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3-Oxazolines (I)

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α -Hydroxy- α -methyl ketones react with ammonia and aromatic aldehydes in the presence of calcium chloride and ammonium chloride to yield 2-aryl-3-oxazolines.

It has been previously shown that α -hydroxy ketones, whose hydroxy group is tertiary, react with ammonia to yield the hitherto unknown 3-oxazolines (2). The formation of substituted 3,4-dihydropyrrolenine-3,4-diols results when either R or R' in I is hydrogen (2).

Bernhauer and Hoffmann prepared 2,4,5-trisubstituted imidazoles by the reaction of acyloins with benzaldehyde or formaldehyde and aqueous ammonia in the presence of copper acetate (3). This reaction was used by Ebel, *et al.*, for the preparation of histamine from the reaction of 1,4-dihydroxy-2-butanone with formaldehyde and ammonia in the presence of copper salts (4).

This investigation covers the synthesis of 3-oxazolines from the reaction of α -hydroxy- α -methyl ketones with aromatic aldehydes and ammonia in the presence of calcium chloride and ammonium chloride.

R in equation 2 is an alkyl group and Ar is phenyl, substituted phenyl or 2-furyl.

The formation of II is hindered by the presence of Lewis Acids, as only small yields of II are obtained when the reaction is run in the presence of ammonium chloride. Acid hydrolysis of III yields the starting reactants and an ammonium salt. This was also shown to be true for II (2).

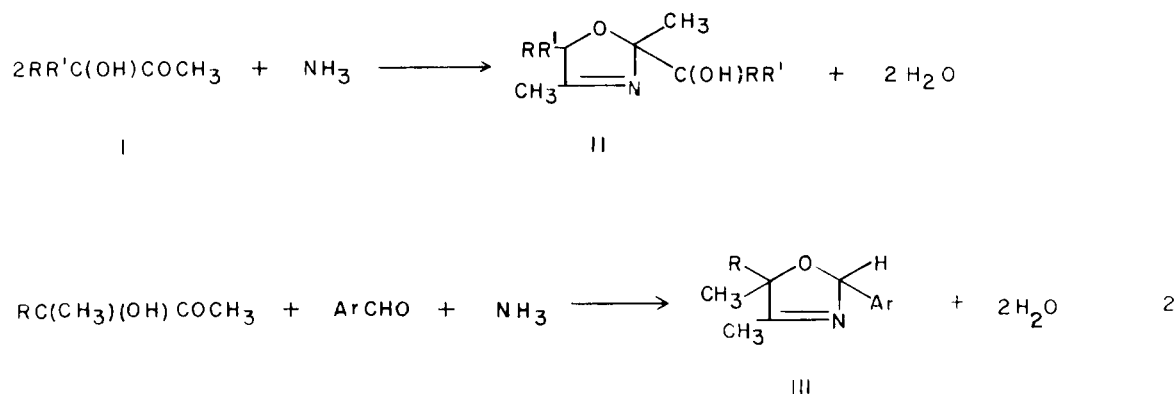
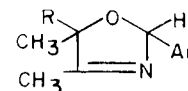


TABLE I
3-Oxazolines

Compound	R	Ar	Yield	Formula	Anal. %					
					C		H		N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
IV	Me	C ₆ H ₅	96	C ₁₂ H ₁₅ NO	76.15	76.32	7.99	8.16	7.40	7.20
V	Et	C ₆ H ₅	27	C ₁₃ H ₁₇ NO	76.81	76.69	8.43	8.48	6.89	6.73
VI	<i>i</i> -Bu	C ₆ H ₅	26	C ₁₅ H ₂₁ NO	77.88	77.76	9.15	9.13	6.06	6.03
VII	Me	2-Furyl	33	C ₁₀ H ₁₃ NO ₂	67.02	67.01	7.31	7.28	7.82	7.73
VIII	Et	2-Furyl	29	C ₁₁ H ₁₅ NO ₂	68.37	68.25	7.82	7.87	7.25	7.16
IX	Me	<i>o</i> -HOC ₆ H ₄	54	C ₁₂ H ₁₅ NO ₂	70.22	70.14	7.37	7.31	6.82	6.93
X	Et	<i>o</i> -HOC ₆ H ₄	47	C ₁₃ H ₁₇ NO ₂	71.21	71.34	7.81	7.84	6.39	6.47
XI	<i>i</i> -Bu	<i>o</i> -HOC ₆ H ₄	33	C ₁₅ H ₂₁ NO ₂	72.84	72.76	8.56	8.59	5.66	5.51
XII	Me	<i>p</i> -CH ₃ OC ₆ H ₄	76	C ₁₃ H ₁₇ NO ₂	71.20	71.14	7.81	7.80	6.39	6.46
XIII	Et	<i>p</i> -CH ₃ OC ₆ H ₄	40	C ₁₄ H ₁₉ NO ₂	72.07	71.98	8.21	8.21	6.00	6.12
XIV	<i>i</i> -Bu	<i>p</i> -CH ₃ OC ₆ H ₄	33	C ₁₆ H ₂₃ NO ₂	73.53	73.43	8.87	8.86	5.35	5.31
XV	Me	<i>p</i> -ClC ₆ H ₄	59	C ₁₂ H ₁₄ ClNO	64.43	64.35	6.31	6.28	6.26	6.18
XVI	Et	<i>p</i> -ClC ₆ H ₄	15	C ₁₃ H ₁₆ ClNO	65.68	65.61	6.78	6.77	5.89	5.98

TABLE II
3-Oxazolines from $RC(CH_3)(OH)COCH_3$ and $ArCHO$ (a)



Compound	Reaction conditions (temp., °C at press p. s. i. g.)	Time, hr.	B. p., °C (press)	M. p., °C (solvent)	n_D^{20}	d_4^{25}
V	110 at 540	4	86-88(0.3)		1.5149	1.002
VI	130 at 440	9	101-103(0.35)	99 (Et ₂ O)		
VII	110-130 at 250-350	4	73-74(1.2)		1.4832	1.049
VIII	100-120 at 500-540	4	64-65(0.35)		1.4746	0.998
IX	50-80 at 90-100	3		161 (95% EtOH)		
XI	70-80 at 160-175	4		95 (95% EtOH)		
XII	60-80 at 200-280	4	124-126(0.72)		1.5258	1.063
XIII	80-120 at 300-350	4, 5	133-135(0.72)		1.5305	1.062
XIV	90-120 at 250-350	6	142-144(0.78)		1.5201	1.031
XV	80-100 at 200-300	4	70-72(1.6)	45		
XVI	80-100 at 200-250	5	68-70(0.65)	87		

(a) Refer to Table I for values of R and Ar.

Gaines and Lidel (2) have established infrared absorption bands for the O-C-N system in 3-oxazolines; the O-C-N system has three bands (at 1149-1185, 1116-1139, and 1086-1114 cm^{-1} , respectively) in the 1000-1200 cm^{-1} region. The absorption of the aliphatic C-N bond in a 5-membered ring is well known (2, 5), lying at about 1670 cm^{-1} .

The infrared spectra of compounds IV - XVI had three bands at 1149-1193, 1107-1151, and 1064-1106 cm^{-1} , respectively and an absorption band for the C-N bond at 1664-1672 (3).

EXPERIMENTAL

All melting points are uncorrected and were taken in a modified Hershberg melting point apparatus. Yields correspond to the quantity of product isolated. The aldehydes were purchased commercially and purified by redistillation or recrystallization.

α -Hydroxy ketones.

3-Hydroxy-3-methyl-2-butanone and 3-hydroxy-3-methyl-2-pentanone were prepared from the corresponding acetylenic alcohols (available commercially) by a modified procedure of a British patent (7), as described by Gaines and Lidel (2). 3,5-Dimethyl-3-hydroxy-2-hexanone was prepared according to the procedure of Hennion and Watson (8).

2-Phenyl-4,5,5-trimethyl-3-oxazoline (IV).

A pressure reaction apparatus (Parr Series 4500, medium-pressure, stirrer type, 1000-ml. capacity) was charged with 102 g. (1 mole) of 3-hydroxy-3-methyl-2-butanone, 106 g. (1 mole) of benzaldehyde, 8 g. of calcium chloride, and 2 g. of ammonium chloride. Anhydrous ammonia was introduced, with stirring, until a pressure of 80 p. s. i. g. was obtained. The bomb was heated to 90-100° (pressure at 300-400 p. s. i. g.) and this temperature was maintained for 4 hr. The bomb was vented and the product extracted from the reaction

mixture with 100 ml. of ether. After removal of the solvent, fractionation of the residue at reduced pressure yielded 181.8 g. (96%) of the oxazoline, b. p. 94-96° (2.3 mm.), n_D^{20} 1.5168, d_4^{25} 1.007.

4,5-Dimethyl-5-ethyl-2-(4-hydroxyphenyl)-3-oxazoline (X).

A pressure reaction apparatus was charged with 116 g. (1 mole) of 3-hydroxy-3-methyl-2-pentanone, 122 g. (1 mole) of salicylaldehyde, 8 g. of calcium chloride, and 2 g. of ammonium chloride. Anhydrous ammonia was introduced, with stirring, until a pressure of 80 p. s. i. g. was obtained. The bomb was heated to 70-80° (pressure at 100-135 p. s. i. g.) and this temperature was maintained for 4 hr. The bomb was vented and the product was extracted from the resinous reaction mixture with five 50 ml. portions of ether. The solvent was removed by aspiration and the solid residue was recrystallized from 95% ethanol to yield 103.1 g. (47%) of the oxazoline, m. p. 133°.

Table II lists the conditions of preparation and the physical constants for eleven oxazolines. The procedure used in each synthesis was essentially the same as the method described for 2-phenyl-4,5,5-trimethyl-3-oxazoline or 4,5-dimethyl-5-ethyl-2-(4-hydroxyphenyl)-3-oxazoline.

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