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POLY-*ISO*OXAZOLES

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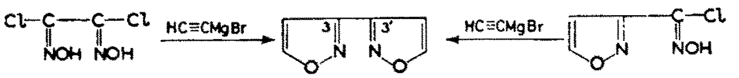
Abstract—The reaction of hydroximic chlorides on acetylenic Grignard reagents has been applied to the synthesis of unknown *poly*-iso*oxazoles*. Some linear poly-*iso*oxazoles of unequivocal structure, viz. 3:3′:5′:3″-tri-*iso*oxazole (IX), 3:3′:5′:5″-tri-*iso*oxazole (XIV), 3:3′:5′:5″:3″:3‴-tetra-*iso*oxazole (XV) and 3:3′:5′:5″:3″:3‴:5‴:5^{IV}:$3^{IV}3^{V}$-hexa-*iso*oxazole (XVII) have been prepared.

IN previous papers[1] we have reported the synthesis of three of the six theoretically possible bi-*iso*oxazoles (I) namely 3:3′-(II), 5:5′-(III) and 3:5′-bi-*iso*oxazole (IV).

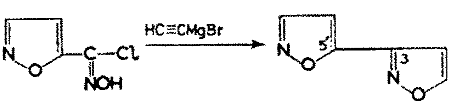
I

These substances have been prepared by the following reactions:

(a) action of suitable hydroximic chlorides (dichloroglyoxime, 3- and 5-*iso*-oxazolylformohydroximic chloride) on ethynylmagnesium bromide:

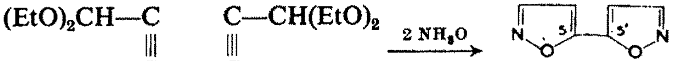


II



IV

(b) action of hydroxylamine on hexadiindial tetraethylacetal:



III

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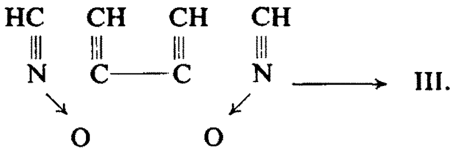
[1] A. Quilico, G. Gaudiano and A. Ricca, *Gazz. Chim. Ital.* **87**, 638 (1957); G. Gaudiano and A. Ricca, *Ibid.* **89**, (1959); A. Ricca and G. Gaudiano, *Reudic. Acc. Naz. Lincei* [VIII], **26**, In press (1959). P. Grünanger and E. Fabbri, *Ibid.* **89**, (1959); A. Quilico, G. Gaudiano and L. Merlini, *Tetrahedron* **2**, 359 (1958).

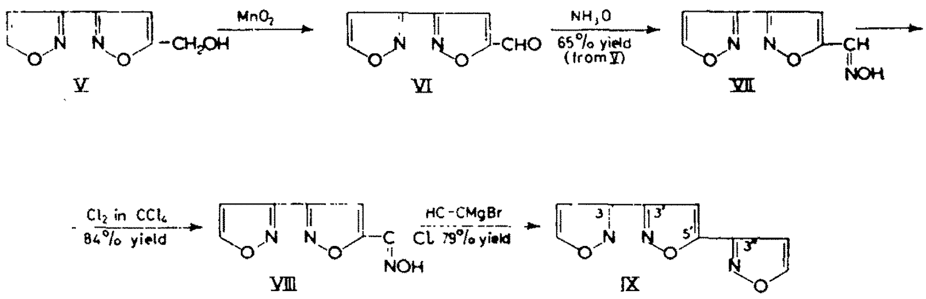
(c) addition of fulminic acid on diacetylene



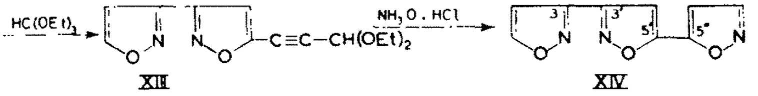
$$\begin{matrix} HC & CH & CH & CH \\ ||| & ||| & ||| & ||| \\ N & C-\!\!- & C & N \\ \searrow & & & \swarrow \\ O & & & O \end{matrix} \longrightarrow \text{III.}$$

By extending reactions (a) and (b) to hydroximic chlorides and acetylene derivatives containing one or two *iso*oxazole rings we have succeeded in synthesizing linear poly-*iso*oxazoles of unequivocal structure in which three, four and six *iso*oxazole rings are present to form a normal skeleton of respectively nine, twelve and eighteen carbon atoms.

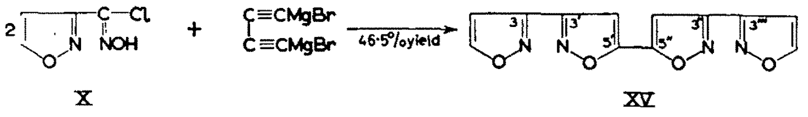
3:3′:5 :3″-*Tri*-iso*oxazole* (IX)* has been synthesized from 5′-hydroxymethyl-3:3′-bi-*iso*oxazole (V)[1] according to the reactions in an overall yield of 43 per cent.



The isomeric 3:3′:5′:5″-*tri*-iso*oxazole* (XIV), was prepared as follows from 3-*iso*oxazolylformohydroximic chloride (X).



3:3′:5′:5″:3″:3‴-*Tetra*-iso*oxazole* (XV) was obtained by reacting 3-*iso*oxazolylformohydroximic chloride (X) with diacetylene organomagnesium bis-derivative:



Since in the preparation of butadiinylmagnesium bromide it is impossible to prevent the formation of the bis-derivative, an appreciable quantity of tetra-*iso*oxazole (XV) is formed in the preparation of ethynyl-bi-*iso*oxazole (XI). In the above reaction

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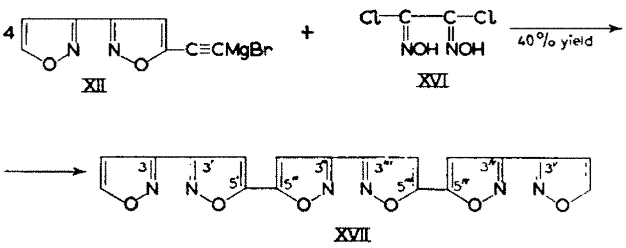
* 3:3′-Dimethyl-5:5′:3′:5″-tri-*iso*oxazole, 5:5″-dimethyl-3:3′:5′:3″-tri-*iso*oxazole and a mixture of the 3:5″-dimethylderivatives of 5:5′:3′:3″- and 5,3′:5′:3″-tri-*iso*oxazole had been reported by Musante, *Gazz. Chim. Ital.* **71**, 172 (1941). They were prepared by treatment of *iso*oxazole β-diketones with hydroxylamine.

owing to the presence of some diacetylene monomagnesium derivative, a certain amount of the hydroximic chloride (X) is converted into ethynyl-bi-*iso*oxazole.

Application of reaction (a) to ethynyl-bi-*iso*oxazole (XI) led to the synthesis of linear $3{:}3'{:}5'{:}5''{:}3''{:}3'''{:}5'''{:}5^{IV}{:}3^{IV}{:}3^{V}$-*hexa-*iso*oxazole* (XVII). It was obtained (in 40 per cent yield on the chloroxime) by treating dichloroglyoxime (XVI) with an excess of bi-*iso*oxazolylethynylmagnesium bromide (XII).



The new poly-*iso*oxazoles are crystalline solids which can be sublimed undecomposed *in vacuo*. As expected, their melting points (Table 1) rise with the molecular weight, whereas their solubility in the usual organic solvents rapidly diminishes. They are not fluorescent at the Wood's light.

The *U.V. Spectra* of the new poly-*iso*oxazoles are reported in Fig. 1 in comparison with the bi-*iso*oxazoles already described. As Speroni *et al.* pointed out, 3:3′-bi-*iso*oxazole ($\lambda_{max} = 214$ mμ) practically contains the same chromophore as *iso*oxazole itself ($\lambda_{max} = 214$ mμ) because the 3:3′-linkage prevents the conjugation of the two *iso*oxazole rings.[2] In 5:5′-bi-*iso*oxazole a strong interaction between the two rings occurs with the appearance of a new chromophore ($\lambda_{max} = 260$ mμ). 3:5′-Bi-*iso*oxazole

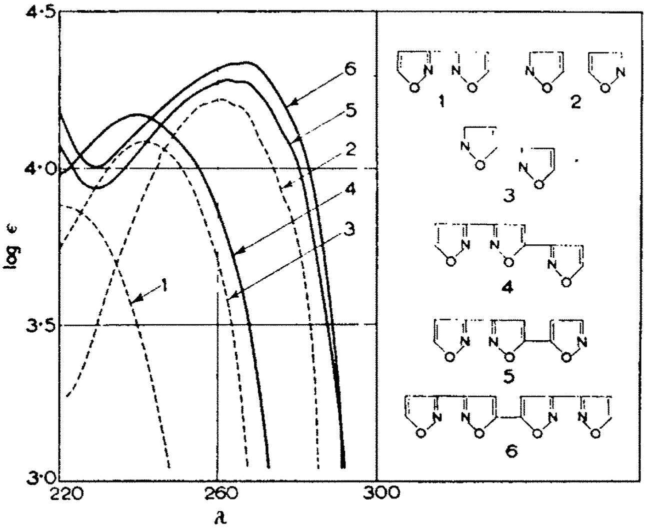


FIG. 1. Ultra-violet spectra of poly-*iso*oxazoles (in ethanol).

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[2] S. Califano, G. Speroni and D. Tafuri, private communication.

U.V. spectrum exhibit a well defined maximum at 242 in a position which is intermediate between those of 3:3′- and 5:5′-bi-*iso*oxazole maxima.

From the point of view of their spectrochemical behaviour the new poly-*iso*oxazoles can be classified as follows:

(i) Those which contain a 5:5-linkage conjointly with 3:3-linkages (3:3′:5′:5″-tri-*iso*oxazole and 3:3′:5′:5″:3″:3‴-tetra-*iso*oxazole) show a U.V. spectrum similar to that of 5:5′-bi-*iso*oxazole (λ_{max} at about 265 mμ) as well for the position of the maximum as for the presence of a clearly recognizable fine structure.

TABLE 1. PHYSICAL PROPERTIES OF POLY-*iso*OXAZOLES

Compound	m.p.	U.V. Spectrum in ethanol	
		λ_{max}, mμ	log ε
3:3′-Bi-*iso*oxazole (II)	73–73·5°	210	3·90
5:5′-Bi-*iso*oxazole (III)	116–117·5°	260	4·21
3:5′-Bi-*iso*oxazole (IV)	86–87°	242	4·08
3:3′:5′:3″-Tri-*iso*oxazole (IX)	153–155°	239	4·175
3:3′:5′:5″-Tri-*iso*oxazole (XIV)	160–161°	263	4·28
3:3′:5′:5″:3″:3‴-Tetra*iso*oxazole (XV)	265°	267	4·335
3:3′:5′:5″:3″:3‴:5‴:5^{IV}:3^{IV}:3^{V}-Hexa-*iso*oxazole (XVII)	370° dec	*	*

* Not determined, being insoluble in ethanol.

(ii) Those which contain a 3:5-linkage conjointly with 3:3 linkages (3:3′:5′:3″-tri-*iso*oxazole) show a U.V. spectrum very similar to that of 3:5′-bi-*iso*oxazole with a single maximum at about 240 mμ.

This investigation will be completed by the study of poly-*iso*oxazoles containing 3:5-and 5:5-linkages, whose synthesis is in progress; it can however be anticipated that conclusive information about the structure of poly-*iso*oxazole systems is supplied by the study of U.V. spectra.

The *I.R. spectra* of the new poly-*iso*oxazoles are reported in Fig. 2. Especially characteristic for the constancy of their position and intensity are the bands located at 3·2, 6·5 and 9·0 μ.

Syntheses of octa-*iso*oxazoles and still higher linear poly-*iso*oxazoles are in progress.

EXPERIMENTAL

Oxime of 3:3′-*bi*-*isooxazole*-5′-*aldehyde* (VII). Precipitated MnO_2 (55 g) was added to a solution of 5′-hydroxymethyl-3:3′-bi-*iso*oxazole (7·7 g) in acetone (500 ml), and the mixture allowed to stay at room temp for 20 hr. The MnO_2 was then filtered off and washed repeatedly with acetone. The combined filtrate and washings, evaporated under reduced pressure, left a solid residue of 3:3′-bi-*iso*oxazole-5′-aldehyde and unreacted carbinol. The mixture was refluxed for about 15 min with a solution of $NH_3O.HCl$ (6·0 g) and Na_2CO_3 (4·6 g) in water (100 ml); on cooling, crystals of the oxime of (VII) and unchanged carbinol separated.

The reaction mixture was rendered slightly alkaline with N NaOH and the undissolved carbinol (3·4 g) recovered by filtration. The alkaline filtrate on treatment with 10% HCl gave the oxime (1·7 g); from the filtered acid solution a further 1·9 g of carbinol were recovered by extraction with ether. Yield of oxime 65% based on the reacted carbinol.

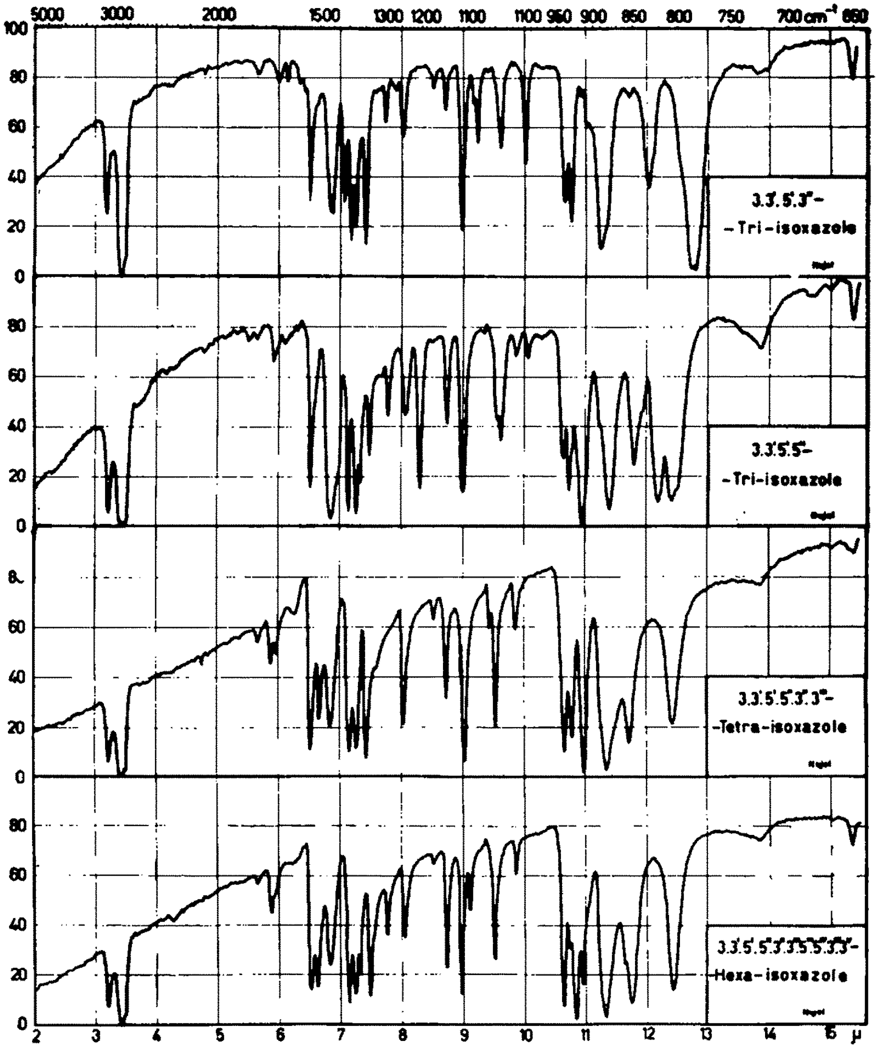

FIG. 2. Infra-red spectra of poly-*iso*oxazoles.

3:3'-Bi-*iso*oxazole-5'-aldoxime crystallizes from hot water in soft white needles m.p. 187–189°. (Found: N, 23·60; $C_7H_5O_3N_3$ requires: N, 23·46%).

3:3'-Bi-iso*oxazolyl-5'-formohydroximic chloride* (VIII). A suspension of VII (1·0 g) in dry carbon tetrachloride (20 ml) was cooled with ice and treated for 10 min with a slow stream of chlorine. After remaining overnight at 0–5° the crystallized hydroximic chloride was filtered and washed with dry CCl_4. Yield 1·0 g (84%). The product was purified by sublimation *in vacuo* (at 150–170° under 0·5 mm Hg). Pure hydroximic chloride (VIII) forms a microcrystalline powder m.p. 219–221°. (Found: N, 19·66; $C_7H_4ClO_3N_3$ requires: N, 19·67%).

Synthesis of 3:3':5':3"-*tri*-iso*oxazole* (IX). A suspension of VIII (2 g) in tetrahydrofuran (20 ml) was added in small portions, over a period of 15 min with continual stirring and cooling with water, to the solution of ethynylmagnesium bromide in tetrahydrofuran prepared from 0·53 g of magnesium.[8] After 3 hr stirring the reaction mixture was left overnight at room temp, decomposed with ice and HCl, and then extracted with ether. On distilling the ether solution (dried over Na_2SO_4) a solid residue (1·5 g) of crude tri-*iso*oxazole was obtained (79%). Pure tri-*iso*oxazole crystallizes from hot

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[8] E. R. H. Jones, K. L. Skattebol and M. C. Whiting, *J. Chem. Soc.* 4765 (1956).

water in small needles m.p. 153–155° and can readily be sublimed at reduced pressure. (Found: N, 20·64; $C_9H_5O_3N_3$ requires: N, 20·69%). U.V. and I.R. spectra are reported in Figs. 1 and 2.

*5′-Ethynyl-3:3′-bi-*isooxazole (XI). A solution of X[1] (10 g) in tetrahydrofuran (100 ml) was added over a period of 10 min with continual stirring and cooling with ice-water to the suspension of butadiinylmagnesium bromide prepared from 4·0 g of magnesium.[3] During the reaction dissolution of the diacetylene organomagnesium derivative and separation of a fine whitish precipitate were observed. After 6 hr stirring the mixture was left overnight at room temp and then decomposed with ice and HCl. The white powder left undissolved after this treatment (dry 1·8 g) consisted of pure 3:3′:5′:5″:3″:3‴-tetra-*iso*oxazole (XV) (19% yield). The aqueous solution from the filtration of XV was repeatedly extracted with ether. The combined extracts, dried over Na_2SO_4 and decolorized with Norit gave, after removal of the solvent, a solid residue which recrystallized from hexane (about 200 ml) as pure 5′-ethynyl-3:3′-*iso*oxazole (5 g). A further portion (1·3 g) was recovered from the hexane mother liquors. Overall yield was 77%.

Pure ethynyl-bi-*iso*oxazole crystallizes from hexane in white needles m.p. 82–83°. The product is volatile in steam and sublimes easily. (Found: N, 17·31; $C_8H_4O_2N_2$ requires: N, 17·50%).

3:3′-*Bi-*isooxazolyl*-5′-propargylic aldehyde diethylacetal* (XIII). A solution of XI (5 g) in dry ether (50 ml) was added in about 30 min with continual stirring to the cooled solution of ethylmagnesium bromide prepared from 0·84 g of magnesium. After additional 30 min stirring 5·1 g of freshly distilled ethyl orthoformate dissolved in 100 ml of dry benzene were added dropwise with constant stirring and cooling. Most of the ether was then removed by distillation and the reaction completed by refluxing on the water bath for 4 hr. The dark coloured reaction mixture obtained was decomposed with ice-water and ammonium acetate (10 g) and then extracted with ether. The organic layer dried over K_2CO_3 left, after removal of the solvent and unreacted ethyl orthoformate *in vacuo*, the crude diethylacetal (XIII) as a brown oil which was used without further purification for the synthesis of 3:3′:5′:5″-tri-*iso*oxazole.

Synthesis of 3:3′:5′:5″*-tri-*isooxazole (XIV). XIII was refluxed for 2½ hr with $NH_3O.HCl$ (2·5 g) dissolved in aqueous ethanol (30 ml ethanol + 10 ml water). After removing most of the ethanol, at reduced pressure, the reaction mixture was diluted with water and the yellowish precipitate collected on a filter. It weighed when dry 0·4 g. Purified by recrystallization from hot water 3:3′:5′:5″-tri-*iso*oxazole forms soft needles m.p. 160–161°. The product is not volatile in steam and is very soluble in ethanol. (Found: N, 20·76; $C_9H_5O_3N_3$ requires: N, 20·69%). U.V. and I.R. spectra are shown in Figs. 1 and 2.

Synthesis of 3:3′:5′:5″:3″:3‴*-tetra-*isooxazole (XV). A solution of diacetylene (1·7 g) in tetrahydrofuran (15 ml) was added over a period of 5 min to the solution of ethylmagnesium bromide prepared from 1·5 g of magnesium in 80 ml of tetrahydrofuran.[4] During the reaction the mixture was continually stirred and cooled with ice-water. After additional 2½ hr stirring at room temp, a solution of dichloroglyoxime (5 g) in tetrahydrofuran (50 ml) was added dropwise in about 20 min. The mixture was left overnight and then decomposed with ice-water and HCl. The crude tetra-*iso*oxazole was precipitated as a fine powder (2·1 g 46·5%). The product is sparingly soluble in most organic solvents; from boiling ethanol or benzene it crystallizes as microscopic needles m.p. 265° which sublime when heated *in vacuo*. (Found: N, 20·53; $C_{12}H_6O_4N_4$ requires: N, 20·74%). U.V. and I.R. spectra are reported in Figs. 1 and 2.

The acid solution recovered after filtration of the tetra-*iso*oxazole and extracted with ether gave XI (0·8 g 14·7%).

Synthesis of 3:3′:5′:5″:3″:3‴:5‴:5^{IV}:3^{IV}:3^{V}*-hexa*isooxazole (XVII). A solution of XI (5 g) in tetrahydrofuran (25 ml) was added in 10 min with continual stirring and cooling with water, to the solution of ethylmagnesium bromide prepared as usual from 0·84 g of magnesium in 30 ml of the same solvent. The formation of the ethynyl-bi-*iso*oxazole magnesium derivative was completed by heating on the water-bath at 40° for 20 min.

After cooling the dark coloured clear solution with ice dichloroglyoxime (1·37 g) dissolved in tetrahydrofuran (10 ml) was added in 10 min with continual stirring. A fine precipitate was immediately formed. The reaction mixture was stirred at ordinary temp for 1½ hr, allowed to remain overnight, and then decomposed with ice-water and HCl. The light-brown precipitate of crude hexa-*iso*oxazole was collected on a filter, washed with water, ethanol and ether (dry 1·3 g, 40%). From the aqueous solution unchanged ethynyl-bi-*iso*oxazole (2 g) were recovered by extraction with ether.

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[4] J. B. Armitage, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* 46 (1951).

Hexa-*iso*oxazole is practically insoluble in ethanol and in most organic solvents, sparingly soluble in boiling nitrobenzene from which it separates as microscopic shining needles. It is most conveniently purified by sublimation at reduced pressure (250–280° under 0·5 mm Hg). At temp above 300° at ordinary pressure it sublimes unaffected. When heated in a sealed capillary tube it melts at 370° with decomposition. (Found N, 20·82; $C_{18}H_8O_6N_6$ requires: N, 20·79%). For its I.R. spectrum see Fig. 2.