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The syntheses of new tris (XII) and tetraoxazole compounds (XIII and XIV) are reported; all synthons have been described. New isoxazole chlorooximes (V and VIII) have been prepared for this purpose and their behavior was examined.

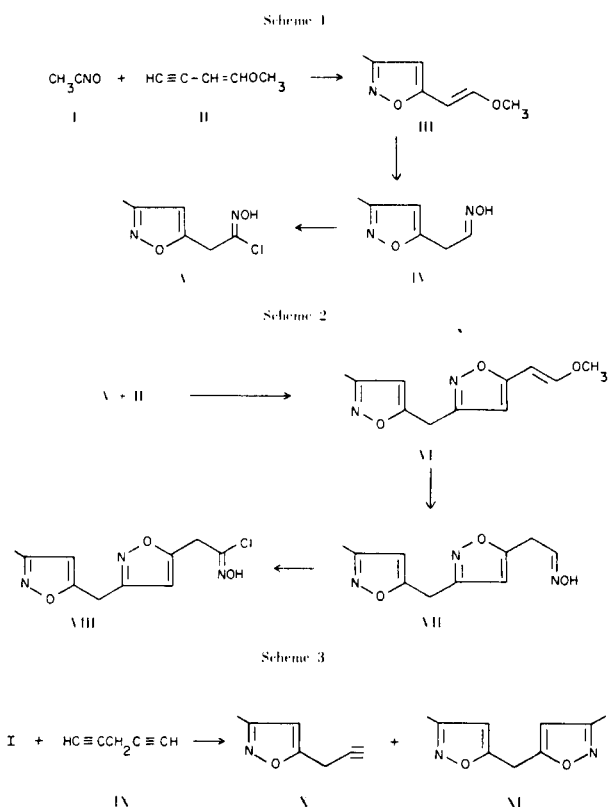
J. Heterocyclic Chem., 14, 667 (1977).

We have been long since interested in the synthesis of methylene polyisoxazoles (1), the isoxazole ring being considered as a masked β -diketonic system capable of being transformed into a β -diketone (2). In particular, hydrogenolysis of isoxazole rings linked through methylene bridges between position 3 and 5 may supply imino derivatives of linear β -polyketones. These are of great interest in view of the variety of products they can give by subsequent cyclisation (3).

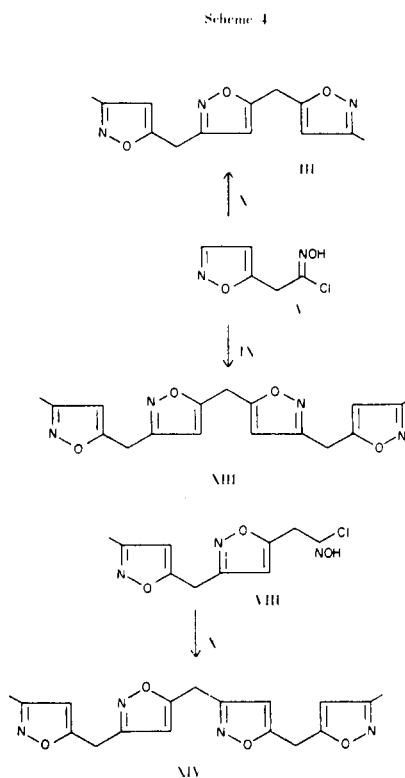
Here we wish to report the synthesis of methylene polyisoxazoles, with three and four rings. The synthons V, VIII and X (4), which may be differently combined to prepare the desired polyisoxazoles were obtained as shown in Schemes 1, 2 and 3.

amine, even *in situ*; the reaction between V and II, and those of Scheme 4, were carried out by heating the reagents in an inert solvent. In this case fairly good yields are obtained. The conditions for the hydrolysis of the enoethers III and VI and for their reaction with hydroxylamine have been carefully selected, so that the yields are optimized.

By appropriate combination of VIII, IX and X, many-membered methylene polyisoxazole chains can be obtained. Scheme 4 shows the synthesis of a methylene triisoxazole XII (5) and of two isomeric methylene tetraoxazoles XIII and XIV.



The chlorooxime V was prepared *via* the methoxyvinylisoxazole III (Scheme 1), in its turn easily obtained by the well-known reaction of a nitrile oxide with an acetylenic compound, *viz.* II. As, however, isoxazole chlorooximes do not react satisfactorily with acetylenic compounds if the nitrile oxide is evolved with triethyl-



Work is in progress to extend the scope of the reaction, particularly to the synthesis of methylene polyisoxazoles with a higher number of rings.

EXPERIMENTAL

All melting points are uncorrected. Nuclear magnetic resonance spectra were determined with a Varian Associates model A60 spectrometer. Chemical shifts in δ ppm were measured with

tetramethylsilane as the internal standard. Mass spectra were taken on a "Hitachi-Perkin-Elmer" RMU 6D single focusing spectrometer.

3-Methyl-5-(2'-methoxyvinyl)isoxazole (III).

Triethylamine (66.5 g.) was added under stirring at 0° to a mixture of acetalchlorooxime (42 g.) and 1-methoxy-1-buten-3-yne (200 ml.). The mixture was allowed to stand overnight at 0°, treated with water and extracted with ether. The extract was dried over sodium sulphate, and the solvent evaporated, yield 70% of III, b.p. 90° (3 mm Hg); nmr (deuteriochloroform) δ ppm: 5.73 (1H) s; 5.60 (1H) s; 4.78 (1H) d; 3.13 (3H) s; 1.57 (3H) s.

Anal. Calcd. for $C_7H_9O_2N$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.31; H, 6.48; N, 10.02.

Oxime of 3-Methylisoxazolyl-5-acetaldehyde (IV).

Isloxazole III (17 g.) was added to a 0.16N solution of hydrochloric acid (300 ml.). The mixture was refluxed for 1 hour and a solution of hydroxylamine (12 g.) was added. After cooling ether extraction was performed. The extract was dried over sodium sulphate and the solvent evaporated. Eleven g. (70%) of IV were obtained, b.p. 126° (1 mm Hg); nmr (deuteriochloroform) δ ppm: 7.54, 6.94 (1H) t (Z and E forms); 6.0 (1H) s; 3.85, 3.65 (2H) d (Z and E forms); 2.28 (3H) s; MS: m/e 140 (M^+ , 43); 122 (21); 97 (30); 82 (100); 54 (61).

Anal. Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.21; H, 5.71; N, 19.92.

Chlorooxime of 3-Methylisoxazolyl-5-acetaldehyde (V).

Chlorine was bubbled through a solution of 10 g. of IV in distilled ether (200 ml.) until the solution was saturated. Removal of the ether in the cold gave a solid product, yield 80%; nmr (deuteriochloroform) δ ppm: 6.10 (1H) s; 3.94 (2H) s; 2.28 (3H) s; m.p. 72° from hexane.

3-Methyl-5'-(2''-methoxyvinyl)-5,3'-diisoxazolymethane (VI).

A mixture of V (7 g.) and 1-methoxy-1-buten-3-yne (10 g.) dissolved in toluene (200 ml.) was refluxed in a nitrogen stream until no more hydrogen chloride was evolved. The solvent was evaporated and the residual oil was subjected to chromatography on silica gel with chloroform, yield 25%; nmr (deuteriochloroform) δ ppm: 6.38 (1H) s; 6.37 (1H) d; 5.97 (1H) s; 5.47 (1H) s; 4.12 (2H) s; 3.87 (3H) s; 2.27 (3H) s.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.85; H, 5.45; N, 12.69.

Oxime of 3-Methyl-5'-formylmethyl-5,3'-diisoxazolymethane (VII).

Compound VI (4 g.) was added to a solution of 90 ml. of 0.16N hydrochloric acid. The mixture was refluxed for 1 hour; a solution of hydroxylamine (3 g.) was added. After cooling ether extraction was performed. The extract was dried on sodium sulphate and the solvent was evaporated, the crude oil was subjected to chromatography on silica gel with chloroform, yield 22%, m.p. 88°, from hexane; nmr (deuteriochloroform) δ ppm: 7.53, 6.92 (1H) t (Z and E forms); 6.15 (1H) s; 4.13 (2H) s; 3.88, 3.68 (2H) d (Z and E forms); 2.25 (3H) s; MS: m/e 221 (M^+ 100); 178 (83); 122 (21); 96 (87); 82 (37).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.08; H, 4.96; N, 18.95.

Chlorooxime of 3-Methyl-5'-formylmethyl-5,3'-diisoxazolymethane (VIII).

Chlorine was bubbled through a solution of 1 g. of VII in distilled ether (40 ml.) until the solution was saturated. Removal of the ether in the cold gave 0.8 g. of crude VIII, yield 70%;

nmr (deuteriochloroform) δ ppm: 6.27 (1H) s; 6.02 (1H) s; 4.15 (2H) s; 4.01 (2H) s; 2.27 (3H) s.

3-Methyl-5-(2'-propynyl)isoxazole (X).

Freshly distilled triethylamine (44 ml.) was added slowly under stirring at 0° to a mixture of acetalchlorooxime (29 g.) and 1,4-pentadiyne (190 g. of a 10% solution in THF). The mixture was allowed to stand overnight at 0°. Water was added and ether extraction was performed. After drying over sodium sulphate and evaporation of the solvent, an oil is obtained, which is fractionally distilled to give X, b.p. 38° at 2 mm Hg, yield 30%; nmr (deuteriochloroform) δ ppm: 6.07 (1H) s; 3.68 (2H) d; 2.48 (1H) t; 2.17 (3H) s.

Anal. Calcd. for C_7H_7NO : C, 69.40; H, 5.83; N, 11.56. Found: C, 69.25; H, 5.79; N, 11.51.

3-[(3-Methyl-5-isoxazolyl)methyl]-5-[(3-methyl-5-isoxazolyl)methyl]isoxazole (XII).

A mixture of V (6.15 g.) and X (4.32 g.) dissolved in toluene (200 ml.) was refluxed in a nitrogen stream until no more hydrogen chloride was evolved. The mixture was filtered and the solvent evaporated. Crystallization from hexane gave needles, m.p. 89°, yield 40%; nmr (deuteriochloroform) δ ppm: 6.11 (1H) s; 5.98 (1H) s; 5.94 (1H) s; 4.21 (2H) s; 4.12 (2H) s; 2.28 (6H) s; MS: m/e 259 (6); 122 (100); 96 (61); 82 (36); 67 (32).

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.10; H, 5.04; N, 16.31.

Bis[3-(3-Methyl-5-isoxazolyl)methyl-5-isoxazolyl]methane (XIII).

A mixture of V (1 g.) and IX (0.3 g.) dissolved in toluene (100 ml.), was refluxed in a nitrogen stream until no more hydrochloric acid developed. The mixture was filtered and the solvent evaporated, yield 30% of XIII was obtained, m.p. 123° from methanol; nmr (deuteriochloroform) δ ppm: 6.32 (1H) s; 5.98 (1H) s; 4.50 (2H) s; 4.13 (4H) s; 2.28 (6H) s; MS: m/e 340 (M^+); 259 (2); 136 (10); 122 (100); 96 (75).

Anal. Calcd. for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 59.90; H, 4.70; N, 16.42.

[3-(3-Methyl-5-isoxazolyl)methyl-5-isoxazolyl][5-(3-methyl-5-isoxazolyl)methyl-3-isoxazolyl]methane (XIV).

A mixture of VIII (1 g.) and X (0.5 g.) dissolved in toluene (100 ml.), was refluxed in a nitrogen stream until no more hydrogen chloride was evolved. The mixture was filtered and the solvent evaporated. Chromatography of the crude oil gave XIV (yield 25%), crystallized from methanol m.p. 114°; nmr (deuteriochloroform) δ ppm: 6.08 (2H) s; 5.98 (1H) s; 5.92 (1H) s; 4.20 (2H) s; 4.12 (2H) s; 4.08 (2H) s; 2.26 (6H) s; MS: m/e 340 (M^+ 96); 244 (15); 205 (25); 178 (21); 149 (92); 122 (67); 96 (100).

Anal. Calcd. for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 59.82; H, 4.60; N, 16.40.

REFERENCES AND NOTES

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- (3) S. Auricchio, S. Morricchi and A. Ricca, *Tetrahedron Letters*, 2793 (1974); S. Auricchio, A. Ricca and O. Vajna de Pava, *Chim. Ind. (Milan)*, **58**, 699 (1976).
- (4) Variable amount of bis-adduct XI contemporaneously is

formed; compound XI has been identified by comparison with an authentic sample; see reference 1a.

(5) The synthesis of isomer compound 3-[(3-methyl-5-is-

oxazolyl)methyl]-5-[(5-methyl-3-isoxazolyl)methyl]isoxazole has been reported by T. Tanaka, M. Miyazaki and I. Jijma, *J. Chem. Soc., Chem. Commun.*, 233 (1973).