethyl-2-alkyl(aryl)amino-5,6-dihydro-4H-1,3-oxazines (VI) and Their Hydriodides (V)

Compound	R	mp, °C (from hexane)	Empirical formula	Found, %			Calc., %			Yield, %	Hydriodides of VI (V)*	
				C	H	N	C	H	N		mp, °C (iso-PrOH)	yield, %
VIa	C_6H_5	98,5—99	$C_{13}H_{18}N_2O$	71,4	8,2	12,9	71,5	8,3	12,8	93	182—183	80
VIb	p-$C_6H_4OCH_3$	111—112	$C_{14}H_{20}N_2O_2$	67,8	7,9	11,5	67,7	8,1	11,3	92	141—142	83
VIc	m-$C_6H_4CH_3$	85—86	$C_{14}H_{20}N_2O$	72,2	8,6	12,2	72,4	8,7	12,1	85	105—106	84
VId	p-$C_6H_4CH_3$	92—92,5	$C_{14}H_{20}N_2O$	72,3	8,8	12,1	72,4	8,7	12,1	91	205—206	86
VIe	p-$C_6H_4OC_2H_5$	124—125	$C_{15}H_{22}N_2O_2$	68,8	8,5	10,7	68,7	8,5	10,7	92	—	—
VIg	m-C_6H_4Cl	111,5—112,5	$C_{13}H_{17}ClN_2O$	—	14,6	11,1	—	14,0	11,1	91	113—114	85
VIf	p-C_6H_4Br	153—154,5	$C_{13}H_{17}BrN_2O$	52,7	5,5	58,9	52,5	5,8	9,4	90	—	—
VIh	CH_3	55—56	$C_8H_{16}N_2O$	61,4	10,2	17,8	61,5	10,3	17,9	70	161,5—162	90

*The compositions of V (VI · HI) were confirmed by determination of the I and N content and, for Vb, d, and h, the C and H content.

TABLE 2. N-Aryl-N'-(2-methyl-4-hydroxy-2-amyl)thioureas (VIIa-g)

Comp.	R	mp, °C (from alcohol)	Empirical formula	Found, %		Calc., %		Yield, %
				N	S	N	S	
VII[a]	H	151—152	$C_{13}H_{20}N_2OS$	11,0	12,9	11,1	12,7	99
VII[b]	*p*-OCH_3	135,5—136	$C_{14}H_{22}N_2O_2S$	9,8	11,2	9,9	11,4	98
VII[c]	*m*-CH_3	116—116,5	$C_{14}H_{22}N_2OS$	10,0	11,9	10,5	12,0	87
VII[d]	*p*-CH_3	141,5—142,5	$C_{14}H_{22}N_2OS$	10,5	12,2	10,5	12,0	95
VII[e]	*p*-OC_2H_5	122—123	$C_{15}H_{24}N_2O_2S$	9,3	10,7	9,4	10,8	97
VII g	*m*-Cl	106,5—107	$C_{13}H_{19}ClN_2OS$	10,5	12,4	9,8	12,4	82

EXPERIMENTAL

The IR spectra of mineral oil suspensions and $1 \cdot 10^{-2}$ M solutions in chloroform were recorded with a UR-10 spectrometer. The UV spectra of $5 \cdot 10^{-5}$ M alcohol solutions were recorded with a Hitachi spectrophotometer.

4,4,6-Trimethyl-2-methylthio-5,6-dihydro-4H-1,3-oxazine Hydriodide (IV). A 3.2-g (23 mmole) sample of methyl iodide was added at 25° to 3.0 g (21 mmole) of III [13] in 25 ml of acetone. The precipitate that formed after 2 h was removed by filtration and dried to give 5.7 g (95%) of IV with mp 150-150.5° (from isopropyl alcohol). Found: N 4.5; S 10.7%. $C_8H_{14}NOS \cdot HI$. Calculated: N 4.6; S 10.7%.

4,4,6-Trimethyl-2-ethylamino-5,6-dihydro-4H-1,3-oxazine Hydriodide (VII). A 1.5-g (33 mmole) sample of ethylamine in the form of a 40% aqueous solution was added to a solution of 5.0 g (17 mmole) of IV in 15 ml of methanol, and the mixture was allowed to stand at 20° for 12 h. The methanol was removed by distillation to give 4.5 g (90%) of VII with mp 158-159° (from isopropyl alcohol). Found: N 9.3; I 43.8%. $C_9H_{18}N_2O \cdot HI$. Calculated: N 9.4; I 42.6%.

A similar method was used to obtain Va-Vd, Vh (Table 1).

4,4,6-Trimethyl-2-(m-chlorophenylamino)-5,6-dihydro-4H-1,3-oxazine Hydriodide (Vg). A 0.87-g (6.8 mmole) sample of m-chloroaniline was added to a solution of 1 g (3.4 mmole) of IV in 10 ml of ethanol, and the mixture was heated at 55-60° for 40 h. The alcohol was removed by distillation, and the residue was reprecipitated twice from isopropyl alcohol by the addition of dry ether to give 1.08 g of Vg.

N-Phenyl-N'-(2-methyl-4-hydroxy-2-amyl)thiourea (VIIa). A 3.5-g (26 mmole) sample of phenyl isothiocyanate was added at 0° to a solution of 3.0 g (26 mmole) of I [14] in 30 ml of absolute ether. The precipitate that formed after 2 h was removed by filtration and dried to give 6.5 g of VIIa, which was recrystallized from alcohol.

A similar method was used to obtain VIIb and VIIg (Table 2).

N-Phenyl-N'-(2-methyl-4-hydroxy-2-amyl)-S'-methylisothiourea Hydriodide (VIIIa). A 0.62-g (4 mmole) sample of methyl iodide was added to a solution of 1 g (4 mmole) of VIIa in 25 ml of acetone, and the mixture was allowed to stand at 20° for 2 h. Ether (20 ml) was added, and the precipitate was removed by filtration and reprecipitated three times from methanol by the addition of dry ether to give 1.4 g (90%) of VIIIa with mp 133.5-134°. Found: C 42.6; H 5.9%. $C_{14}H_{22}N_2OS \cdot HI$. Calculated: C 42.4; H 5.9%.

4,4,6-Trimethyl-2-phenylamino-5,6-dihydro-4H-1,3-oxazine (VIa). A. A 2-g (0.058 mole) sample of Va was dissolved in 25 ml of water, and the solution was neutralized with saturated potassium carbonate solution. The organic portion was extracted with ether, and the ether extract was dried with magnesium sulfate. The ether was removed by distillation to give 1.1 g of VIa, which was recrystallized from hexane.

B. a) A solution of 6.3 g (16 mmole) of VIIIa in 100 ml of water was heated at 90-95° for 30 min. The solution was cooled to 20° and neutralized with potassium carbonate. The resulting crystals were removed by filtration to give 3.2 g of VIa, which was recrystallized from hexane.

b) A 5.5-g (22 mmole) sample of VIIa was dissolved in 50 ml of 3 N potassium hydroxide solution in methanol, 6.2 g (0.044 mole) of methyl iodide was added, and the mixture was allowed to stand at 20° for 8 h. The methanol was removed by distillation, and the residue was extracted repeatedly with boiling hexane. The hexane was removed by distillation to give 4.4 g of VIa, which was recrystallized from hexane.

A similar method was used to obtain VIb-VIg.

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