gestive of uvaol [lit. (5) mp 222–224°]. The diacetate had a melting point of 151–152° [lit. (6) mp 150–151°]. An authentic specimen of uvaol, prepared by the lithium aluminum hydride reduction of methyl ursolate (7), had a melting point of 223–224°, which was undepressed upon admixture with the sample from *V. corymbosa*.

Anal.—Calc. for $C_{30}H_{50}O_2$: C, 81.38; H, 11.38. Found: C, 81.51; H, 11.67.

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Preparation of Tri- and Tetramethyleneisoxazoles

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Abstract □ The syntheses of several tri- and tetramethyleneisoxazoles resulting from the condensation of C(α)O-dilithioximes with esters, followed by acid cyclization, are described.

Keyphrases □ Isoxazoles, tri- and tetramethylene—synthesized by condensation of 1,4-dianions with esters followed by acid cyclization □ Tri- and tetramethyleneisoxazoles—synthesized by condensation of 1,4-dianions with esters followed by acid cyclization

The preparation of various trimethyleneisoxazoles and tetramethyleneisoxazoles was accomplished by the condensation of the 1,4-dianions of cyclopentanone and cyclohexanone oximes with several esters.

DISCUSSION

One major use of isoxazoles and their derivatives is in the preparation of various pharmacologically important agents. These isoxazoles are prepared by synthetic routes which give more than one isomeric product, and separation of these materials can be difficult. Until the initial report on the preparation of unsymmetrical 3,5-disubstituted isoxazoles from the 1,4-dianions of aromatic oximes containing an α-hydrogen atom (1), no fundamentally new synthetic routes appeared (2).

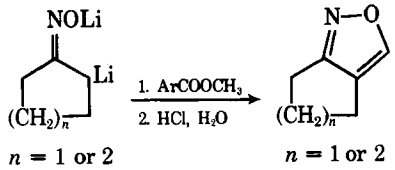
For example, the most widely applicable method for the preparation of the isoxazole ring system is by the reaction of hydroxylamine with a 1,3-dicarbonyl compound (3); since two bonds are being formed to close the heterocyclic ring, two isomers (A and B) are formed.

A: one bond formed

B: two bonds formed

This investigation focused on the preparation of tri- and tetramethyleneisoxazoles. The literature indicates that these materials can be obtained from the 1,3-dicarbonyl compounds, benzoylcyclopentanone and benzoylcyclohexanone, which are not common reagents and are difficult to prepare (4). In addition, two products are possible; they were isolated and characterized previously.

This report deals with the preparation of these isoxazoles by the condensation of the 1,4-dianions of cyclopentanone and cyclohexanone oximes with esters such as methyl nicotinate, methyl furoate, and methyl anisate (Scheme I). The precyclization intermediate was not isolated.



$n = 1$ or 2 $\qquad$ $n = 1$ or 2

Scheme I

All atoms of the heterocyclic ring are in position prior to cyclization, and the cyclization involves the formation of only one bond, which means only one isomer is formed and not a mixture of isomers. Table I gives the analytical and absorption spectral data for new material.

The syntheses described for the preparation of these isoxazoles have several advantages over other methods (2, 3, 5). The experimental procedure is efficient and requires the use of readily available starting materials; it is an unequivocal method for the preparation of a single isomer of unsymmetrically substituted isoxazoles.

EXPERIMENTAL

To a stirred solution of 0.025 mole of oxime in 100 ml of tetrahydrofuran, which was cooled to 0° under a nitrogen atmosphere, was added 0.05 mole of 1.6 *M* *n*-butyllithium[1] during 5 min. The mixture was stirred for 45 min and condensed with a 0.0125-mole sample of ester dissolved in 50–75 ml of tetrahydrofuran. After stirring for 15–30 min at 0°, the mixture was neutralized with 100 ml of 3 *N* hydrochloric acid.

The entire mixture was heated, with good stirring, under reflux for 1 hr and cooled; the phases separated. The aqueous layer was neutralized with sodium bicarbonate and extracted with three 75-ml portions of ether. The combined organic extracts were dried over

[1] Lithium Corporation of America, Bessemer City, N.C.

Table I—Tri- and Tetramethyleneisoxazoles[a]

Compound	Substitution	Empirical Formula	Yield, %	Melting Point[b]
I	5-(*p*-Methoxyphenyl)-3,4-tetramethylene	$C_{14}H_{15}NO_2$ [a,c,d]	30	78–79.5°
II	5-Phenyl-3,4-tetramethylene	$C_{13}H_{13}NO$	30	65–67°[e]
III	5-(*p*-Tolyl)-3,4-tetramethylene	$C_{14}H_{15}NO$	64	93–95°[f]
IV	5-(*p*-Chlorophenyl)-3,4-tetramethylene	$C_{13}H_{12}ClNO$	66	135–138°[g]
V	5-(*m*-Tolyl)-3,4-tetramethylene	$C_{14}H_{15}NO$[d,h]	29	44.5–45.5°
VI	5-(*m*-Chlorophenyl)-3,4-tetramethylene	$C_{13}H_{12}ClNO$[f]	46	53–55°[d,i]
VII	5-Phenyl-3,4-trimethylene	$C_{12}H_{11}NO$	74	104–106°[j]
VIII	5-(*p*-Chlorophenyl)-3,4-trimethylene	$C_{12}H_{10}ClNO$	29	139–140°[k]
IX	5-(*p*-Methoxyphenyl)-3,4-trimethylene	$C_{13}H_{13}NO_2$[i]	29	91–94°[d,l]
X	5-(*m*-Tolyl)-3,4-trimethylene	$C_{13}H_{13}NO$[j]	20	55–65°[d,m]
XI	5-(Nicotinyl)-3,4-tetramethylene	$C_{12}H_{12}N_2O$[k]	26	111–113°[d,n]
XII	5-(2-Furanyl)-3,4-tetramethylene	$C_{11}H_{11}NO_2$[l]	47	73–74°[d,o]

[a] The IR spectra of I–XII are consistent with the proposed structure. One or two absorption bands were noted between 6.03 and 6.29 μm (2, 6), which could be assigned to the unsaturated nitrogen stretching vibration and the aromatic moiety at position 5. [b] Melting points were taken on samples in open capillary tubes in a Thomas Hoover melting-point apparatus. [c] Calc. for: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.41; H, 6.78; N, 6.05. NMR ($CDCl_3$): δ 1.58–2.00 and 2.50–4.58 [m, 8H, $(CH_2)_4$], 3.80 (s, 3H, OCH_3), and 6.87–7.72 (m, 4H, ArH). [d] Combustion analyses were performed by Robertson Laboratory, Florham Park, N.J. NMR spectra were obtained from a Varian Associates A-60 NMR spectrometer, and chemical shifts are reported in parts per million (ppm) downfield from an internal tetramethylsilane standard. IR spectra were obtained from a Perkin-Elmer 700 spectrometer using sodium chloride cells (0.1 mm). [e] Lit. (4) mp 67°. [f] Lit. (4) mp 95°. [g] Lit. (4) mp 137°. [h] Calc. for: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.63; H, 7.15; N, 6.34. NMR ($CDCl_3$): δ 1.60–197 and 2.58–2.77 [m, 8H, $(CH_2)_4$], 2.38 (s, 3H, $ArCH_3$), and 7.02–7.63 (m, 4H, ArH). [i] Calc. for: C, 66.82; H, 5.18; N, 5.95. Found: C, 66.58; H, 5.28; N, 5.86. NMR ($CDCl_3$): δ 1.67–1.93 and 2.60–2.88 [m, 8H, $(CH_2)_4$] and 7.25–7.73 (m, 3H, ArH). [j] Lit. (4) mp 108–109°. [k] Lit. (4) mp 140°. [l] Calc. for: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.25; H, 6.21; N, 6.25. NMR ($CDCl_3$): δ 2.58–2.79 [m, 6H, $(CH_2)_3$], 3.82 (s, 3H, OCH_3), and 6.85–7.68 (m, 4H, ArH). [m] Calc. for: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.14; H, 6.77; N, 6.76. NMR ($CDCl_3$): δ 2.33 (s, 3H, $ArCH_3$), 2.42–2.95 [m, 6H, $(CH_2)_3$], and 6.93–7.35 (m, 4H, ArH). [n] Calc. for: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.77; H, 6.17; N, 13.78. IR ($CHCl_3$): 6.10 (C=N) and 6.23 (C_5H_5N) μm. [o] Calc. for: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.03; H, 6.16; N, 7.11. IR (CCl_4): 6.03 (C=N) μm.

anhydrous magnesium sulfate, filtered, and concentrated; the compounds were recrystallized from 95% ethanol.

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