CONVERSION OF N-(1-KETO-1-ARYL-2-ALKYL)NITRONES TO 4-HYDROXY-2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINES

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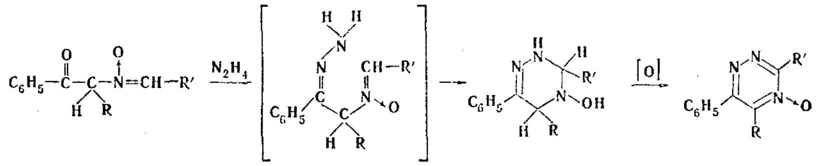
The reaction of N-(1-keto-1-aryl-2-alkyl)nitrones with hydrazine gives 4-hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines, the oxidation of which with lead dioxide gives 1,2,4-triazine 4-oxides.

N-Substituted nitrones decompose on reaction with hydrazine to give N-substituted hyroxylamines [1, 2]. In order to obtain α-hydroxylamino ketones or their hydrazones, N-(1-keto-1-phenyl-2-ethyl)-α-phenylnitrone (I) and N-(1-keto-1-phenyl-2-propyl)-α-phenylnitrone (II) were treated with excess hydrazine hydrate at 20°C. Compounds III and IV, to which the 4-hydroxy-2,3,4,5-tetrahydro-1,2,4-triazine derivative structure (Table 1) can be assigned on the basis of the UV and IR spectra [absence of the absorption bands of a nitrone group [3] and presence of absorption at 3420 cm^{-1} (NH) and 3595 cm^{-1} (OH) [4, 5]], were isolated from the reaction mixture. The PMR spectrum of III (in dimethyl sulfoxide) contains a singlet at 6.10 ppm,* the position and intensity of which correspond to the hydrogen atoms of the CH_2 group in the 5 position of the triazine ring, a singlet of a hydrogen atom in the 3 position at 5.32 ppm, a singlet of an OH group in the 4 position at 1.86 ppm, and a complex band of 10 hydrogen atoms of two benzene rings in the 3 and 6 positions centered at 2.58 ppm. The PMR spectrum of IV (in CD_3OD) is close to the spectrum of III (Table 2) but contains a doublet at 8.73 ppm and a quartet at 5.86 ppm of a CH_3CH group instead of the band of a CH_2 group. On the basis of these data, the 4-hydroxy-3,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (III) and 4-hydroxy-5-methyl-3,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (IV) structures were assigned to III and IV.

A crystalline product, which is apparently hydrazone VI ($R = R' = CH_3$), is initially formed in the reaction of N-(1-keto-1-phenyl-2-propyl)-α-methylnitrone (V) with hydrazine hydrate in alcohol at −10°. This compound is unstable and was not identified. On standing or heating in alcohol, VI is converted to 4-hydroxy-3,5-dimethyl-6-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine (VII).



I, II, V VI III, IV, VII VIII-X

I, III, VIII $R = H$, $R' = C_6H_5$; II, IV, IX $R = CH_3$, $R' = C_6H_5$; V, VII, X $R = R' = CH_3$

To confirm the structures, III, IV, and VII were oxidized with lead dioxide in benzene or chloroform at 20°. Yellow crystalline substances, to which the 3,6-diphenyl-1,2,4-triazine 4-oxide (VIII) [6], 5-methyl-3,6-diphenyl-1,2,4-triazine 4-oxide (IX) and 3,5-dimethyl-6-phenyl-1,2,4-triazine 4-oxide (X) structures were assigned on the basis of spectral characteristics (Table 1), were isolated in good yields from the

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*The chemical shifts are given on the τ scale.

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TABLE 1. 4-Hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines (III, IV, VII) and 1,2,4-Triazine 4-Oxides (IX, X)

Compound	mp, °C	Empirical formula	Found, %			Calc., %			UV spectrum		IR spectrum, cm-1		Yield, %
			C	H	N	C	H	N	λ_{max}, nm	lg ε	NH	OH	
III	172—174^{a}	$C_{15}H_{15}N_3O$	71,3	6,0	16,5	71,2	6,0	16,6	286^{e}	4,07	3420	3595	81
IV	181—183^{b} (dec.)	$C_{16}H_{17}N_3O$	71,8	6,3	15,7	72,0	6,4	15,7	283^{e}	4,06	3420	3595	58
VII	154—155^{c}	$C_{11}H_{15}N_3O$	64,2	7,5	20,8	64,5	7,5	20,5	286	4,04	3420	3595	49
IX	131—133^{b}	$C_{16}H_{13}N_3O$	73,5	5,1	15,9	73,0	4,9	16,0	271	4,52	—	—	70
X	122—124^{d}	$C_{11}H_{11}N_3O$	65,7	5,6	20,6	65,7	5,5	20,6	278	3,9	—	—	70

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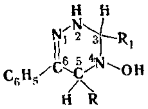
[a] From methanol. [b] From alcohol. [c] From dichloroethane. [d] From cyclohexane. [e] According to [9], λ_{max} 297 nm (log ε 4.07) for 3-oxo-2-methyl-6-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine.

TABLE 2. PMR Spectra



Compound	Solvent	Position of the groups and H atoms, chemical shifts τ, ppm (J, Hz)				
		3-H	5-H	5-R	3-R_1	6-C_6H_5
III	Dimethyl sulfoxide	5,32	CH_2 6,10		$(C_6H_5)_2$ 2,58^{a}	
IV	CD_3OD	5,49	5,82 (7,0)^{c}	CH_3^{b} 8,73 (7,0)	$(C_6H_5)_2$ 2,57^{a}	
VII	CD_3OD	5,86^{a}	5,86^{a}	CH_3^{b} 8,77 (6,0)	CH_3^{b} 8,71 (6,0)	C_6H_5 2,56^{a}

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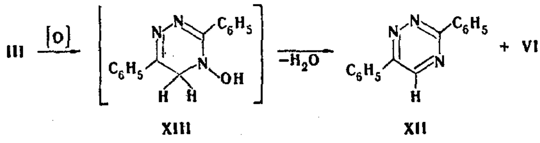
[a] Complex band. [b] Doublet (1:1). [c] Quartet (1:3:3:1).

reaction media. The reduction of X with sodium bisulfate in aqueous alcohol solution [7] gave 3,5-dimethyl-6-phenyl-1,2,4-triazine (XI) in 20% yield; this product was identical to a sample synthesized via the method in [8]. The known [4] 3,6-diphenyl-1,2,4-triazine (XII) was isolated along with 1,2,4-triazine 4-oxide (VIII) from the reaction mixture in the oxidation of III by chromatography on aluminum oxide. This makes it possible to assume that the initial product in the oxidation is 4-hydroxy-4,5-dihydro-1,2,4-triazine (XIII), which may subsequently be oxidized to VIII or dehydrated to XII.



The oxidation of 4-hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines is a new method for the preparation of compounds of the little-investigated class of 1,2,4-triazine 4-oxides [6].

EXPERIMENTAL

The IR spectra of KBr pellets (0.25%, 1-mm-thick pellets) and CCl_4 solutions were recorded with a UR-10 spectrophotometer. The UV spectra of alcohol solutions were recorded with a Unicam SP-700 C spectrophotometer. The PMR spectra were recorded with a Varian A-56-60 A spectrometer with hexamethyldisiloxane (9.96 ppm) as the internal standard.

The melting points, elementary composition data, and spectral characteristics of the 2,3,4,5-tetrahydro-1,2,4-triazines and 1,2,4-triazine 4-oxides are presented in Tables 1 and 2.

4-Hydroxy-3,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (III). A 0.42-g (8.4 mmole) sample of hydrazine hydrate was added to a solution of 1 g (4.2 mmole) of nitrone I in 10 ml of alcohol, and the mixture was allowed to stand at 20° for 10 h. The precipitated III (0.85 g) was then removed by filtration.

4-Hydroxy-5-methyl-3,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (IV). A solution of 5 g (0.02 mole) of II in 70 ml of alcohol and 2 g (0.04 mole) of hydrazine hydrate was allowed to stand at 20° for 15 h. The solution was evaporated to two-thirds of its original volume and cooled. The precipitated IV was removed by filtration and washed with alcohol to give 3.1 g of product.

4-Hydroxy-3,5-dimethyl-6-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine (VII). A 1-g (0.02 mole) sample of hydrazine hydrate was added to a cooled (to −10°) solution of 2 g (0.01 mole) of nitrone V in 10 ml of alcohol, and the mixture was allowed to stand at −10° for 15 h. The precipitate was separated and dissolved in alcohol, and the solution was refluxed for 2 h. The solvent was removed, dry ether was added to the residue, and the solution was cooled to precipitate 1.05 g of VII.

3,6-Diphenyl-1,2,4-triazine 4-Oxide (VIII). A suspension of 1.2 g (0.005 mole) of III and 12 g (0.05 mole) of lead dioxide in 30 ml of chloroform was stirred at 20° for 24 h. The solvent was then evaporated and 0.14 g (12%) of XII with mp 155-157° was initially isolated from the solid residue by chromatography on activity IV aluminum oxide with petroleum ether−ether (1:1); UV spectrum: λ_{max} 286 nm, log ε 4.45 (mp 156-157°; λ_{max} 285 nm, log ε 4.45 [4]). Elution with chloroform then gave 0.58 g (51%) of VIII with mp 168-169° (mp 171° [6]). IR spectrum: 1250 cm^{-1} (N→O); UV spectrum: λ_{max} 286, log ε 4.57; PMR spectrum ($CDCl_3$): singlet at 0.89 ppm, 5-H, complex bands centered at 1.80 and 2.48 ppm, 3,6-$(C_6H_5)_2$ [according to the data in [6] (from a DMSO solution), the 5-H singlet is found at 0.68 ppm].

Under the same conditions, 5-methyl-3,6-diphenyl-1,2,4-triazine 4-oxide (IX) was obtained from IV. PMR spectrum (in CD_3OD): 7.51 ppm, 5-CH_3; complex bands centered at 1.73 and 2.46 ppm, 3,6-$(C_6H_5)_2$. Oxidation of VII in benzene for 6 h gave 3,5-dimethyl-6-phenyl-1,2,4-triazine 4-oxide (X) in quantitative yield. PMR spectrum (in CD_3OD): singlet 7.56 ppm, 5-CH_3, singlet 7.24 ppm (see [6]), and complex band centered at 2.46 ppm, 6-C_6H_5.

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