Synthesis of Some Propionamidoketones and 2,5-Diethyl-1,3-oxazoles

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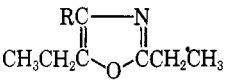
The synthesis of a series of previously unreported propionamidoketones and their cyclization to 2,5-diethyl-1,3-oxazoles are reported. The compounds were characterized through the determination of appropriate physical properties, including those of derivatives.

The Dakin-West reaction has been used to prepare propionamidoketones from propionic anhydride and amino acids *(1)*. The propionamidoketones were cyclized to 2,5-diethyl-1,3-oxazoles through polyphosphoric acid (PPA). PPA as a cyclizing agent is of value in the cyclization of acetamidoketones to 2,5-dimethyl-1,3-oxazoles *(4)*.

$$(CH_3CH_2CO)_2O + RCH(NH_2)COOH \xrightarrow{\text{Pyridine}}$$

$$CH_3CH_2CO{-}CHR{-}NH{-}COCH_2CH_3 \xrightarrow{\text{PPA}}$$



Experimental

Reactants were obtained commercially and used without further purification, including practical grade propionic anhydride. 2-Aminobutanoic acid, *nor*-valine, and *nor*-leucine were obtained from the Sigma Chemical Co., St. Louis, Mo. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. 2,4-Dinitrophenylhydrazones were made by established procedures *(3)*. Recrystallization was accomplished from ethanol–methanol. Mercuric chloride complexes were formed from the addition of the oxazole to an excess of a saturated water solution of mercuric chloride. After one day the precipitate was filtered.

The propionamidoketones (Table I) were prepared by a modification of the method of Wiley and Borum *(5)*. Propionic anhydride (0.91 mole), the respective amino acid (0.15 mole), and pyridine (0.76 mole) were heated and stirred with boiling stones at gentle reflux for 9 hr. The volatile components were removed under reduced pressure and the propionamidoketones distilled from the residue.

The 2,5-diethyl-1,3-oxazoles (Table II) were prepared as previously reported *(4)*. A 15 to 1 weight ratio of polyphosphoric acid to the respective propionamidoketone (0.1 mole) was stirred at 150° ± 5°C. The reaction mixture was protected from moisture by means of a calcium chloride drying tube. After 4 hr the mixture was poured in a thin stream into rapidly stirred crushed ice (100 grams). While stirring in an ice bath, 50% aqueous sodium hydroxide (250 ml) was added dropwise over a 1-hr period. The oily layer which separated was decanted and the aqueous layer was extracted with ether. The ether extracts were combined with the decanted oily layer and distilled.

Elemental analyses (C, H, N) for the 1,3-oxazoles are in agreement with theoretical values and were submitted for review. All elemental analyses were made by Atlantic Microlab, Inc., Atlanta, Ga.

Table I. Propionamidoketones

R	Yield, %[a]	Bp, °C/mm[b]	$n^{20}D$	2,4-DNPH mp, °C[c]
H	68	119.5–114/1–2	1.4618	153.5–154.5
CH_3	77	101–117.5/1	1.4581	156–158
C_2H_5	57	138.5–147.5/7	1.4597	178–179.5
n-C_3H_7	77	111–117/0.5	1.4616	191–193
n-C_4H_9	81	121.5–130.5/1–2	1.4606	167–169

[a] Redistilled product. [b] Temperature range over which redistilled product was collected. [c] 2,4-Dinitrophenylhydrazone.

Table II. 2,5-Diethyl-1,3-oxazoles

R	Yield, %[a]	Bp, °C[b]	$n^{20}D$	$HgCl_2$ complex mp, °C
H	54	157–160	1.4402	103–104
CH_3	74	166–169	1.4431	65.6–68
C_2H_5	71	176–180[c]	1.4474	105–108.5
n-C_3H_7	66	193–197	1.4491	74–75.5
n-C_4H_9	80	208–212	1.4503	

[a] Redistilled product. [b] Temperature range over which redistilled product was collected. [c] Lit. *(2)* bp 62–64°C/9mm.

Literature Cited

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