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

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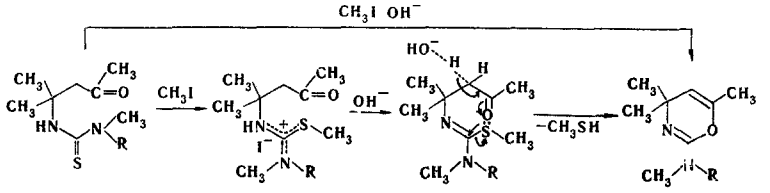
4,4,6-Trimethyl-2-methylarylamino-4H-1,3-oxazines were synthesized by intramolecular cyclization of N-oxoalkyl-S-methylisothioureas.

The synthesis of a number of 2-alkyl(aryl)-4H-1,3-oxazines by reaction of β-halo ketones with nitriles in the presence of Lewis acids has been described [1, 2], but 1,3-oxazines with functional groups attached to the C_2 atom were unknown up until now [3].

We undertook the synthesis of 4,4,6-trimethyl-2-amino-4H-1,3-oxazines (IVa-f), which are oxygen analogs of 2-amino-4H-1,3-thiazines [4], from N-methyl-N-aryl-N'-(2-methyl-4-oxo-2-amyl)thioureas (Ia-e), which were converted to N-methyl-N-aryl-N'-(2-methyl-4-oxo-2-amyl)-S-methylisothiourea hydriodides (IIa-e). The latter are cyclized on treatment with alkali to aminooxazines IVa-e with methyl mercaptan evolution. The method is similar to the method previously proposed for the synthesis of 2-amino-5,6-dihydro-4H-1,3-oxazines [5].

Aminooxazine IVf was similarly obtained from N,N-dimethyl-N'-(2-methyl-4-oxo-2-amyl)thiourea (If). Compounds IVa-f can also be obtained in one step by methylation of Ia-f with methyl iodide in an alcohol solution of potassium hydroxide. We also obtained IVf by cyclization of thiourea If in refluxing benzene in the presence of red mercuric oxide. The first method was more convenient from a preparative point of view.



I II III IV

I—IVa R=*p*-$CH_3OC_6H_4$; b R=*m*-$CH_3OC_6H_4$; c R=*p*-$CH_3C_6H_4$; d R=*m*-$CH_3C_6H_4$; e R=C_6H_5; f R=CH_3

The cyclization of II apparently proceeds through the enol form of bases III or, which is more probable, via a push–pull mechanism with synchronous cyclic transfer of the pair of electrons along the system of H–CH–C=O bonds, preceded by stripping of a proton from the C_α atom in the oxoalkyl portion of the molecule, which occurs in alkaline media. A consequence of this is an increase in the electron density on the oxygen atom, and this terminates with intramolecular nucleophilic attack of the carbon atom of the amidine fragment of the molecule.

In an attempt to synthesize 3,4,4,6-tetramethyl-2-phenylimino-2,3-dihydro-4H-1,3-oxazine (VI) via a similar path from N-phenyl-N'-methyl-N'-(2-methyl-4-oxo-2-amyl)-S-methylisothiourea (V), we isolated N-methyl-N'-phenyl-O-ethylisourea (in yields greater than 80%), which is formed as a result of destruction of the molecule at the N'–C bond and nucleophilic substitution of the methylthio group by an ethoxy group in the starting V or in the initially formed N-methyl-N'-phenyl-S-methylisothiourea (VII), instead

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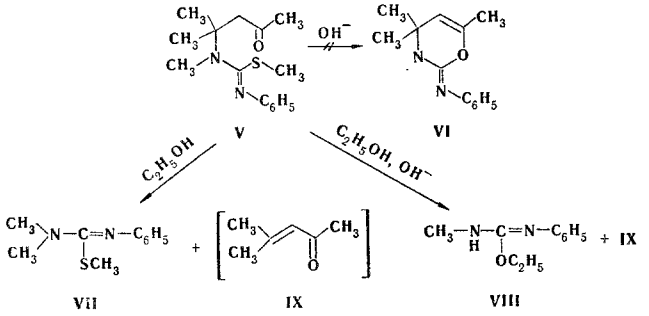
TABLE 1. Substituted 2-Amino-4H-1,3-oxazines (IVa-f) and Their Picrates

Compound	R	n_D^{20}	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H	IR spectra $\nu_{C=C}$, cm^{-1}	IR spectra $\nu_{C=N}$, cm^{-1}	UV spectra, λ_{max}, nm, log ε	Yield, %	mp of picrates IV, °C (from alcohol)*
a	*p*-CH_3O—C_6H_4	1,5381	$C_{15}H_{20}N_2O_2$	68,6	7,7	69,2	7,7	1712	1665	247 (4,02)	40	182—182,5
b	—$CH_3OC_6H_4$	1,5418	$C_{15}H_{20}N_2O_2$	69,7	7,7	69,2	7,7	1715	1659	254 (4,01)	62	141—141,5
c	*p*-CH_3—C_6H_4	1,5338	$C_{15}H_{20}N_2O$	74,0	8,1	73,8	8,2	1720	1660	252 (4,03)	36	176—177
d	—CH_3—C_6H_4	1,5405	$C_{15}H_{20}N_2O$	74,0	8,3	73,8	8,2	1718	1658	251 (4,01)	60	158—158,5
e	C_6H_5	1,5374	$C_{14}H_{18}N_2O$	72,6	7,8	73,0	7,9	1720	1665	253 (4,02)	55	133—133,5
f	CH_3	1,4688	$C_9H_{16}N_2O$	64,5	9,6	64,3	9,6	1720	1665	205 (4,08)	60	134—135

*The composition of the picrates was confirmed by determination of the percentage of C, H, and N.

of the expected VI. Thus when a CH_3 group is attached to the N' nitrogen atom, the rate of cleavage of the molecule apparently exceeds the rate of cyclization of V to VI; this may be associated with both the unfavorable configuration of imino structure V as compared with II (as a consequence of steric interaction of the methyl groups attached to the N' atom and the adjacent carbon atom) and with the different electronic states of the N' nitrogen atom in III and V. As a consequence of p—π interaction of the electrons of the C=N bond and the N' nitrogen, the latter acquires excess positive charge, and this promotes cleavage of the N'—C bond.

The tendency for the V molecule to undergo cleavage is so great that S-methylisothiourea VII is formed even on brief heating in alcohol.



Compounds IV, VII, and VIII were isolated and identified by means of their IR and PMR spectra; VII was also identified by comparison with a sample of known structure.

The IR spectra of aminooxazines IVa-f contain the absorption band of the stretching vibrations of the C=N bond at 1658-1665 cm^{-1}; a similar band is also present in the spectra of 2-methylarylamino-5,6-dihydro-4H-1,3-oxazines [5]. In addition, the $\nu_{C=C}$ ring band is observed at 1712-1720 cm^{-1}; the unusually high frequency for this band is apparently associated with the peculiarities of the interaction of the ring oxygen atom of IV with the π electrons of the C=C bond and the C=N bond of the amidine system. Thus, for example, anomalously high $\nu_{C=C}$ values were noted in the IR spectra of vinyl fluorides [6], pyrimidine-2-thiones [7], oxazolines [8], and 2-alkyl(aryl)-4H-1,3-oxazine salts [9], in which the electrons of the heteroatom in the α position relative to the C=C bond interact effectively with the C=O, C=S, or H—$\overset{+}{N}$=C groups mesomerically, as a consequence of which the −I effect of the heteroatom with respect to the C=C bond increases. Similar reasons apparently explain the $\nu_{C=C}$ frequency in the spectra of IVa-f.

The signal of six protons of geminal methyl groups (1.05-1.13 ppm), a broadened singlet of the protons of a CH_3 group attached to a C=C bond (1.60-1.72), a weak resolved quartet of an H—C= proton (4.54-4.58), a singlet of CH_3—N protons (3.08-3.10), and a multiplet of aromatic protons (6.70-6.90) are observed in the PMR spectra of IVa-f.

EXPERIMENTAL

The IR spectra of thin layers of the compounds were recorded with a UR-10 spectrometer. The UV spectra of ethanol solutions of the substances ($1 \cdot 10^{-5}$–$5 \cdot 10^{-5}$ M) were recorded with a Hitachi spectrophotometer. The PMR spectra were measured with an RS-60 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard.

N-Methyl-N-phenyl-N'-(2-methyl-4-oxo-2-amyl)-S-methylisothiourea Hydriodide (IIe). A mixture of 2.2 g (8.0 mmole) of Ie [4] and 1.3 g (9.0 mmole) of methyl iodide was allowed to stand at 25° for 10 h. The acetone was vacuum evaporated to give 3.2 g (96%) of IIe with mp 121.5–122.5° (purified by reprecipitation from methanol solution by the addition of ether). Found: N 6.7; S 8.1; I 31.5%. $C_{15}H_{23}N_2OS \cdot HI$. Calculated: N 6.9; S 7.9; I 31.5%. A similar procedure was used to obtain IIa-d, f, which were converted to IVa-d, f without additional purification.

4,4,6-Trimethyl-2-methylphenylamino-4H-1,3-oxazine (IVe). A 3.2-g (7.9 mmole) sample of hydriodide IIe was dissolved in 80 ml of a 3 N methanol solution of sodium hydroxide. The methanol was removed by distillation after 24 h, and the residue was extracted with boiling hexane. The hexane wax removed from the extract by distillation, and 30 ml of a saturated alcohol solution of picric acid was added to the residue. The precipitate that formed after 4 h was removed by filtration to give 2.0 g (57%) of the picrate of oxazine IVe. The picrate was mixed with 10 g of activity II aluminum oxide, and 10 ml of a 3 N solution of potassium hydroxide in methanol was added. The methanol was vacuum evaporated, and the dry residue was chromatographed on aluminum oxide with elution by hexane–ether (1 : 1) to give 0.98 g of oxazine IVe. A similar method was used to obtain IVa-d, e as colorless oils that were stable on storage and resistant to alkaline hydrolysis.

4,4,6-Trimethyl-2-methyl(p-tolyl)amino-4H-1,3-oxazine (IVc). A mixture of 1.0 g (3.4 mmole) of Ic and 0.6 g (4.1 mmole) of methyl iodide in 30 ml of a 3 N solution of potassium hydroxide in methanol was allowed to stand at 25° for 30 h. The methanol was then removed by distillation, and the residue was extracted with boiling hexane. The hexane was removed from the extract by distillation, 10 ml of a saturated alcohol solution of picric acid was added to the residue, and the resulting precipitate was removed by filtration to give 0.80 g (38%) of the picrate of oxazine IV, from which oxazine IVc was obtained as described above.

4,4,6-Trimethyl-2-dimethylamino-4H-1,3-oxazine (IVf). A 5.5-g (1.4 mmole) sample of If and 22.1 g (3.3 mmole) of red mercuric oxide were refluxed in 20 ml of dry benzene for 2 h, after which the mercuric sulfide and excess mercuric oxide were removed by filtration, the benzene was removed by distillation, and 20 ml of a saturated alcohol solution of picric acid was added to the residue. The resulting precipitate was removed by filtration to give 6.8 g (62%) of the picrate of oxazine IVf, from which oxazine IVf was isolated.

N-Methyl-N-phenyl-S-methylisothiourea (VII). A solution of 3.0 g (9.2 mmole) of V in 20 ml of alcohol was heated at 78° for 2 h, after which the alcohol was removed by distillation. The residue was chromatographed with a column filled with activity II aluminum oxide and elution by hexane–ether (2 : 1) to give 1.2 g (71%) of isothiourea VII with mp 56–57° (from hexane): Found: N 15.8%. $C_9H_{12}N_2S$. Calculated: N 15.5%.

N-Methyl-N'-phenyl-O-ethylisourea (VIII). A 2.0 g (6.1 mmole) sample of V was added to 30 ml of a 3 N alcohol solution of sodium hydroxide, and the mixture was allowed to stand at 25° for 10 h. The alcohol was removed by distillation, and the residue was extracted with hexane. The hexane was removed by distillation to give 0.9 g (82%) of isourea VIII as a colorless oil. PMR spectrum (in CCl_4): 1.18 (CH_3–C, t), 2.25 (CH_3–N, s), 3.73 (NH, s), 3.99 (CH_2, q), and 6.85 (C_6H_5, m).

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