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Reduction of Oxazolinium Salts to Oxazolidines: A New Route from Carboxylic Acids to Aldehydes

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Oxazolidines have been prepared by sodium and alcohol reduction (1) of oxazolines; however, the products were not characterized by hydrolysis. Other examples of reductions (2) of either oxazoles or oxazolines result in ring cleavage to give β -hydroxy-ethylamines.

Some oxazolinium salts have been reduced (3) by hydrogen with platinum, sodium trimethoxyborohydride and in particular with sodium borohydride to give ring opened products.

We have found that 3,4,4-trimethyl- Δ^2 -oxazolinium iodides having a variety of substituents (Table I) at the two position are reduced with sodium borohydride in alcoholic solutions to the corresponding 2-substituted 3,4,4-trimethyloxazolidines. Subjecting the corresponding oxazolines to the same reducing conditions gave no reduction products, only starting material was recovered.

The oxazolidine produced must not be in equilibrium with a ring opened form in the reaction medium, since iminium salts and enamines would be reduced with sodium borohydride to amines under the weakly basic reaction conditions (4).

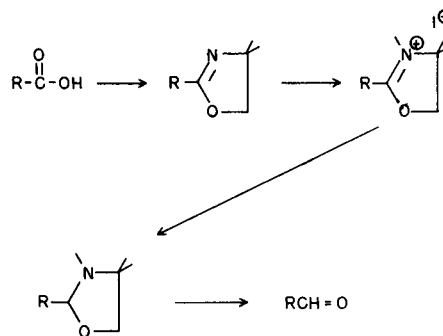
Hydrolysis of the reduction products gave the corresponding aldehydes which were identified by boiling point, infrared spectra and carbonyl derivatives (Table II). The oxazolidines were further characterized by elemental analysis, characteristic bands (Table III) of their infrared spectra in the 1000-1200 cm^{-1} region (5) along with the absence of the $>\text{C}=\text{N}<$ absorption (*ca.* 1660 cm^{-1} , see Table I).

The nmr spectra of both the oxazolinium salts and the oxazolidines were in agreement for the proposed heterocyclic systems (Tables I and III).

The sequence constitutes a new method for reduction of carboxylic acids to aldehydes. The four examples represent reduction to an aryl aldehyde and to aliphatic aldehydes with two, one and no α -protons. These structural variations seem to have no striking effect on the yield or ease of this reduction process. All four oxazolidines were very bad foamers causing abnormally large boiling temperature ranges and low yields. That the low yields were due to this property was confirmed by direct hydrolysis of the crude reduction products, in the first two examples, and quantitative determination (6) of the aldehydes as the 2,4-dinitrophenylhydrazones. This procedure indicated that significantly higher yields of the oxazolidines had been produced.

The reductions have been done in either dry methanol at about 5° or in dry ethanol at about 25° with reaction times varying from 1 to 14 hours without significant variations in yield. However, no systematic study of these variables has been made.

Two of the oxazolines and their corresponding oxazolinium salts were known compounds, R = phenyl and *t*-butyl (7). The other analogs of these compounds were prepared by the same procedures.



EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were determined in potassium bromide pellets or as liquid films on a Beckman IR-9 spectrophotometer. The nmr spectra were determined on a Varian A-60 spectrometer using deuteriochloroform as solvent with tetramethylsilane as the internal standard.

2-Cyclohexyl-4,4-dimethyl- Δ^2 -oxazoline (I).

This compound was prepared by the method described by P. Allen and J. Ginos (7) from 110 g. (0.86 mole) of cyclohexanecarboxylic acid and 76.5 g. (0.86 mole) of 2-amino-2-methyl-1-propanol to give 98.0 g. (63%) of product, b. p. 95-97°/14 mm.

Anal. Calcd. for $\text{C}_{11}\text{H}_{19}\text{NO}$ (181.3): C, 72.87; H, 10.56. Found: C, 72.92; H, 10.81.

TABLE I

2-Substituted 3,4,4-trimethyloxazolinium Iodide

R	Yield %	m. p. °C	IR (cm^{-1})		NMR (δ)	
			$\text{C}=\text{N}^{\oplus}$	$-\text{CH}_2-$	N- CH_3	(CH_3) ₂
Phenyl (a)	86	192-195	1647	5.10	3.57	1.75
Cyclohexyl	81	219-222	1668	4.87	3.46	1.64
<i>t</i> -Butyl (a)	85	182-188	1675	4.92	3.52	1.71
2-Phenylethyl	97	166-169	1663	4.78	3.12	1.49

(a) Reference 7.

TABLE II

Aldehydes				
R-CH=O				
R	Yield %	m. p. 2,4-D	Lit. m. p. 2,4-D (a)	Ref. (a) Page No.
Phenyl	86 (b)	238-240°	237°	70
Cyclohexyl	78 (b)	170-172° (c)	172°	70
<i>t</i> -Butyl	95 (d)	209-210°	210°	68
2-Phenylethyl	72 (e)	148-149°	149°	72

(a) C. D. Hodgman, "Tables for Identification of Organic Compounds," Chemical Rubber Publishing Company, Cleveland, Ohio, 1960. (b) By 2,4-dinitrophenylhydrazone quantitative analysis (5) of acidified reduction mixture. (c) Semicarbazone, m. p. 173-175°, Ref. (a) p. 70, m. p. 173; 176. (d) By 2,4-dinitrophenylhydrazone quantitative analysis (6) of hydrolyzed pure oxazolidine. (e) By weight of distilled product (b. p. 91-96°/8 mm) from hydrolysis of pure oxazolidine.

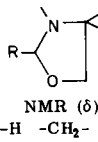
The reaction mixture was diluted with 200 ml. of 5% sodium hydroxide solution and extracted with ether. The extract was dried over magnesium sulfate and the solvent removed by distillation. The residue was distilled to give 18.0 g. of crude product, boiling from 135 to 155° at 9 mm. This material was redistilled slowly and the fraction boiling from 137° to 142° at 8 mm was collected to give 14.4 g. (66%) of pure V. The analysis is in Table III.

Cyclohexanecarboxaldehyde 2,4-Dinitrophenylhydrazone.

This procedure illustrates the direct quantitative analysis for aldehyde of the hydrolyzed reduction mixture. An 8.10 g. (2.5 mmoles) sample of III in 50 ml. of ethanol was stirred as 1 g. (25 mmoles) of sodium borohydride was added portionwise during 30 minutes with the temperature maintained below 28°. After stirring 4 hours at room temperature the reaction mixture was diluted to 100 ml. with 2*N* hydrochloric acid. Two 10 ml. aliquots were added to 150 ml. of 2,4-dinitrophenylhydrazine reagent (5) and heated on the steam bath for 1 hour. The cooled samples were collected on weighed funnels and washed with 2*N* hydrochloric acid and with water and then dried at 110° overnight to give 0.57 g. (78%) of product from each aliquot. These samples melted at 170-171°. After combining and recrystallizing from ethanol the melting point was 170-172° (Table II).

TABLE III

2-Substituted 3,4,4-trimethyloxazolidines



R	Yield %	b. p. (°C)(mm)	IR (cm ⁻¹) (1000-1200 Region)	NMR (δ)					gem Formula	Carbon %		Hydrogen %	
				-C-H	-CH ₂ -	N-CH ₃	CH ₃	CH ₃		Calcd	Found	Calcd	Found
Phenyl	58	127-131 (14)	1059, 1150	4.82	3.77	2.01	1.18	1.07	C ₁₂ H ₁₇ NO	75.37	75.10	8.96	9.18
Cyclohexyl	63	100-104 (8)	1042, 1110, 1155	3.90	3.55	2.13	1.06	0.97	C ₁₂ H ₂₃ NO	73.05	73.05	11.75	11.89
<i>t</i> -Butyl	70	60-64 (11)	1078, 1150	3.64	3.42	2.19	1.02	0.97	C ₁₀ H ₂₁ NO	70.11	69.91	12.36	12.19
2-Phenylethyl	66	137-142 (8)	1058, 1100	4.10	3.62	2.11	1.08	0.95	C ₁₄ H ₂₁ NO	76.67	76.65	9.65	9.95

2-(2-Phenylethyl)-4,4-dimethyl-Δ²-oxazoline (II).

This compound was prepared as the previous compound (7) from 300 g. (2 moles) of hydrocinnamic acid and 178 g. (2 moles) of 2-amino-2-methyl-1-propanol to give 297 g. (72%) of product, b. p. 134-137°/11 mm.

Anal. Calcd. for C₁₅H₁₇NO (203.3): C, 76.80; H, 8.43. Found: C, 76.92; H, 8.28.

2-Cyclohexyl-3,4,4-trimethyl-Δ²-oxazolinium Iodide (III).

This compound was prepared by heating a solution of 54.3 g. (0.3 mole) of I and 64 g. (0.45 mole) of methyl iodide in 135 ml. of nitromethane at about 70° overnight. The cooled reaction mixture was diluted with an equal volume of ether and after ice cooling the crystalline product was collected to give 94.3 g. (97%), m. p. 218-220°. Recrystallization from acetonitrile gave 79 g. (81%) of analytical material, m. p. 219-222°.

Anal. Calcd. for C₁₂H₂₂INO (323.2): C, 44.59; H, 6.86. Found: C, 44.51; H, 6.94.

2-(2-Phenylethyl)-3,4,4-trimethyl-Δ²-oxazolinium Iodide (IV).

This compound was prepared as III above from 203 g. (1 mole) of II and 212 g. (1.5 moles) of methyl iodide in 450 ml. of nitromethane to give 334 g. (97%) of product, m. p. 166-169°.

Anal. Calcd. for C₁₄H₂₀INO (345.2): C, 48.71; H, 5.84. Found: C, 48.62; H, 5.66.

2-(2-Phenylethyl)-3,4,4-trimethyloxazolidine (V).

The following procedure illustrates the general method used for reduction when the oxazolidine is isolated. A partially dissolved 34.5 g. (0.1 mole) sample of IV in 100 ml. of methanol was maintained below 5° while sodium borohydride, 1.9 g. (0.05 mole), was added portionwise over 1 hour. Shortly after the last of the sodium borohydride had been added a clear solution was obtained. Stirring at 5° was continued for 2 hours.

Attempted Reduction of 2-Cyclohexyl-4,4-dimethyl-Δ²-oxazoline.

A 36.2 g. (0.2 mole) sample of I was dissolved in 100 ml. of ethanol and 3.8 g. (0.1 mole) of sodium borohydride was added portionwise. The reaction mixture was stirred at 26° overnight and then diluted with 100 ml. of 5% sodium hydroxide and 500 ml. of water. After extraction with ether the extract was dried over magnesium sulfate and the solvent removed by distillation. The residue was distilled to give 27.3 g. of material boiling at 87-88° at 9 mm. The infrared spectrum of this material was identical to that of Compound I.

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