

## The Synthesis and Structure Determination of Tetrasubstituted 4,4'-Biisoxazoles\*

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Tetrasubstituted 4,4'-biisoxazoles were synthesized as a mixture of isomers by treatment of enolic tautomers of 3,4-diaroyl-2,5-hexanedione with hydroxylamine hydrochloride. A single isomer, 3,3'-diphenyl-5,5'-dimethyl-4,4'-biisoxazole was isolated from the reaction product mixture.

The structure of these compounds has been determined by spectrometric measurements (ir, <sup>1</sup>H NMR and mass spectra). Mass spectra have been studied in detail. The determination of metastable transitions and accurate masses of important fragment ions led to the construction of fragmentation schemes.

### INTRODUCTION

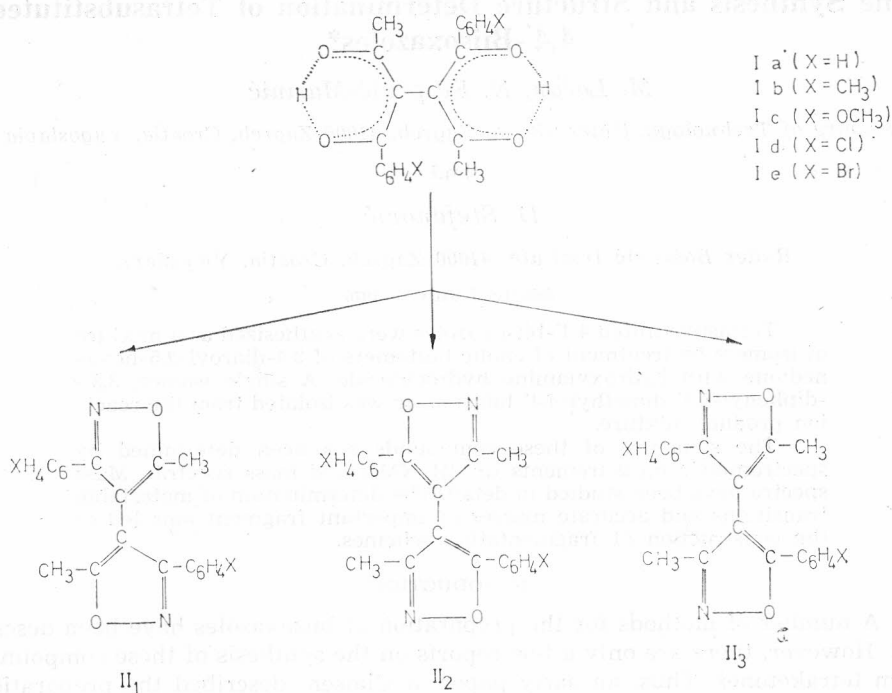
A number of methods for the preparation of biisoxazoles have been described. However, there are only a few reports on the synthesis of these compounds from tetraketones. Thus, an early paper of Claisen<sup>1</sup> described the preparation of a mixture of biisoxazoles from oxalyldiacetone. Recently, Fusco and Zumin<sup>2</sup> prepared 3,3'-biisoxazoles, Gaudiano et al.<sup>3</sup> the 4,4'- and Ghosh and Chowdhury<sup>4</sup> the 4,5'-biisoxazoles, all of which were made by reacting various tetraketones with hydroxylamine.

During our studies of tetraketones chemistry, we became interested in the preparation of some hitherto unknown 4,4'-biisoxazoles from unsymmetrical tetraketones. It is known<sup>5</sup> that by a similar synthetic procedure, in which unsymmetrical 1,3-diketones react with hydroxylamine, two isomeric isoxazoles can be formed. This is in accordance with the possibility of hydroxylamine nucleophilic attack on either of the two reactive carbon atoms. The preference for the attack and thereby the composition of products mixture is determined mostly by electron density at possible reaction sites.

Enolic tautomers of 3,4-aroyl-2,5-hexanedione (I), prepared by published procedure<sup>6</sup>, served as a starting material in our synthesis of 4,4'-biisoxazoles. In order to study the influence of electron density at reaction sites on the

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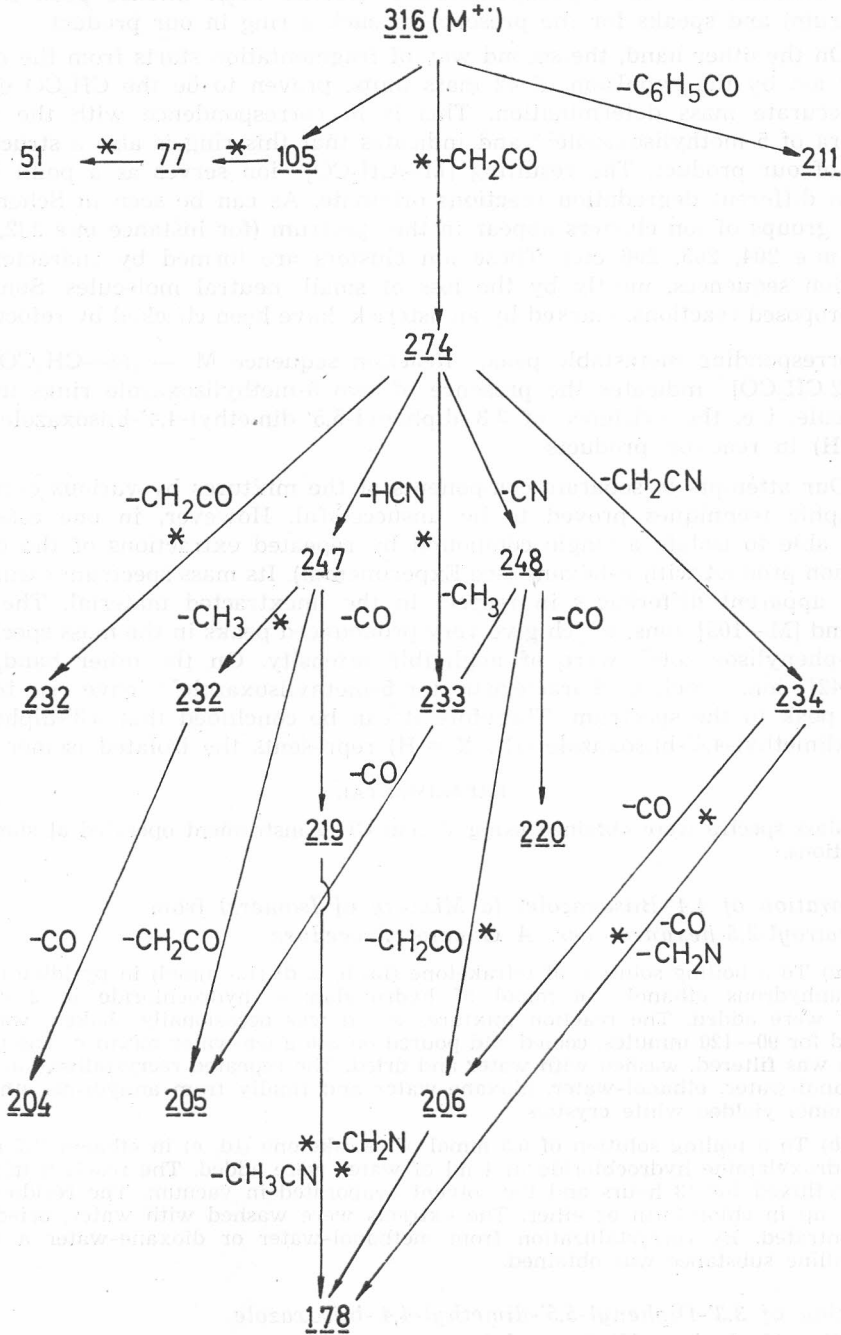
preference for the initial attack and thereby on the composition of reaction products, the following phenyl *para*-substituents (X) have been used: —H, —CH<sub>3</sub>, —OCH<sub>3</sub>, —Cl and Br. Depending on relative electron affinity of substituted phenyl- versus methyl-group in tetraketones, the reaction product can consist of either a single 4,4'-biisoxazole (II<sub>1</sub> or II<sub>2</sub>), as in case of a great difference in electron affinity, or of a mixture of at most three isomeric 4,4'-biisoxazoles (II<sub>1,2,3</sub>).



The reactions of tetraketones (I) with excess hydroxylamine hydrochloride were carried out in boiling ethanol. The crude reaction product was isolated, purified, recrystallized and analysed by ir spectrophotometry and mass spectrometry.

In all synthesis the desired biisoxazoles (II) have been obtained. In ir spectra the absorption bands of starting compounds disappeared, while the characteristic bands of the isoxazole ring were present. Moreover, in mass spectra the molecular ion showed the *m/e* value expected for a given substituted biisoxazole and was quite abundant.

The inspection of fragmentation pathways reveals that in all synthesis, regardless of the nature of phenyl substituent, a mixture of reaction products has been formed. The fragmentation process is generally directed in two ways. In the first one the molecular ion splits into two prominent fragment ions: [XC<sub>6</sub>H<sub>4</sub>CO]<sup>+</sup> and [M—XC<sub>6</sub>H<sub>4</sub>CO]<sup>+</sup>, X being —H, —CH<sub>3</sub>, —OCH<sub>3</sub>, —Cl or —Br. For unsubstituted biisoxazole (X = H) these two fragment ions can be found at *m/e* 105 and *m/e* 211, respectively (Scheme 1). A formation of *m/e* 105 is



Scheme 1. Fragmentation scheme of dimethyldiphenyl-4,4'-biisoxazole (a mixture of isomers).

very characteristic for 5-phenylisoxazole<sup>7</sup> (second most intense peak in the spectrum) and speaks for the presence of such a ring in our product.

On the other hand, the second way of fragmentation starts from the molecular ion by the expulsion of 42 mass units, proven to be the CH<sub>2</sub>CO entity by accurate mass determination. This is in correspondence with the mass spectra of 5-methylisoxazole<sup>7,8</sup> and indicates that this ring is also a structural part of our product. The resulting [M—CH<sub>2</sub>CO]<sup>+</sup> ion serves as a point from which different degradation reactions originate. As can be seen in Scheme 1, some groups of ion clusters appear in the spectrum (for instance *m/e* 232, 233, 234; *m/e* 204, 205, 206 etc). These ion clusters are formed by characteristic reaction sequences, mostly by the loss of small, neutral molecules. Some of the proposed reactions, marked by an asterisk, have been checked by refocusing of corresponding metastable peaks. Reaction sequence  $M^+ \xrightarrow{*} [M-CH_2CO]^+ \xrightarrow{*} [M-2CH_2CO]^+$  indicates the presence of two 5-methylisoxazole rings in the molecule, i. e. the existence of 3,3'-diphenyl-5,5'-dimethyl-4,4'-biisoxazole (II<sub>1</sub>, X = H) in reaction products.

Our attempts to separate components of the mixtures by various chromatographic techniques proved to be unsuccessful. However, in one case we were able to isolate a single compound by repeated extractions of the crude reaction product with *n*-hexane (see Experimental). Its mass spectrum exhibited some apparent differences in respect to the unextracted material. The *m/e* 105 and [M—105]<sup>+</sup> ions, which give very pronounced peaks in the mass spectrum of 5-phenylisoxazole<sup>7</sup>, were of negligible intensity. On the other hand, the [M—42]<sup>+</sup> ion, which is characteristic for 5-methylisoxazole<sup>7,8</sup>, gave rise to the base peak in the spectrum. Therefore it can be concluded that 3,3'-diphenyl-5,5'-dimethyl-4,4'-biisoxazole (II<sub>1</sub>, X = H) represents the isolated isomer.

#### EXPERIMENTAL

Mass spectra were obtained using Varian CH 7 instrument operated at standard conditions.

#### *Preparation of 4,4'-Biisoxazoles (a Mixture of Isomers) from 3,4-Diaroyl-2,5-hexanediones. A General Procedure*

(a) To a boiling solution of tetraketone (Ia, b, c, d) (1.5 mmol) in pyridine (1 ml) and anhydrous ethanol, 5.6 mmol of hydroxylamine hydrochloride in 2 ml of water were added. The reaction mixture, which was occasionally shaken, was refluxed for 90—120 minutes, cooled and poured on 300 g ice-water mixture. The precipitate was filtered, washed with water and dried. The repeated recrystallization from methanol-water, ethanol-water, dioxane-water and finally from anhydrous ethanol-methanol yielded white crystals.

(b) To a boiling solution of 0.5 mmol of tetraketone (Id, e) in ethanol, 1.2 mmol of hydroxylamine hydrochloride in 4 ml of water were added. The reaction mixture was refluxed for 13 hours and the solvent evaporated in vacuum. The residue was taken up in chloroform or ether. The extracts were washed with water, dried and concentrated. By recrystallization from methanol-water or dioxane-water a white crystalline substance was obtained.

#### *Isolation of 3,3'-Diphenyl-5,5'-dimethyl-4,4'-biisoxazole (II<sub>1</sub>, X = H) from a Mixture of Isomers*

The crude reaction product was repeatedly washed under reflux with 20 ml portions of *n*-hexane until washings were colourless. Removal of *n*-hexane from

combined washings afforded a white residue from which a pure product was obtained in low yield (18%) by recrystallization from methanol-water, ethanol-water and anhydrous methanol or ethanol.

*Anal.* C<sub>20</sub>H<sub>16</sub>O<sub>2</sub>N<sub>2</sub> (316) calc'd: C 75.33; H 5.10; N 8.86  
found: C 75.81; H 5.39; N 8.74

Ir spectrum: 3080, 2940, 2860, 1660, 1600, 1580, 1510, 1475, 1440, 1410, 1380, 1310, 1260, 1130, 1100, 1080, 1030, 1000, 950, 920, 850, 780, 750, 710, 690, 645.

<sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) δ values: 2.03 (s, 6 H, methyl H); 7.47 (m, 10 H, phenyl H).

Molecular ion, *m/e* 316.

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#### SAŽETAK

##### Sinteza i određivanje strukture tetrasupstituiranih 4,4'-biizoksazola

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Reakcijom enolnih tautomera 3,4-diaroil-2,5-heksandiona s hidroksilaminhidrokloridom sintetizirani su izomerni tetrasupstituirani 4,4'-biizoksazoli. Strukture dobitvenih spojeva određene su na temelju podataka dobivenih snimanjem spektara masa, <sup>1</sup>H-nuklearne magnetske rezonancije kao i infracrvenih spektara.

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