CONVERSIONS OF 5-HYDROXY-5, 6-DIHYDRO-4H-1, 2, 5-OXADIAZINES

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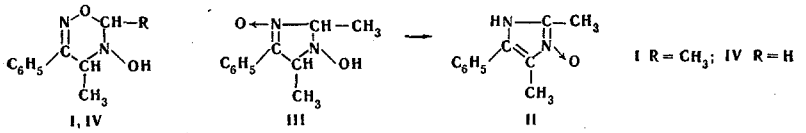
Oxidation of 5-hydroxy-5, 6-dihydro-4H-1, 2, 5-oxadiazines leads to the formation of 6H-1, 2, 5-oxadiazine-5-oxides. Acid treatment of 5, 6-dihydro-4H-1, 2, 5-oxadiazines and 6H-1, 2, 5-oxadiazine-5-oxides results in heterocyclic-ring contraction with the formation of imidazole 3-oxides and 1-hydroxyimidazole 3-oxides. The structures of the products are established by their spectral properties and confirmed by independent synthesis.

Information in the literature on compounds containing the 1, 2, 5-oxadiazine ring structure is extremely limited. Those to which the 4H-1, 2, 5-oxadiazine structure had been attributed proved to be imidazole derivatives [1].

It has recently been shown by PMR spectroscopy that 5-hydroxy-5, 6-dihydro-4H-1, 2, 5-oxadiazines, obtained by condensation of syn-α-hydroxylaminoximes with aliphatic aldehydes, are present in solution as a mixture of two tautomeric forms, cyclic (5-hydroxy-5, 6-dihydro-4H-1, 2, 5-oxadiazine) and open-chain [N-(2-hydroxyimino)-substituted nitrone] [2]. Acylation leads to the formation of 1, 2, 5-oxadiazines which cannot undergo this tautomerism. In continuation of work on the properties of heterocycles derived from α-hydroxylaminooximes [3], we have examined the conversions of 5-hydroxy-5, 6-dihydro-4H-1, 2, 5-oxadiazines.

It is known that 5, 6-dihydro-4H-1, 2, 5-oxadiazines, on heating in acetic acid, give 3-imidazoline 3-oxides, which on subsequent dehydration yield imidazoles [4, 5]. On heating 5-hydroxy-4, 6-dimethyl-3-phenyl-5, 6-dihydro-4H-1, 2, 5-oxadiazine (I) in acetic acid, 2, 4-dimethyl-5-phenylimidazole 3-oxide (II) was obtained. This, as has previously been shown, is the dehydration product of 1-hydroxy-2, 5-dimethyl-4-phenyl-3-imidazoline 3-oxide (III) on treatment with HCl. The conversion of I into II appears to involve initial formation of the 3-imidazoline 3-oxide III, which is converted under the reaction conditions into II. The data obtained not only support structure I, but they also indicate that loss of water is a secondary process [3].



I, IV III II I R = CH_3; IV R = H

Oxidation of I and IV results in the formation of compounds with the "fixed" 1, 2, 5-oxadiazole ring structure. When a mixture of 5-hydroxy-4-methyl-3-phenyl-5, 6-dihydro-4H-1, 2, 5-oxadiazine with lead dioxide in benzene was allowed to stand, a compound with the composition $C_{11}H_{12}N_2O_2$ (V) was formed. The IR spectrum of V showed a strong band at 1218 cm^{-1}, which could be attributed to N → O stretching [6], but hydroxyl absorption at 3600 cm^{-1} was absent. The UV spectrum showed absorption at λ_{max} 294 nm (log ε 3.70), which is characteristic of compounds with the conjugated nitrone grouping [7]. The results indicate that V is 4-methyl-3-phenyl-6H-1, 2, 5-oxadiazine 5-oxide. This is in agreement with the PMR spectrum, which contains three signals at 7.95, 4.89, and 2.57 τ, corresponding to the methyl and methylene groups and to the five hydrogen atoms of the benzene ring.

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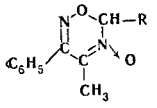
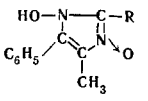
Under the same oxidation conditions, I gave VI, which according to its IR and UV spectra closely resembled V. The PMR spectrum of VI showed a doublet and a quartet due to the CH_3–CH group at 8.32 and 4.96τ (J = 6 Hz), a methyl signal at 7.98τ and a singlet due to the five hydrogen atoms of the benzene ring, at 2.58τ. The splitting of the methyl and methylene signals in V (J = 1.2 Hz) and of the methyl in the 5 position and the methine group in VI(J = 1.5 Hz) is apparently due to long-range coupling.

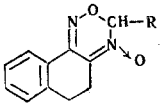
Similarly, the appropriate 5-hydroxy-5, 6-dihydro-4H-1, 2, 5-oxadiazines [5] afforded 1', 2', 3', 4'-tetrahydronaphth[1', 2':3, 4]-6H-1, 2, 5-oxadiazine 5-oxides (VII and VIII).



V, VI



IX X



VII, VIII

V R = H; VI R = CH_3;
VII R = H; VIII R = CH_3;
IX R = H; X R = CH_3

The oxidation products (V, VI, VII, and VIII) were colorless, monomeric, crystalline substances, which are related to the heterocyclic nitrones [8]. Treatment of V and VI with 10% hydrochloric acid or with glacial acetic acid containing traces of HCl gave the hydrochlorides of IX and X, which were isomeric with the starting materials. The PMR spectrum of X (free base, in CD_3OD), showed singlets at 7.81, 7.63, and 2.55 τ corresponding to the two methyl groups and the 5 hydrogen atoms of the benzene ring, and the UV spectrum did not show absorption at 298 nm. These results suggest that X is 1-hydroxy-2, 4(5)-dimethyl-5(4)-phenylimidazole 3-oxide, and this conclusion was confirmed by an independent synthesis [9]. By analogy, IX was assigned the structure 1-hydroxy-4(5)-methyl-5(4)-phenylimidazole 3-oxide.

Thus, 6H-1, 2, 5-oxadiazine 5-oxides, on treatment with acid, also undergo heterocyclic-ring contraction.

EXPERIMENTAL

The IR spectra were recorded on a UR-10 spectrophotometer in KBr (concentration 0.25%, disk thickness 1 mm), and in solution in CCl_4 (concentration 1%, layer thickness 0.1 mm). The UV spectra were recorded on a Unicam SP 700c spectrophotometer in alcohol. The PMR spectra were recorded on a Varian A-56-60A instrument as 4-5% solutions in CCl_4 and in deuteromethanol (CD_3OD). The standard used was hexamethyldisiloxane (9.96 τ).

Action of Glacial Acetic Acid on 5-Hydroxy-4, 6-dimethyl-5-phenyl-5, 6-dihydro-4H-1, 2, 5-oxadiazine (I). To 0.15 g (0.72 mmole) of I was added 3 ml of glacial acetic acid, and the mixture was heated for 1 h 30 min at 90°. The solution was evaporated, and the residue was dissolved in absolute alcohol and diluted with dry ether. The precipitate of II was filtered off, mp 158-160°. It was identical with the imidazole 3-oxide, obtained as in [3]. PMR spectrum of II: 7.66 (CH_3); 7.51 (CH_3); 2.50 (C_6H_5)τ.

Oxidation of 5-Hydroxy-5, 6-dihydro-4H-1, 2, 5-oxadiazines. To 0.48 g (2.5 mmole) of I was added 4.2 g (17.5 mmole) of lead dioxide, and the mixture was kept for a day in 50 ml of benzene. The solution was evaporated, and the residue of VI (0.40 g) was recrystallized from alcohol. Under the same conditions, V was obtained in 65% yield. In the preparation of VII and VIII, the addition of a few drops of acetic acid to the benzene improved the yield to about 70%.

TABLE 1. 6H-1, 2, 5-Oxadiazine-5-Oxides

Compound	Mp, °C	Molecular formula	Found, %			Calc., %			λmax, nm (log ε)
			C	H	N	C	H	N	
V	133—134	$C_{10}H_{10}N_2O_2$	63,2 63,2	5,3 5,3	14,7 14,9	63,1	5,3	14,7	204 (4,09), 236 (3,99), 294 (3,91)
VI	135—136	$C_{11}H_{12}N_2O_2$	64,6 64,9	5,9 5,8	13,6 13,6	64,6	5,9	13,7	202 (4,16), 237 (4,01), 298 (3,92)
VII	94—96*	$C_{11}H_{10}N_2O_2$	65,1 65,3	5,0 4,8	14,1 14,2	65,4	4,9	13,9	204 (4,27), 238 (4,07), 304 (3,95)
VIII	107—108*	$C_{12}H_{12}N_2O_2$	67,0 66,8	5,5 5,2	13,0 12,8	67,0	5,6	13,0	201 (4,20), 239 (4,03), 306 (3,91)

* With decomposition.

The mp's and analytical data for the compounds obtained are given in the table. The molecular weights of V and VI were determined by isothermal distillation in acetone: V, found, 184, 186; calculated, 190: VI, found, 203, 205; calculated, 204.

Action of Hydrochloric Acid on 4, 6-Dimethyl-3-phenyl-6H-1, 2, 5-oxadiazine-5-oxide (VI). To 0.3 g (1.47 mmole) of VI was added 3 ml of 10% HCl, and the mixture was kept for a day. The precipitated hydrochloride of X (needles) was filtered off (0.25 g), mp 222-224° (from absolute alcohol). Found: C 54.8; 55.0; H 5.0; 5.2; N 11.8; 11.9; Cl 14.6; 14.6%. $C_{11}H_{12}N_2O_2 \cdot HCl$ Calculated: C 55.0; H 5.4; N 11.7; Cl 14.8%. X (free base) was isolated by neutralizing the aqueous solution. mp 200-201°.

By saturating with hydrogen chloride a solution of isonitrosopropiophenone and acetaldoxime in methanol, as in [9], there was obtained 1-hydroxy-2, 4(5)-dimethyl-5(4)-phenylimidazole 3-oxide hydrochloride, which was identical by mp and IR spectrum with X hydrochloride.

Reaction of 4-methyl-3-phenyl-6H-1, 2, 5-oxadiazine 5-oxide (V) with 10% HCl afforded 1-hydroxy-4(5)-methyl-5(4)-phenylimidazole 3-oxide hydrochloride, mp 152-153° (alcohol–ether). Found: C 53.2; 53.2; H 4.5; 4.7; N 12.4; 12.6; Cl 16.1; 16.0%. $C_{10}H_{10}N_2O \cdot HCl$. Calculated: C 52.7; H 4.8; N 12.3; Cl 15.6%.

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