Vinyl Derivatives of Heterocyclic Systems and their Polymers: Isoxazole Derivatives

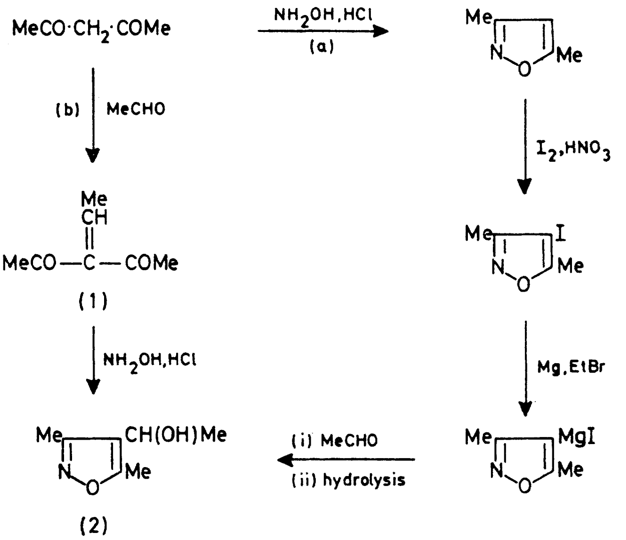
By **Vincenzo Bertini,* Angela De Munno, and Marco Pocci,** Istituto di Chimica Organica della Facoltà di Scienze, Via Risorgimento 35, 56100 Pisa, Italy

3,5-Dimethyl-4-vinylisoxazole (3) has been prepared from pentane-2,4-dione by way of 1-(3,5-dimethylisoxazol-4-yl)ethanol (2) by two different methods, one of which gives an overall yield greater than 75%. Compound (3), in the presence of radical initiators, is transformed into polymers with pendant isoxazole rings.

PREVIOUS work in this field has been concerned with 3,5-dimethyl-4-vinylisoxazole,[1] 5-vinylisoxazole,[2] 3-vinyl-1,2,5-thiadiazole,[3] and their polymers and copolymers. The monomers afford macromolecular products with pendant heterocycles, susceptible to reducing or nucleophilic agents, and easily convertible by such reagents into polyfunctional systems containing groups such as amine, imine, carbonyl, and nitrile.[4] The polyfunctional macromolecules show high reactivity (see for instance the intramolecular formation of new rings [5]) and appear useful for the preparation of metal complexes of potential interest in the field of supported catalysis. 3,5-Dimethyl-4-vinylisoxazole (3) appeared particularly promising as a consequence of its ready formation of polymers and then of poly-iminocarbonyl systems by catalytic hydrogenation, and of the stability towards bases of the isoxazole ring, which could permit stereoregular polymerization by anionic initiators.

Our previous synthesis of compound (3) [1] has been reconsidered and a new route, more suitable for preparative purposes, has been devised. We report here the details of both routes and some preliminary information on the radical polymerization of the product.

In both syntheses pentane-2,4-dione was converted into 1-(3,5-dimethylisoxazol-4-yl)ethanol (2). In the first procedure the dione was transformed into 3,5-dimethylisoxazole by hydroxylamine hydrochloride, then into 4-iodo-3,5-dimethylisoxazole [6] by iodine and concentrated nitric acid, then into 3,5-dimethylisoxazol-4-ylmagnesium iodide [7] by magnesium and ethyl bromide, and finally into the isoxazolylethanol (2) by treatment with acetaldehyde and subsequent hydrolysis [Scheme 1, path (a)] (overall yield 31% from the dione). The production of the alcohol (2) was accompanied by the formation of bis-1-(3,5-dimethylisoxazol-4-yl)ethyl ether (4), in a proportion dependent on the hydrolysis conditions (see Experimental section). In the second procedure, recommended for preparative purposes, the dione was condensed with acetaldehyde to give the ethylidene derivative (1), which was cyclised with hydroxylamine hydrochloride [overall yield 90%; Scheme 1, path (b)].



SCHEME 1

For the condensation of pentane-2,4-dione with acetaldehyde known methods were re-examined and new ones devised. The method of Wilson [8] (absence of solvent and catalyst at room temperature) in our hands was ineffectual. The Knoevenagel method as modified by McEntee *et al.*,[9] carried out by us with a 0.14N-solution of hydrogen chloride in chloroform at 45 °C for 20 h, gave yields greater than 85%. However heating a mixture of dione and acetaldehyde without solvent in the presence of dry, finely powdered, colourless dehydrating silica gel (see Experimental section) gave the product in 91% yield, and 95% yield was achieved by treating the mixture of the reagents with hydrogen chloride in chloroform in the presence of finely powdered dehydrating silica gel.

Compound (1), described in the literature as an oil, was obtained pure by our methods and it was easily converted into white crystals. We did not investigate the mode of action of the silica gel. Other heterogeneous agents (Schuchardt molecular sieves type 5 A

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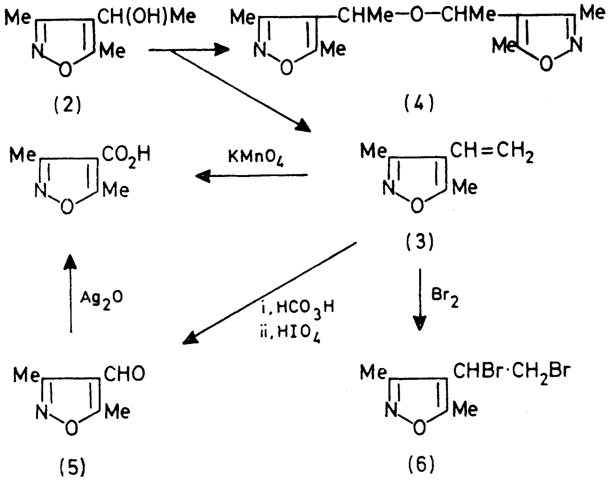
or column chromatography silica gel) used in place of dehydrating silica gel without solvent slowly yielded 4,6-diacetyl-3-hydroxy-3,5-dimethylcyclohexanone, the same product as obtained[10] by treating pentane-2,4-dione with acetaldehyde in presence of piperidine.

The cyclization of compound (1) with hydroxylamine hydrochloride was carried out in acidic aqueous solution at various temperatures. In each case an easily separable mixture of compound (2) with a small amount of the ether (4) was obtained. High temperatures favoured the production of compound (4) and low temperatures that of compound (2). At room temperature good yields of (2) were obtained [95% of (2), 4% of (4)] without depressing the reaction rate too much. Attempts to bring about reaction in neutral or alkaline aqueous solution yielded an oily product, distillable with difficulty, and not investigated further.



SCHEME 2

Compound (2) was purified by the usual methods of distillation and crystallization; however as a recovery procedure the formation of a complex with cadmium chloride could be employed. Compound (2) yields a white precipitate with a saturated aqueous solution of cadmium chloride. The precipitate releases compound (2) when the aqueous suspension is extracted with diisopropyl ether at 40—50 °C.

Dehydration of the alcohol (2) afforded 3,5-dimethyl-4-vinylisoxazole (3) and the ether derivative (4) (Scheme 2). The best method for obtaining the ether (4) involved heating in the presence of aqueous hydrogen chloride. Satisfactory preparations of the vinyl derivative (3) were achieved (i) by refluxing (2) in benzene solution in the presence of phosphorus pentaoxide (yield 84%); (ii) by heating (2) in benzene solution in the presence of toluene-*p*-sulphonic acid (yield 68%); and (iii) by distillation of (2) over potassium hydrogen sulphate (yield 70%). For purity of the product and brevity of the process, method (iii) is recommended. Compound (3) of high purity, as required for polymerization reactions, was obtained by refluxing over potassium hydroxide pellets and distillation.

New products were identified by elemental analyses and i.r. and n.m.r. spectra; several reactions confirmed their molecular structures. Compounds (2) and (4) were transformed into the same ester by treatment with 3,5-dinitrobenzoyl chloride. Compound (3) was (i) oxidized with potassium permanganate to 3,5-dimethylisoxazole-4-carboxylic acid,[11] (ii) converted into 3,5-dimethylisoxazole-4-carbaldehyde (5)[12] by reaction with performic acid then with periodic acid, and (iii) brominated to give 4-(1,2-dibromoethyl)-3,5-dimethylisoxazole (6) (Scheme 2). Compound (3) forms insoluble crystalline complexes with several heavy metal salts, including cadmium chloride; the cadmium chloride complex, in contrast to the analogous complex of compound (2), releases the progenitor (3) only with difficulty.

The aldehyde (5) was oxidized to the acid by silver oxide in water, and was transformed into several crystalline derivatives (see Experimental section). The n.m.r. spectrum of the dibromide (6) showed non-equivalence of the methylene protons, as in the case of 1,2-dibromo-1-phenylethane.[13]

With regard to the radical polymerization of (3), this compound spontaneously polymerizes slowly at room temperature without stabilizers, or on heating, or on addition of ether not freed from peroxides. Polymerization, in solution or in bulk, in the presence of 2,2′-azobis-(2-methylpropionitrile), yielded polymers soluble in butan-2-one and in methylene chloride; i.r. spectra showed that these contained 3,5-dimethylisoxazole systems.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus, or for samples in sealed capillary tubes. I.r. spectra were recorded with a Perkin-Elmer 225 spectrophotometer, n.m.r. spectra with a JEOL 100 MHz instrument (Me_4Si as internal standard), and u.v. spectra with a Hilger-Watts Uvispek H700 apparatus. Mass spectra were recorded with a Varian MAT CH5 spectrometer, operating at 70 eV.

Condensation between Pentane-2,4-dione and Acetaldehyde.—(a) *In the presence of dehydrating silica gel.* A mixture of pentane-2,4-dione (10.00 g, 99.88 mmol) and acetaldehyde (8.01 g, 0.18 mol) was treated with colourless dehydrating silica gel (6.66 g) previously powdered, sieved (150—230 mesh), and heated at 120 °C for 10 h. The mixture was shaken in a sealed Pyrex tube at 55 °C for 200 h, then the silica gel was filtered off and extracted with ether. The liquid phase, combined with the extract, was evaporated and the residue was distilled at reduced pressure. At 68—70° and 1.5 Torr 3-acetylpent-3-en-2-one (1) was obtained (11.49 g, 91.08 mmol) which after crystallization from ether at −30 °C (m.p. 25°) showed i.r. and n.m.r. spectra as reported.[14]

(b) *In the presence of anhydrous hydrogen chloride and*

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dehydrating silica gel in chloroform. A mixture of pentane-2,4-dione (10.00 g, 99.88 mmol), acetaldehyde (8.94 g, 0.203 mol), and dehydrating silica gel (10.00 g) prepared as described in method (a), was added to a 0.14N-solution (100 ml) of hydrogen chloride in chloroform prepared by bubbling the dry gas into the anhydrous solvent. The mixture was stirred in a stoppered flask for 20 h at 45 °C. The liquid phase was washed with aqueous 10% w/w sodium hydrogen carbonate then with water, dried (Na_2SO_4), and evaporated, and the residue was distilled as described in method (a) to give 3-acetylpent-3-en-2-one (1) (11.98 g, 94.96 mmol).

(c) *In the presence of molecular sieves or chromatographic silica gel.* A mixture of pentane-2,4-dione (4.00 g, 39.95 mmol), acetaldehyde (1.30 g, 29.51 mmol), and Schuchardt sieves type 5 A (0.75 g) previously heated at 140 °C for 10 h at 0.01 Torr, was kept for 4 months in a sealed Pyrex tube with occasional shaking. The white precipitate, separated from molecular sieves by flotation with ether, filtered off, and washed with the same solvent, yielded 4,6-diacetyl-3-hydroxy-3,5-dimethylcyclohexanone (1.34 g, 5.92 mmol), m.p. 101—105°. The product, after crystallization from ethanol (m.p. 107—108°), showed i.r. and n.m.r. spectra identical with those of an authentic sample.[10] Analogous results were obtained with 10.00 g of dione and 6.66 g of column chromatographic Merck silica gel (65—250 mesh) heated at 120 °C for 10 h.

1-(3,5-*Dimethylisoxazol*-4-*yl*)*ethanol* (2).—(a) *By cyclization of* 3-*acetylpent*-3-*en*-2-*one*. The ketone (1) (20.00 g, 158.5 mmol) was added to a solution of hydroxylamine hydrochloride (16.6 g, 238.9 mmol) in water (70 ml) during *ca.* 5 min and the mixture was stirred at 20 °C for 40 h. White crystals of bis-1-(3,5-dimethylisoxazol-4-yl)ethyl ether (4) were filtered off, washed with water, and dried at reduced pressure over phosphorus pentaoxide [yield 0.853 g, 3.23 mmol; m.p. 142—144° (145° after crystallization from n-heptane)]. The liquid phase was neutralized with solid potassium carbonate, made alkaline with potassium hydroxide pellets, extracted with ether in a separatory funnel and then in a continuous extractor. The extracts were combined, dried (Na_2SO_4), and evaporated; distillation of the residue at 74° and 0.02 Torr gave the *alcohol* (2) (21.35 g, 151.2 mmol), which was further purified by crystallization from ether at low temperature; m.p. 32—34°; n_D^{25} 1.4770; $\lambda_{max.}$(H_2O) 220 nm (log ε 3.72); $\nu_{max.}$ (melt) 3 398 (OH), 1 082 (C–O), 1 632, 1 493, 1 446, 1 423, and 1 013 cm^{-1} (ring); δ(CCl_4) 1.37 (3 H, d, *J* 7 Hz, MeC·O), 2.13 (3 H, s, 3-Me), 2.30 (3 H, s, 5-Me), 3.95 (1 H, s, OH), and 4.66 (1 H, q, *J* 7 Hz, CH); *m/e* 141 (18%, M^+), 126 (100, $M^+ - CH_3$), 123 (11, $M^+ - H_2O$), and 43 (27%, $CH_3-C\equiv O^+$) (Found: C, 5.95; H, 7.85; N, 9.85. $C_7H_{11}NO_2$ requires C, 5.95; H, 7.85; N, 9.9%).

A sample of the alcohol (2), after heating for 30 min on a water-bath with 3,5-dinitrobenzoyl chloride, was treated with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ether, and the extracts were dried (Na_2SO_4) and evaporated. The residue gave the *dinitrobenzoate* (60%), m.p. (from methanol) 142—143° (Found: C, 50.0; H, 4.0; N, 12.7. $C_{14}H_{13}N_3O_7$ requires C, 50.15; H, 3.9; N, 12.55%).

(b) *By Grignard reagent.* (3,5-Dimethylisoxazol-4-yl)-magnesium iodide in ether [prepared[7] from magnesium (5.71 g, 234.9 mmol), ethyl bromide (18.01 g, 165.2 mmol), and 4-iodo-3,5-dimethylisoxazole (16.61 g, 74.48 mmol)] was treated dropwise with acetaldehyde (10.93 g, 248.1 mmol) and stirred at room temperature for 1 h. The mixture was hydrolysed with a small quantity of iced water and extracted with ether; the extract was dried (Na_2SO_4) and evaporated and the residue distilled at reduced pressure. Compound (2) was collected at 78—80° and 0.04 Torr (5.47 g, 38.75 mmol). Repetition of the reaction, but with hydrolysis of the mixture in the presence of hydrogen chloride, yielded an undistillable solid residue which, after decolourization with carbon in benzene solution and crystallization from iso-octane, gave the ether (4) (3.74 g, 14.15 mmol), m.p. 145°, identical (i.r. spectrum) with the compound obtained from pure (2) by heating with hydrogen chloride.

Bis-1-(3,5-*dimethylisoxazol*-4-*yl*)*ethyl Ether* (4).—A mixture of the alcohol (2) (0.50 g, 3.54 mmol) and 5.45N-hydrochloric acid (5 ml) was heated at 55 °C for 30 h with stirring, then made alkaline with saturated aqueous potassium carbonate and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated by distillation; cooling yielded the *ether* (4) (0.253 g, 0.96 mmol), m.p. (from n-heptane) 145°; $\nu_{max.}$(KBr) 1 080 (C–O), 1 638, 1 493, 1 447, 1 424, and 1 012 cm^{-1} (ring); δ($CDCl_3$) 1.36 (3 H, d, *J* 6.3 Hz, MeC·O), 2.19 (6 H, s, 3- and 3′-Me), 2.20 (6 H, s, 5- and 5′-Me), and 4.10 (1 H, q, *J* 6.3 Hz, CH); *m/e* 264 (19%, $R-O-R^+$), 124 (100, R^+), and 43 (98, $CH_3-C\equiv O^+$); $\lambda_{max.}$ (iso-octane) 216 nm (log ε 3.89) (Found: C, 63.7; H, 7.6; N, 10.75. $C_{14}H_{20}N_2O_3$ requires C, 63.6; H, 7.65; N, 10.6%).

Heating the ether (4) with 3,5-dinitrobenzoyl chloride and zinc chloride, yielded, after making alkaline, extraction, and purification, a dinitrobenzoate identical with the derivative obtained from compound (2) (mixed m.p. 142—143°).

3,5-*Dimethyl*-4-*vinylisoxazole* (3).—(a) *By dehydration of the alcohol* (2) *with potassium hydrogen sulphate.* The alcohol (2) (10.00 g, 70.84 mmol) and potassium hydrogen sulphate (20 g), heated at 120—130° and 15 Torr for 40 min, gave a two-phase distillate. The organic layer was 3,5-*dimethyl*-4-*vinylisoxazole* (3), separated after solidification of the aqueous phase by cooling at −20°; yield 6.09 g (49.45 mmol). Compound (3) was purified by refluxing and distillation over potassium hydroxide pellets, then by distillation from a fractionating column under nitrogen; b.p. 44° at 0.15 Torr; m.p. −26 to −25°; n_D^{24} 1.4894; $\lambda_{max.}$ (iso-octane) 230 nm (log ε 4.07); $\nu_{max.}$ (film) 3 096, 3 012, 1 631, 1 410, 988, 902 (vinyl), 1 654, 1 496, 1 452, 1 435, and 1 012 cm^{-1} (ring); δ(CCl_4) 2.19 (3 H, s, 3-Me), 2.27 (3 H, s, 5-Me), 5.14 (1 H, q, H_{cis} of vinylic CH_2), 5.29 (1 H, q, H_{trans} of vinylic CH_2), and 6.28 (1 H, q, CH); J_{gem} 1.5, J_{trans} 18.2, J_{cis} 11.4 Hz; *m/e* 123 (100%, M^+), 80 (34, $M^+ - CH_3 - CO$), and 43 (62, $CH_3-C\equiv O^+$) (Found: C, 68.45; H, 7.45; N, 11.35. C_7H_9NO requires C, 68.25; H, 7.35; N, 11.35%).

(b) *By dehydration of the alcohol* (2) *with phosphorus pentaoxide.* A solution of the alcohol (3.70 g, 26.21 mmol) in dry benzene (200 ml) was added to phosphorus pentaoxide (15.2 g) and refluxed for 2 days with stirring. The organic layer was evaporated and the residue distilled at reduced pressure to give compound (3), b.p. 54° at 0.7 Torr (2.72 g, 22.09 mmol).

(c) *By dehydration of the alcohol* (2) *with toluene*-p-*sulphonic acid.* A mixture of the alcohol (2) (5.00 g, 35.42 mmol) and toluene-p-sulphonic acid (6.00 g) in dry benzene (150 ml) was refluxed for 1 day with stirring, then neutralized with aqueous 2N-sodium hydroxide. The organic phase, treated as described under (b) yielded compound (3) (2.96 g, 24.03 mmol).

Oxidation of Compound (3) *to the* 4-*Carboxylic Acid.*—Compound (3) (0.07 g, 0.57 mmol) was treated at room temperature with aqueous 0.066M-potassium permanganate until the colour persisted, then the solution was filtered. The filtrate was acidified with 1 : 1 sulphuric acid, and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated at reduced pressure, yielding 3,5-dimethylisoxazole-4-carboxylic acid (0.059 g, 0.42 mmol), m.p. (after sublimation) at 141—142° (lit.,[11] 142°).

3,5-*Dimethylisoxazole*-4-*carbaldehyde* (5).—Compound (3) (3.66 g, 29.72 mmol) was treated with 99% formic acid (35 ml) and 36% hydrogen peroxide (2.90 g) and stirred at 40 °C for 24 h. The mixture was added to a solution of periodic acid dihydrate (6.91 g) in water (51 ml), stirred for 2 h at room temperature, made alkaline with solid sodium hydrogen carbonate (to pH 10) and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated; distillation of the residue at 58—60° and 0.12 Torr afforded the crude *aldehyde* (5) (2.52 g, 20.14 mmol). Further distillation and crystallization from ether at low temperature gave white crystals, m.p. 37—38°; $\nu_{max.}$ (melt) 2 845, 2 745 (aldehyde CH), 1 688 (C=O), 1 600, 1 504, 1 452, 1 428, and 1 013 cm^{-1} (ring); δ(CCl_4) 2.41 (3 H, s, 3-Me), 2.67 (3 H, s, 5-Me), and 9.88 (1 H, s, CHO) (Found: C, 57.7; H, 5.75; N, 11.2. $C_6H_7NO_2$ requires C, 57.6; H, 5.65; N, 11.2%). The semicarbazone had m.p. (from ethanol) 222—223° (lit.,[12] 243°); the oxime had m.p. (after sublimation) 150—151° (lit.,[12] 156°); the phenylhydrazone had m.p. (from ethanol) 155—160° (decomp.); and the *p*-nitrophenylhydrazone had m.p. (from glacial acetic acid) 261° (decomp.).

The aldehyde (5) (0.05 g, 0.40 mmol) was treated with silver oxide [from silver nitrate (0.3 g) and sodium hydroxide (0.162 g) in water (1.5 ml)]. The mixture was heated for 2 h at 50 °C with stirring, filtered, acidified with 1 : 1 aqueous nitric acid, and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated, yielded 3,5-dimethylisoxazole-4-carboxylic acid (0.051 g, 0.36 mmol), m.p. 141° (from petroleum), identical (i.r. spectrum) with the compound obtained from oxidation of (3).

(±)-4-(1,2-*Dibromoethyl*)-3,5-*dimethylisoxazole* (6).—Compound (3) (0.51 g, 4.14 mmol) cooled in iced water was treated dropwise with bromine (1.05 g, 6.57 mmol). The resulting red oily mixture was distilled at reduced pressure (81—83° at 0.02 Torr) to give the *dibromide* (6) (0.84 g, 2.97 mmol), which slowly solidified. The solid, after crystallization from ether at low temperature and sublimation at 50° and 0.003 Torr, melted at 52—54°; $\nu_{max.}$ (melt) 1 625, 1 498, 1 444, 1 422 and 1 010 (ring), and 590 cm^{-1} (C–Br); δ(CCl_4) 2.31 (3 H, s, 3-Me), 2.42 (3 H, s, 5-Me), 3.94 (2 H, m, CH_2), and 5.01 (1 H, q, CH) (Found: C, 29.85; H, 3.2; Br, 56.5; N, 5.1. $C_7H_9Br_2NO$ requires C, 29.7; H, 3.2; Br, 56.5; N, 4.95%).

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