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

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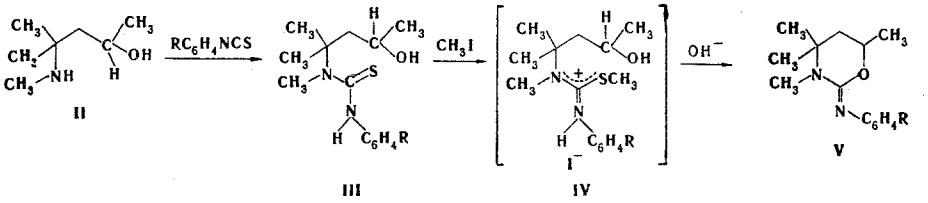
3,4,4,6-Tetramethyl-2-aryliminotetrahydro-1,3-oxazines were synthesized by intramolecular cyclization of N-aryl-N'-methyl-N'-(2-methyl-4-hydroxy-2-pentyl)-S-methylisothioureas. 4,4,6-Trimethyl-2-(N-methyl-N-arylamino)-5,6-dihydro-4H-1,3-oxazines were obtained by methylation of 4,4,6-trimethyl-2-arylamino-5,6-dihydro-4H-1,3-oxazines.

In our preceding communication [1] we described the synthesis of 4,4,6-trimethyl-2-alkyl(aryl)amino-5,6-dihydro-4H-1,3-oxazines (I) that are capable of existing in two tautomeric forms – amino form IA and imino form IB. In order to study the amino form–imino form tautomerism IA ⇌ IB, we synthesized model oxazines that have fixed imino and amino structures.

We synthesized the imino-form models – 3,4,4,6-tetramethyl-2-aryliminotetrahydro-1,3-oxazines (V) – from 2-methylamino-2-methyl-4-pentanol (II). N-Aryl-N'-methyl-N'-(2-methyl-4-hydroxy-2-pentyl)-



II III IV V

thioureas (III) were obtained by the reaction of amino alcohol II with substituted aryl isothiocyanates in ether. In contrast to N-aryl-N'-(2-methyl-4-hydroxy-2-pentyl)thioureas [1], III are unstable and decompose even during their preparation and also on storage and recrystallization to give aryl isothiocyanates, amino alcohol II, and other decomposition products. The reason for the lability of thioureas III is apparently the steric interaction of the methyl groups attached to the nitrogen atom and the α-carbon atom, inasmuch as N-phenyl-N,N'-dimethylthiourea, which is a simple model of thioureas III and which we obtained under similar conditions in 40% yield, has high stability on prolonged storage and heating in various solvents at 50-80°C.

TABLE 1. 3,4,4,6-Tetramethyl-2-aryliminotetrahydro-1,3-oxazines (Va-f)

Compound	R	mp, °C (from hexane)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
Va	*p*-OC_2H_5	79,5—80	$C_{16}H_{24}N_2O_2$	69,5	8,7	10,0	69,5	8,7	10,1	68
Vb	*p*-CH_3	99,5—100	$C_{15}H_{22}N_2O$	73,5	8,8	11,4	73,1	9,0	11,4	72
Vc	*m*-CH_3	41—42	$C_{15}H_{22}N_2O$	73,2	8,7	11,7	73,1	9,0	11,4	61
Vd	H	59,5—60	$C_{14}H_{20}N_2O$	72,2	8,6	12,4	72,4	8,7	12,1	73
Ve	*p*-Br	67—68	$C_{14}H_{19}BrN_2O$	54,0	5,9	9,0	54,0	6,1	9,0	65
Ve	*m*-Cl	78—79	$C_{14}H_{19}ClN_2O$	62,8	7,3	10,0	63,0	7,2	10,5	70

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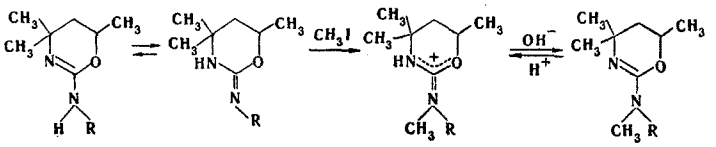
TABLE 2. 4,4,6-Trimethyl-2-(N-methyl-N-arylamino)-5,6-dihydro-4H-1,3-oxazines (VIIa-g)

Compound	R	mp, °C (from hexane)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
VIIa	*p*-OCH_3	47—47,5	$C_{15}H_{22}N_2O_2$	68,6	8,4	11,0	68,7	8,4	10,7	91
VIIb	*p*-OC_2H_5	56,5—57	$C_{16}H_{24}N_2O_2$	69,4	8,6	10,3	69,5	8,7	10,1	94
VIIc	*p*-CH_3	65,5—66	$C_{15}H_{22}N_2O$	73,8	9,0	11,5	73,1	9,0	11,4	90
VIId	*m*-CH_3	27—28	$C_{15}H_{22}N_2O$	73,3	8,8	12,0	73,1	9,0	11,4	85
VIIe	H	43—43,5	$C_{14}H_{20}N_2O$	72,1	8,7	12,5	72,4	8,7	12,1	96
VIIf	*p*-Br	61,5—62	$C_{14}H_{19}BrN_2O$	53,9	6,3	9,0	54,0	6,1	9,0	87
VIIg	*m*-Cl	163,5—165*	$C_{14}H_{19}ClN_2O$	62,7	7,2	10,6	63,0	7,2	10,5	82

*This is the melting point (with decomposition) of the hydriodide.

Thioureas III were methylated with excess methyl iodide immediately after isolation from the reaction mixtures. Methylation in acetone or alcohol is accompanied by profound destruction of the starting III and the methylation products. The resulting S-methyl-N-aryl-N'-methyl-N'-(2-methyl-4-hydroxy-2-pentyl)-isothiourea hydriodides (IV) are also extremely labile, and their subsequent transformations were therefore accomplished without isolation and purification; IV are cyclized, with the liberation of methyl mercaptan, to iminooxazines V (Table 1) on reaction with 3 N alcoholic alkali solution.

We synthesized 4,4,6-trimethyl-2-(N-methyl-N-arylamino)-5,6-dihydro-4H-1,3-oxazines (VII), which have a fixed amino structure, by methylation of the corresponding oxazines (I) with methyl iodide in acetone.



IA IB VI VII

The presence of two nucleophilic reaction centers – the endocyclic and exocyclic nitrogen atoms – in I presupposes the possibility of methylation via two directions; this is confirmed by the literature data on the alkylation of heterocyclic systems that contain an amidine fragment. Thus, it is known that 2-aminoquinazolines [2], 2-aminobenzothiazoles [3, 4], and 2-aminothiazolines [5] are alkylated at the ring nitrogen atom. The alkylation of 2-acylamino-1,3,4-oxadiazoles [6] and 2-arylamino-imidazolines [7] proceeds at the exocyclic nitrogen atom. There is no doubt that the direction of alkylation depends on the character of the alkylating agent, the nature of the heterocycle, etc.

We have shown that methylation of aminooxazines IA ⇌ IB proceeds at the exocyclic nitrogen atom to give 4,4,6-trimethyl-2-(N-methyl-N-arylamino)-5,6-dihydro-4H-1,3-oxazine hydriodides (VI) in almost quantitative yields. Salts VI are converted to the corresponding bases on treatment with aqueous potassium carbonate solutions (Table 2). A proof of the methylation of I at the exocyclic nitrogen atom is the difference in the physicochemical characteristics of VII and IV, the structures of which are determined unambiguously by the methods used for their synthesis.

Bands at 1610-1625 cm^{-1}, which are related to the stretching vibrations of the exocyclic C=N bond, are observed in the IR spectra of the crystalline iminooxazines V. The $\nu_{C=N}$ ring bands are observed at 1645-1650 cm^{-1} in the IR spectra of amino forms VII. Substantial differences are also observed in the PMR spectra of V and VII. The spectral characteristics of the synthesized model compounds will be examined in detail in a discussion of the amino-imino tautomerism of aminooxazinones I.

EXPERIMENTAL

N-Phenyl-N'-methyl-N'-(2-methyl-4-hydroxy-2-pentyl)thiourea (IIId, R = H). A 3.1 g (0.023 mole) sample of phenyl isothiocyanate was added to a solution of 3.0 g (0.023 mole) of amino alcohol II in 10 ml of dry ether. The precipitate that formed after 2 h was removed by filtration to give 5.3 g (87%) of thiourea IIId with mp 78-79°. Found: N 10.5; S 12.0%. $C_{14}H_{22}N_2OS$. Calculated: N 10.5; S 12.1%. A similar method was used to obtain IIIa-c, e, f, which were converted to iminooxazines V without additional purification.

3,4,4,6-Tetramethyl-2-phenyliminotetrahydro-1,3-oxazine (Vd). A solution of 5.0 g (0.019 mole) of thiourea IIId in 10 ml of methyl iodide was allowed to stand at 20° for 2-3 h. The excess methyl iodide was

then removed by distillation, and the residual IVd was treated with 30 ml of a 3 N solution of KOH in methanol at 20°. After 4 h, the methanol was removed by distillation, and the residue was extracted with boiling hexane; the hexane was removed by distillation to give 2.9 g of iminooxazine Vd. Compounds Va-c, e, f (Table 1) were obtained by a similar method.

4,4,6-Trimethyl-2-(N-methylanilino)-5,6-dihydro-4H-1,3-oxazine (VIIe). A 3.9 g (0.028 mole) sample of methyl iodide was added to 3.2 g (0.014 mole) of 4,4,6-trimethyl-2-anilino-5,6-dihydro-4H-1,3-oxazine (Ie) in 10 ml of acetone, and the mixture was allowed to stand at 20° for 30 h. Absolute ether (20 ml) was added, and the precipitated crystals were removed by filtration and dried to give 4.9 g (96%) of VIe. The product was dissolved in 50 ml of water, and the solution was neutralized with a saturated potassium carbonate solution. The organic portion was extracted with ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation, and the residue was chromatographed on aluminum oxide [ether–hexane (1:1)]. The eluent was removed by distillation to give 3.0 g of aminooxazine VIIe. A similar method was used to obtain VIIa-d, f (Table 2).

LITERATURE CITED

1. L. A. Ignatova, P. L. Ovechkin, M. Z. Branzburg, A. E. Gekhman, and B. V. Unkovskii, Khim. Geterotsikl. Soedin., 1037 (1972).
2. D. Brown and B. England, Austral. J. Chem., 21, 2813 (1968).
3. M. Conte, R. Guglielmetti, and J. Metzger, Bull. Soc. Chim. France, 2834 (1967).
4. N. P. Grin', A. N. Krasovskii, and P. M. Kochergin, Khim. Geterotsikl. Soedin., 1271 (1972).
5. E. M. Peresleni, Yu. N. Sheinker, N. P. Zosimova, and Yu. I. Pomerantsev, Zh. Fiz. Khim., 37, 2713 (1963).
6. G. Heinz and M. Just, Ann., 703, 136 (1967).
7. H. Shahle and K. Pook, Ann., 751, 159 (1971).