[Chem. Pharm. Bull. 20(1) 122—132 (1972)]

UDC 547.786.2.04.057

Syntheses of 5,5′-Methylenebisisoxazole Derivative and Its Reactions with Electrophiles[1]

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(Received June 25, 1971)

A potential tetra-β-ketide compound, 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) was prepared from 1,4-pentadiyne (I) and carboethoxynitriloxide (II). The bisisoxazole (IV) was also synthesized by way of diethyl 5,5′-methylene-bis(2-isoxazoline)-3,3′-dicarboxylate (VII) (racemi) and (VIII) (meso). The methylene hydrogens of the compound (IV) was shown to have a nature of an active methylene group and to react with various electrophiles. The four position of the isoxazole ring of IV had also nucleophilic character, which was useful for obtaining a cyclohexane derivative. A possibility was presented that the compound (IV) could be an important starting material for a synthesis of poly β-diketone system.

In the preceding paper[1] we reported a synthetic approach to a poly β-ketide system starting from a diacetylenic ketone. This time our object is directed toward another approach in which an isoxazole derivative is regarded as a potential or masked 1,3-diketone system.

With regard to ring opening of isoxazole derivatives, four main modes of reactions have been known[3]: (i) reductive cleavage (mainly by hydrogenation) (type 1) (ii) base catalyzed ring opening initiated by proton removal at 3-position (type 2) (iii) ring opening after a nucleophile attacks a conjugated carbonyl function situated at 3-position. This type includes decarboxylative ring opening of isoxazole-3-carboxylic acid (type 3) (iv) strong base catalyzed ring opening initiated by proton removal at 5-position to give a ketene intermediate (type 4).

Considering these modes of ring opening, 5,5′-methylenebisisoxazole derivative would be most suitable for tetra-β-ketonic compound and syntheses of these derivatives were attempted. The same kind of approach has been done by an Italian group,[4] who reductively cleaved a bisisoxazole compound to obtain a β-tetraketone derivative. In our case we found interesting properties of a synthesized bisisoxazole which reacts with various electrophiles.

1,4-Pentadiyne (I) was prepared from ethynylmagnesium bromide and propargyl bromide by coupling reaction. Although this compound was already known in literatures[4,5] purification was difficult because it condistilled with ether or tetrahydrofuran. Therefore, this substance was titrated according to Evans' method[6] and used in the next reaction without purification. Treatment of this diyne (I) with carbethoxynitriloxide[7] (II) prepared

1) Synthesis of β-Ketide System II. Part I: Y. Kishida, T. Hiraoka and M. Yoshimoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 2161 (1969).
2) Location: *2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo.*
3) *a*) "Five- and Six-Membered Compounds with Nitrogen and Oxygen," ed. by R.H. Wiley; A Quilico, "Isoxazoles and Related Compounds," Interscience Publishers, New York, 1962, p. 1; *b*) "Advances in Heterocyclic Chemistry," ed. by A.R. Katritzky, Vol. 2; N.K. Kochetkov, S.D. Sokolv, "Recent Developments in Isoxazol Chemistry," Academic Press, New York and London, 1963, p. 365.
4) G. Casnati, A. Quilico, A. Ricca and P. Vita-Finzi, *Tetrahedron Letters*, **1966**, 233; *idem*, *Gazz. Chim. Ital.*, **96**, 1064 (1966).
5) F. Serratosa, *Tetrahedron Letters*, **1964**, 895.
6) See G. Eglinton and M.C. Whiting, *J. Chem. Soc.*, **1953**, 3055.
7) G.S. Skinner, *J. Am. Chem. Soc.*, **46**, 731 (1924).

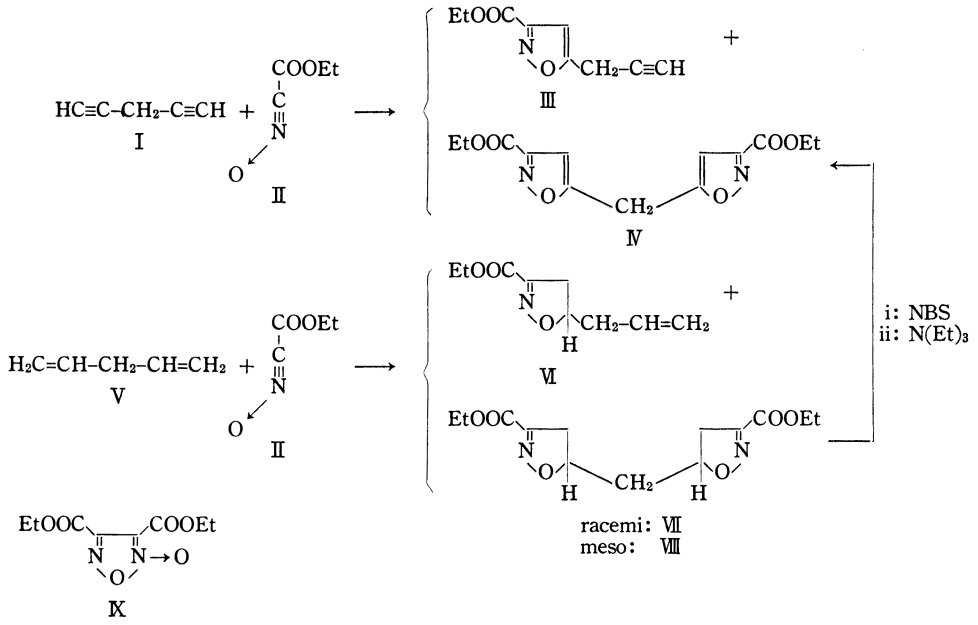

Chart 1

from ethyl chloroximino acetate and triethylamine gave ethyl 5-(2-propynyl)isoxazole-3-carboxylate (III) mp 60.5—61.5° and diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) mp 94—95°. The product ratio of III to IV was deeply affected by the reaction conditions. When one equivalent of I and two equivalent of II were mixed in a low concentration isolable compounds were the monoisoxazole (III) and diethyl furoxane-3,4-dicarboxylate (IX),[8] however, if the reaction was carried out in a high concentration, both III and IV were obtained in addition to by-product (IX). When excess II was used and the reaction was conducted in a high concentration, only bisisoxazole (IV) and IX were obtained. The structure of the compounds (III and IV) were unambiguous on the basis of spectroscopic data and already known analogous reactions.[3] In these reactions, the yield of the desired substance (IV) did not exceed over 20%. Therefore, another synthetic method of IV was investigated. According to literature[9] a double bond is more reactive to 1,3-dipolar species than a triple bond. Then, 1,4-pentadiene (V) was chosen as the 1,3-dipolarophile. Treatment of V with carbethoxy nitriloxide (II) liberated from ethyl chloroximino acetate and triethylamine afforded ethyl 5-(2-propenyl)-2-isoxazoline-3-carboxylate (VI), racemic diethyl 5,5′-methylenebis(2-icoxazoline)-3,3′-dicarboxylate (VII), meso diethyl 5,5′-methylenebis(2-isoxazoline)-3,3′-dicarboxylate (VIII) and the by-product (IX) which were care fully separated by chromatography on silica gel. As in the case of the reaction of I with II the usage of excess II and a high concentration gave higher yield of VII and VIII. Racemic VII and meso- VIII were easily distinguished by comparison of nuclear magnetic resonance (NMR) with that of racemic and meso-2,4-dichloropentane,[10] and racemic and meso-2,4-pentanethiol.[11] The methylene protons between two isoxazole rings of the racemic compound (VII) gave a triplet signal in NMR, whereas those of the meso compound (VIII) showed multiplet peaks which were in good agreement with the literature.[10,11] For the synthesis of IV, separation of VII and VIII

8) H.R. Snyder and N.E. Boyer, *J. Am. Chem. Soc.*, **77**, 4233 (1955).
9) R. Huisgen, *Angew. Chem.*, **75**, 742 (1963).
10) Y. Fujiwara and S. Fujiwara, *Bull. Chem. Soc. Japan*, **37**, 1005 (1964).
11) C.G. Overberger and T. Kurtz, *J. Org. Chem.*, **31**, 288 (1966), and references cited therein.

is unnecessary. Then conversion of VII and/or VIII into IV was examined. Tetrachlorobenzoquinone and dichlorodicyanobenzoquinone (DDQ) were not effective as a dehydrogenation reagent and the starting materials were recovered. Therefore we used Bianchi's method.[12] Isoxazoline (VII) and/or (VIII) were brominated with NBS and the resulting crude dibromo compound was treated with triethyl amine or potassium acetate without purification to give the desired bisisoxazole (IV).

Treatment of IV with hydrochloric acid in aqueous dioxane gave 5,5'-methylenebisisoxazole-3,3'-dicarboxylic acid (X), mp 183—185°. When X was heated to its melting point, this diacid lost carbon dioxide to give a tarry material. Then decarboxylation of the acid (X) was examined in a variety of solvent at 125—200°. Dimethylsulfoxide with triethylamine gave a good result and the product could be recrystallized from ethanol. However, this decarboxylated product was unstable for heating and the recrystallized sample was a polymer. Some polymerization reaction would occur even during decarboxylation reaction in dimethylsulfoxide at 125°, because infrared (IR) spectrum of the recrystallized sample was almost same as that of nonrecrystallized one. An absorption at 2220 cm^{-1} assignable to nitrile group indicated that decarboxylation and ring opening reaction of the isoxazole ring occurred. From the elemental analysis the sample obtained here was a polymer with dehydration.

In order to cleave the isoxazole ring according to type-3 reaction the bisisoxazole (IV) was treated with sodium ethoxide in ethanol to give precipitates, which did not dissolve even by heating. Acidification afforded the starting bisisoxazole (IV). Therefore, the precipi-

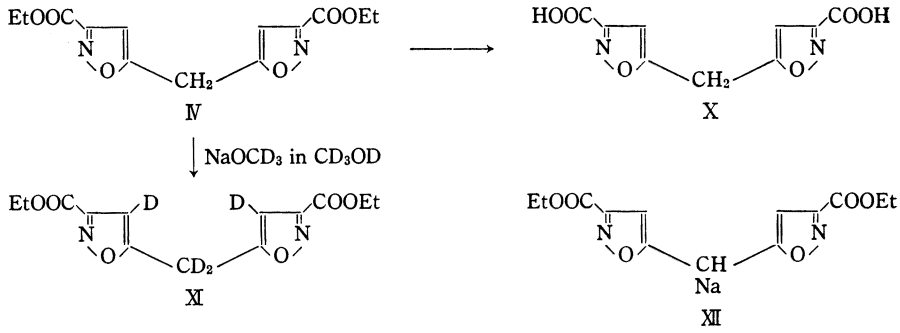

Chart 2

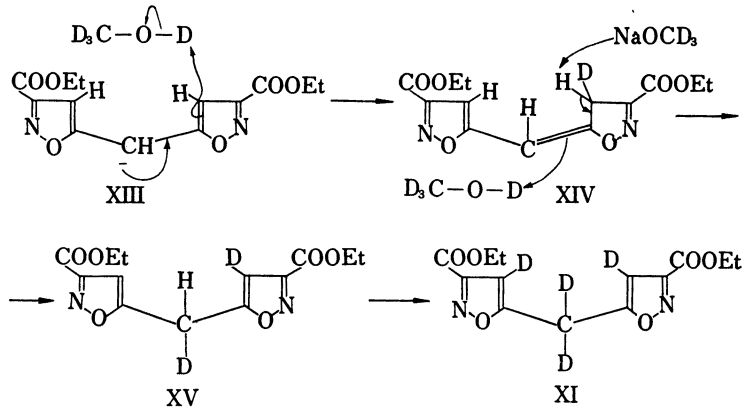

Chart 3

12) G. Bianchi and P. Grunanger, *Tetrahedron*, **21**, 817 (1965).

tates can be concluded as sodium salt of diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (XII). This fact clearly suggests that the methylene hydrogens of the compound (IV) are more acidic than alcoholic -OH hydrogen. The nature of these active hydrogens of IV was further examined by NMR spectroscopy. To 10% solution of IV in deuteriodimethylsulfoxide in a NMR tube was added 2N $NaOCD_3$ in CD_3OD and immediately its NMR was measured. Unexpectedly, both signals of methylene hydrogens between two isoxazole rings and isoxazole hydrogens at 4 position disappeared and only peaks due to ethyl ester groups remained in the spectrum. Thus, the initially formed carbanion (XIII) would isomerize to an isomer (XIV), which would reisomerize to deuterated compound (XV) and finally tetra-

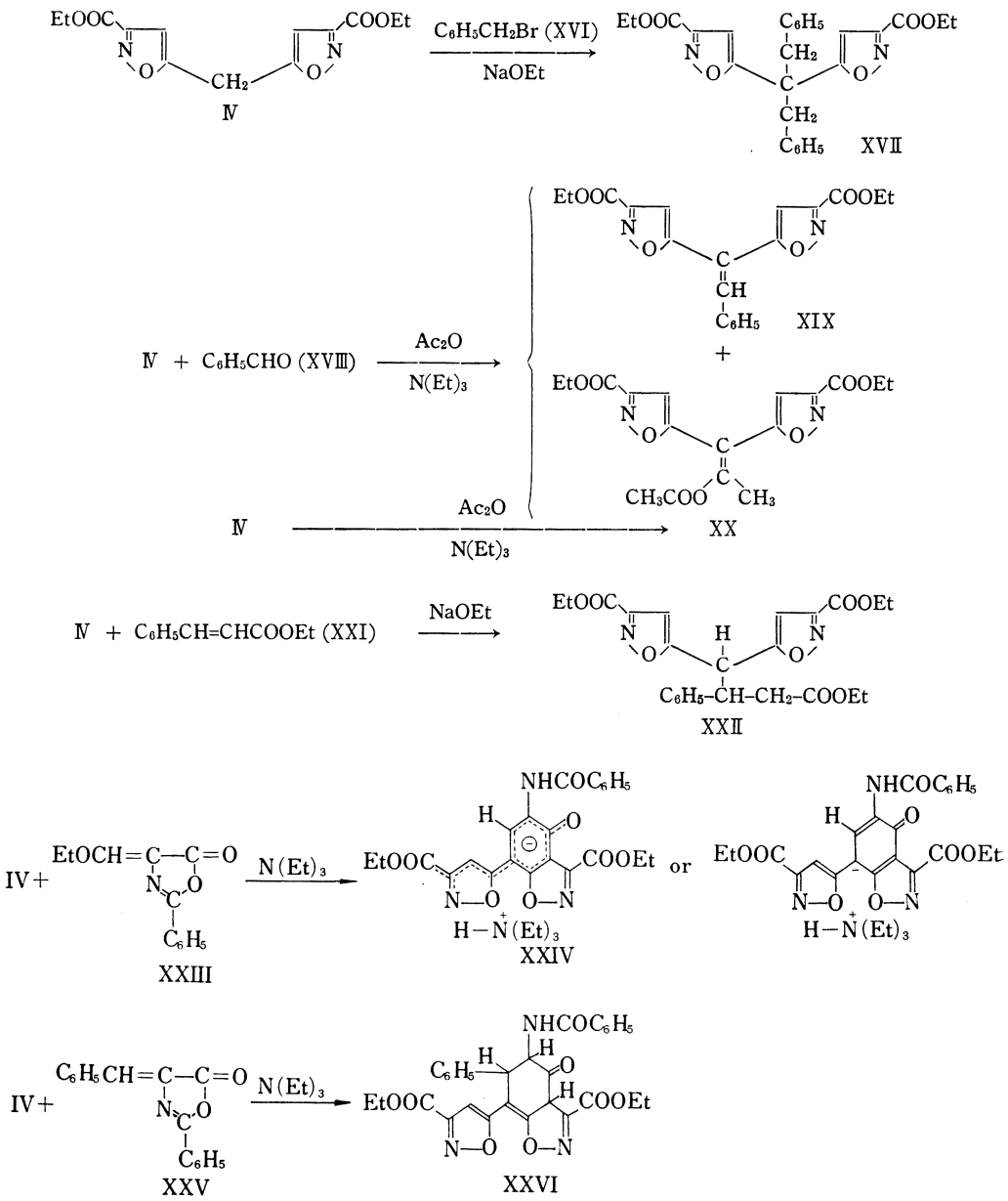

Chart 4

deutero derivative (XI) might be given (Chart 3). This behavior of the bisisoxazole (IV) was further confirmed by the following chemical reactions.

When IV was allowed to react with benzylbromide (XVI) in the presence of sodium ethoxide, 2,2-bis(3-carbethoxy-5-isoxazolyl)-1,3-diphenylpropane (XVII), mp 159—160° was obtained. The NMR spectrum of the compound (XVII) exhibited signals at 3.64 ppm (4H, singlet) ascribable to benzyl hydrogens and 6.34 ppm (2H, singlet) due to isoxazole hydrogens at 4 position in addition to ethyl ester and aromatic hydrogen peaks. From this spectrum the structure of XVII was unequivocal. Monobenzylated compound could not be obtained even if one equivalent of benzylbromide was used.

Treatment of IV with benzaldehyde in acetic anhydride in the presence of triethylamine gave two products, which were separated by silica gel chromatography. The first product (XIX), bp 230—240° (bath temperature) (0.0001 mmHg), had a molecular formula $C_{20}H_{18}O_6N_2$. Its NMR spectrum showed peaks at 6.57 ppm (1H, singlet) and 6.76 ppm (1H, singlet) assignable to two non-equivalent isoxazole hydrogens at 4 position, and 7.83 ppm (1H, singlet) in addition to two non-equivalent ethyl ester and aromatic hydrogen peaks. The ultraviolet (UV) spectrum of XIX showed maxima at 228 (plateau) (4.06), 259.5 (plateau) (3.97) and 314 mμ (4.35). These spectra were well agreed with the structure, 2,2-bis(3-carbethoxy-5-isoxazolyl)styrene (XIX). The second product had a molecular formula $C_{17}H_{18}O_8N_2$ and melted at 66—67°. The NMR spectrum of this product gave signals at 2.28 ppm (3H, singlet), 2.33 ppm (3H, singlet), 6.63 ppm (1H, singlet), 6.78 ppm (1H, singlet) in addition to two non-equivalent ethyl ester peaks, which suggested the four possible structures, (XX), (XXVII), (XXVIII), and (XXIX) (Chart 5). The non-equivalent ethyl

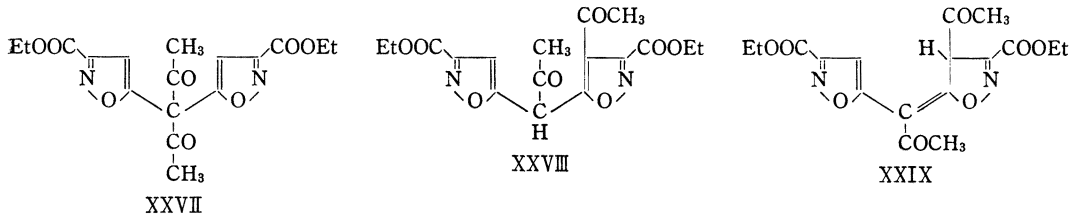

Chart 5

ester and methyl peaks in NMR excluded the structure (XXVII). The IR spectrum showed absorptions at 1732 cm^{-1} assignable to ester carbonyl groups and at 1775 cm^{-1}, which strongly supported the vinyl acetate structure (XX).

The compound (XX) was also prepared frem bisisoxazole (IV) and acetic anhydride in the presence of triethylamine in good yield.

These reactions clearly indicated that the methylene group of 5,5'-methylenebisisoxazole (IV) has a similar active methylene character as that of diethyl malonate.

Then, a Michael reaction of IV with ethyl cinnamate was carried out. An equimolecular mixture of IV and ethyl cinnamate in ethyl alcohol with a catalytic amount of sodium ethoxide was heated under reflux to give, after silica gel chromatography, ethyl 4-bis(3-carbethoxy-5-isoxazolyl)-3-phenylbutyrate (XXII). The structure of XXII was unambiguous on the following grounds: the UV spectrum showed maximum at 237 mμ which was similar to that of the starting bisisoxazole (IV). The NMR spectrum of XXII exhibited signals at 2.75 ppm (2H, doublet, J=7.5 Hz), assignable to the methylene hydrogens adjacent to carbethoxy substituent, 4.06 (1H, multiplet, obscure because of overlapping with methylene peaks of ethyl ester groups) due to benzal proton and 5.00 ppm (1H, doublet, J=9.5 Hz) ascribable to the methine proton between two isoxazole rings, in addition to three kinds of ethyl ester signals and two kinds of isoxazole hydrogen peaks. The nonequivalence of the isoxazole ethyl ester and isoxazole hydrogen peaks are interesting and this phenomenon

would be due to an asymmetric carbon at benzyl position. A similar kind of nonequivalence induced by a remote asymmetric carbon atom has been reported.[13]

When IV was allowed to react with 4-ethoxymethylene-2-phenyl-2-oxazoline-5-one (XXIII) in the presence of equimolecular amount of triethylamine in dimethylsulfoxide, a red crystalline compound (XXIV) mp 153—154° was obtained in good yield. The UV spectrum of the compound (XXIV) showed maxima at 255 mμ (log ε: 4.16), 338 (3.95), 354 (3.96), and 477 (4.58), which suggested that a quinoid type or longer conjugated system was formed. The NMR spectrum (in CD_3SOCD_3) of XXIV showed signals at 1.21 ppm (9H, triplet, J= 7 Hz) and at 3.10 ppm (6H, quartet, J=7 Hz) due to triethylamine moiety, 6.55 ppm (1H, singlet), 7.32 ppm (1H, singlet) and 8.04 ppm (1H, broad singlet) in addition to two nonequivalent ethyl ester peaks and aromatic hydrogen peaks (5H, multiplet). The broad peak at 8.04 ppm did not disappear on addition of deuterium oxide, however, in deuteriochloroform solution this peak vanished on addition of deuterium oxide. Incorporation of triethylamine group into this product suggested that an acidic function was produced. The absorption around 2600 cm^{-1} ($\equiv N^+$-H) in its IR spectrum excluded a possibility of a molecular complex with triethylamine. If the acidic function is assumed to be a carboxylic acid, it should arise from the azlactone moiety because ethyl isoxazole carboxylate (IV) should not be hydrolyzed under the reaction conditions. However, triethylamine salt of a carboxylic acid is highly unlikely according to the known chemical behaviour of azlactones.[14] Then, there remained a possibility of a carbon acid. pK_a value of the starting bisisoxazole (IV) would be 9—13 deduced from the reactions already shown although a decisive determination is not available. If a carbon acid forms a triethylamine salt, pK_a value of the acid might be smaller than five. Therefore, in this reaction product a strong electron attracting substituent would be introduced. Keeping these spectroscopic data and pK_a-inference in mind, we turn our attention to the reactivity of the azlactone (XXIII). The ethoxymethylene group of the compound (XXIII) has been known to be more reactive to a nucleophile than the carbonyl or imine moiety of XXIII.[14] Then the reaction of XXIII with ammonia gave 4-aminomethylene-2-phenyl-2-oxazolin-5-one,[15] and we already found that the reaction of XXIII with diethyl acetone dicarboxylate (XXX) afforded resorcinol derivative (XXXI)[16] (Chart 6). Considering these reactions and the spectroscopic data already described we

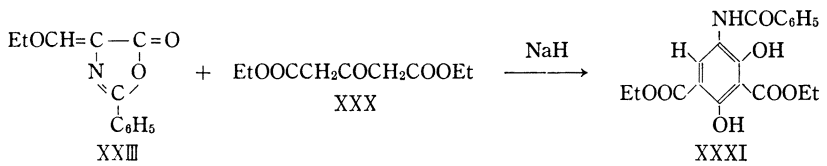

Chart 6

propose a structure (XXIV), *i.e.* triethylamine salt of ethyl 5-benzoylamino-7-(3-carbethoxy-5-isoxazolyl)-4,7-dihydro-4-oxo-1,2-benzisoxazol-3-carboxylate for the reaction product from IV and XXIII. An attempt to eliminate the triethylamine moiety from XXIV with hydrochloric acid or sodium ethoxide was unsuccessful because a number of products were formed and they could not be isolated in pure state.

Treatment of IV with 4-benzal-2-phenyl-2-oxazolin-5-one (XXV) in dimethylformamide in the presence of triethylamine gave a crystalline compound melting at 175—177°. This

13) L.M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, 1959, p. 102.
14) J.W. Conforth, "Oxazoles and Oxazolones," "The Chemistry of Penicillin," edited by H.T. Clark, J.R. Johnson, R. Robinson, Princeton University Press, Princeton N.J., 1949.
15) I.T. Strukov, *Zh. Obshch. Khim.*, **29**, 2359 (1959); *idem*, *Chem. Abstr.*, **54**, 9889^d (1960).
16) T. Hiraoka and Y. Kishida, *Chem. Pharm. Bull.* (Tokyo), **16**, 1576 (1968).

product was analyzed for $C_{29}H_{25}O_8N_3$. The NMR spectrum exhibited signals at 5.57 ppm (1H, doublet, J=11.5 Hz), 5.96 ppm (1H, doublet, J=11.5 Hz), 6.46 ppm (1H, singlet), 6.82 ppm (1H, singlet) and 9.13 ppm (1H, broad singlet, exchangeable with deuterium oxide) in addition to two kinds of ethyl ester peaks and aromatic hydrogen peaks (10H, multiplet). The UV spectrum of the product showed maximum at 237.5 mμ (log ε: 4.42), which was very similar to that of the starting bisisoxazole (IV). The UV spectrum of isoxazole-3-carboxylic acid has been known to show only ROOC-C=N- chromophore[3a] and that of 5-phenylisoxazole is similar to styrene absorptions.[3a] Considering these facts the most reasonable structure for the reaction product from IV and XXV would be ethyl 5-benzoylamino-7-(3-carbethoxy-5-isoxazolyl)-6-phenyl-5,6-dihydro-1,2-benziso-xazol-4(3aH)-oxo-3-carboxylate (XXVI). The reaction mechanism leading to this product could be also reasonable. The first intermediate (XXXII) was attacked by a base at methenyl position between the isoxazole rings, and then 4 position of the isoxazole ring would participate in a nucleophilic attack to the azlactone moiety to give the product (XXVI). Dearomatization of one of the isoxazole rings seems not to be curious because aromatic character of the isoxazole ring is weak.[3a]

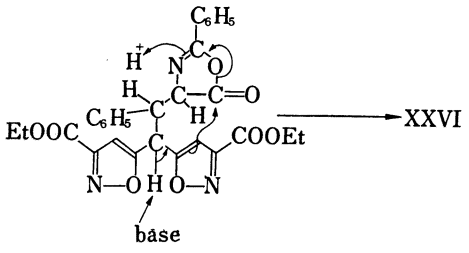

Chart 7

The vicinal hydrogens in the cyclohexene ring of XXVI would be situated in pseudo diaxial positions since the coupling constant between these two hydrogens is relatively large (11.5 Hz).

These reactions described here might be very useful for a synthesis of a natural product originated from a poly acetate unit because the isoxazole ring can be regarded as a potential or a masked β-diketone.

Experimental[17]

Ethyl 5-(2-Propynyl)isoxazole-3-carboxylate (III) and Diethyl 5,5′-Methylenebisisoxazole-3,3′-dicarboxylate (IV)——Ethynylmagnesium bromide solution was prepared from Mg (16.8 g: 3/4 mole), EtBr (81.8 g: 3/4 mole), acetylene gas and dry tetrahydrofuran (750 ml) according to the usual method.[18] After addition of CuCl (1.0 g), propargyl bromide (71.4 g) was dropwise added to this Grignard solution at room temperature during 12 hr. After addition the reaction mixture was stirred at room temperature for 20 hr. Then it was heated at 40° (inner temperature) for 10 hr. The cooled reaction mixture was poured into cold 10% H_2SO_4 solution (1 liter) and extracted with ether. The combined extracts were washed with $NaHCO_3$ solution and saturated NaCl solution until neutral to litmus, and dried over Na_2SO_4. The dried solution was distilled at atmospheric pressure and a distillate boling at 34—68° was collected (410 ml). One mililiter of this solution contained 0.644 milimole (36 mg) of 1,4-pentadiyne (I), $HC{\equiv}C\text{-}CH_2\text{-}C{\equiv}CH$, which was analyzed by titration according to Evans' method.[6] This 1,4-pentadiyne could not be isolated in pure state from ether and tetrahydrofuran. Therefore, it was submitted to the next reaction without purification.

To a mixture of 1,4-pentadiyne (I) [0.644×203 milimole in ether and tetrahydrofuran (203 ml)], ethyl chloroximino acetate[7] (39.7 g: 0.644×203×2 milimole) and dry tetrahydrofuran (300 ml) was dropwise added Et_3N (26.9 g: 0.644×203×2×1.015 milimole) at 24—25° (inner temperature). After addition the reaction mixture was stirred at room temperature (22—26°) for 24 hr. Water and ether were added and the aqueous phase was separated, the organic layer was washed three times with saturated NaCl solution, dried over Na_2SO_4 and evaporated to give an oil (37.1 g). This oil was chromatographed on silica gel (620 g). Elution with *n*-hexane–benzene (2:1 and 1:1) and evaporation gave diethyl furoxane-3,4-dicarboxylate (IX)[8] as an oil (21 g). Elution with *n*-hexane–benzene (1:1) and benzene gave crystalline ethyl 5-(2-propynyl)isoxazole-3-carboxylate (III) (6.5 g, 27.8% yield based on 1,4-pentadiyne). Recrystallization from

17) All melting points were uncorrected. NMR spectra were taken using Varian A-60 and HA-100 spectrometers with tetramethylsilane as an internal standard.
18) L. Skattebøl, E. R. H. Jones and M. C. Whiting, *Org. Synth.*, **39**, 56.

n-hexane gave prisms of mp 60.5—61.5° (4.0 g). *Anal.* Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.19; H, 5.10; N, 8.04. UV λ_{max}^{EtOH} mμ (log ε): 235 (3.56). IR ν_{max}^{Nujol} cm^{-1}: 3260 (C≡C-H), 3170 (isoxazole-H at 4 position), 1737, 1244 (ester), 1600 (isoxazole ring). NMR (10% solution in $CDCl_3$) δ ppm: 1.41 (3H, triplet, J=7.2 Hz, -COOCH$_2$C$\underline{H}_3$), 2.27 (1H, triplet, J=2.8 Hz, -C≡C-H), 3.79 (2H, doublet of doublets, J_1=2.8 Hz, J_2=1 Hz, -C$\underline{H}_2$-C≡C-), 4.46 (2H, quartet, J=7.2 Hz, -COOC$\underline{H}_2$-CH$_3$), 6.68 (1H, triplet, J=1 Hz, isoxazole-H at 4 position).

Elution with $CHCl_3$ and evaporation gave crystalline diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (3.4 g, 7.1% yield based on 1,4-pentadiyne). Recrystallization from *n*-heptane–benzene afforded pure IV, mp 94—95° (2.13 g). *Anal.* Calcd. for $C_{13}H_{14}O_6N_2$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.22; H, 4.80; N, 9.62. UV λ_{max}^{EtOH} mμ (log ε): 236.6 (3.85). IR ν_{max}^{Nujol} cm^{-1}: 3140 (isoxazole-H at 4 position), 1730 (C=O), 1601, 1591 (isoxazole ring). NMR (10% solution in $CDCl_3$) δ ppm: 1.41 (6H, triplet, J=7.3 Hz, 2×COOCH$_2$C$\underline{H}_3$), 4.46 (4H, quartet, J=7.3 Hz, 2×COOC$\underline{H}_2$CH$_3$), 4.46 (2H, triplet, J=0.8 Hz, -CH$_2$-), 6.64 (2H, triplet, J=0.8 Hz, isoxazole-H at 4 position).

In another frun starting from 0.16 mole of 1,4-pentadiyne in ether and tetrahydrofuran (610 ml), ethyl chloroximino acetate (145.4 g: 0.96 mole) and Et_3N (97 g: 0.96 mole), 6.6 g of IV was obtained (14% yield). If the reaction is carried out in high concentration and excess ethyl chloroximino acetate is used, the compound (III) is not obtained.

Ethyl 5-(2-Propenyl)-2-isoxazoline-3-carboxylate (VI) and Diethyl 5,5′-Methylenebis(2-isoxazoline)-3,3′-dicarboxylate [Racemi (VII) and Meso (VIII)]——To a mixture of ethyl chloroximino acetate (35.6 g: 0.334 mole) and 1,4-pentadiene[19] (8.00 g: 0.117 mole) in ether (700 ml) was dropwise added Et_3N (33.8 g: 0.334 mole) at −30——40° (inner temperature) with vigorous stirring during 14 hr. After stirring for 2 hr further ethyl chloroximino acetate (17.8 g: 0.117 mole) and ether (350 ml) were added, followed by addition of Et_3N (16.9 g: 0.117 mole) during 5 hr. Stirring was continued at −10——40° for 3 days. White precipitates (Et_3N·HCl) were filtered off, washed with ether. The combined ethereal filtrate was washed successively with 1N HCl solution, 5% $NaHCO_3$ solution and finally with H_2O until neutral to litmus, dried over Na_2SO_4 and evaporated to give an oil (40 g). The precipitates obtained above were dissolved in H_2O and extracted with ether. The combined extracts were washed successively with 1N HCl solution, 5% $NaHCO_3$ solution and H_2O until neutral to litmus. After drying over Na_2SO_4, ether was evaporated to give an oil (2.0 g), which was combined with the major oil obtained above and chromatographed on silica gel (500 g). Elution with benzene and evaporation afforded diethyl furoxane-3,4-dicarboxylate (IX)[8] (18.6 g). Elution with benzene–ether (97:3) gave ethyl 5-(2-propenyl)-2-isoxazoline-3-carboxylate (VI) (11.4 g) as an oil, bp 89—90° (0.05 mmHg) (56% yield based on 1,4-pentadiene). *Anal.* Calcd. for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.68; H, 7.09; N, 8.10. UV λ_{max}^{EtOH} mμ (log ε): 247.2 (3.76). IR ν_{max}^{liquid} cm^{-1}: 3070 (olefinic hydrogens), 1723 (ester), 1643, 1580 (isoxazole ring). NMR (10% solution in $CDCl_3$) δ ppm: 1.37 (3H, triplet, J=7.3 Hz, -COOCH$_2$C$\underline{H}_3$), 2.48 (2H, triplet, J_1=J_2=6.3 Hz, -C$\underline{H}_2$-CH=CH$_2$), 2.92 (1H, doublet of doublets, J_3=17.1 Hz, J_4=8.7 Hz, one of ring methylene protons, 3.18 (1H, doublet of doublets, J_3=17.1 Hz, J_5=10.3 Hz, another ring methylene protons), 4.37 (2H, quartet, J=7.3 Hz, -COOC$\underline{H}_2$CH$_3$), 6.2—4.6 (4H, multiplets, three vinyl protons and isoxazoline ring methine proton).

Elution with benzene–ether (7:3) afforded a mixture of racemic and meso diethyl 5,5′-methylene-bis-(2-isoxazoline)-3,3′-dicarboxylate (VII and VIII) (3.50 g) (10% yield based on 1,4-pentadiene). Recrystallization of the former eluate from EtOH gave racemic product (VII), mp 94°. *Anal.* Calcd. for $C_{13}H_{18}O_6N_2$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.18; H, 6.23; N, 9.44. UV λ_{max}^{EtOH} mμ (log ε): 246.2 (4.13). IR ν_{max}^{Nujol} cm^{-1}: 1716 (ester), 1588 (-C=N-). NMR (10% solution in $CDCl_3$) δ ppm: 1.36 (6H, triplet, J=7.1 Hz, 2×COOCH$_2$C$\underline{H}_3$), 2.01 (2H, triplet, J=6.8 Hz, methylene protons between two isoxazoline rings), 2.98 (2H, doublet of doublets, J_1=17.4 Hz, J_2=8.3 Hz, 2×-N=C-CH-), 3.25 (2H, doublet of doublets, J_1=17.4 Hz, J_3=10.5 Hz, 2×-N=C-HC-), 4.34 (4H, quartet, J=7.1 Hz, 2×COOC$\underline{H}_2$CH$_3$), 5.05 (2H, tripletting quartet, J_2=8.3 Hz, J_3=10.5 Hz, J_4=6.8 Hz, ring methine protons).

Recrystallization of the latter eluate from ether gave meso-isomer (VIII) as leaflets, mp 73°. *Anal.* Calcd. for $C_{13}H_{18}O_6N_2$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.27; H, 6.15; N, 9.41. UV λ_{max}^{EtOH} mμ (log ε): 246.4 (4.11). IR ν_{max}^{Nujol} cm^{-1}: 1721 (ester), 1595 (C=N). NMR (10% soluton in $CDCl_3$) δ ppm: 1.37 (6H, triplet, J=7.2, 2×COOCH$_2$C$\underline{H}_3$), 2.01 (2H, multiplet, methylene protons between two isoxazoline rings), 3.05 (2H, doublet of doublets, J_1=17.5 Hz, J_2=9.0 Hz, 2×-N=C-CH-), 3.38 (2H, doublet of doublets, J_1=17.5 Hz, J_3=10.3 Hz, 2×-N=C-HC-), 4.38 (4H, quartet, J=7.2 Hz, 2×COOC$\underline{H}_2$CH$_3$), 5.00 (2H, multiplet, ring methine protons).

In another run, starting from 1,4-pentadiene (68 g: 1.0 mole), ethyl chloroximino acetate (966 g: 6.38 mole), tetrahydrofuran (800 ml) and Et_3N (645 g), 240.5 g of a mixture of racemic (VII) and meso (VIII) was obtained (80.8% yield based on 1,4-pentadiene).

Diethyl 5,5′-Methylenebis(2-isoxazoline)-3,3′-dicarboxylate Racemi (VII) and Meso (VIII) from Ethyl 5-(2-Propenyl)-2-isoxazoline-3-carboxylate (VI)——To a mixture of ethyl chloroximino acetate (14.5 g: 0.0954 mole) and ethyl 5-(2-propenyl)-2-isoxazoline-3-carboxylate (VI) (10.99 g: 0.0601 mole) in dry ether

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(500 ml) was dropwise added Et_3N (9.67 g: 0.0954 mole) with vigorous stirring below 10° during 1.5 hr. The reaction mixture was stirred at 23—25° for 21 hr. Precipitates were filtered off, washed three times with ether. The combined filtrate was washed successively with 1N HCl solution, 5% $NaHCO_3$ solution and H_2O until neutral to litmus, dried over Na_2SO_4 and evaporated to give an oil (20.2 g). This oil was chromatographed on silica gel (350 g). Elution with benzene afforded diethyl furoxane-3,4-dicarboxylate (IX)[8] (9.0 g) and recovered ethyl 5-(2-propenyl)-2-isoxazoline-3-carboxylate (VI) (3.9 g). Elution with benzene–ether (7:3) gave a mixture of racemic and meso diethyl 5,5′-methylenebis(2-isoxazoline)-3,3′-dicarboxylate (VII and VIII) (5.73 g, 20.2% yield), whose IR spectrum was identical with that of a mixture of VII and VIII obtained in the former reaction.

Diethyl 5,5′-Methylenebisisoxazole-3,3′-dicarboxylate (IV) from Diethyl 5,5′-Methylenebis(2-isoxazoline)-3,3′-dicarboxylate (VII)——Diethyl 5,5′-methylenebis(2-isoxazoline)-3,3′-dicarboxylate (VII-racemi) (22.0 g: 0.0738 mole) was dissolved in CCl_4 (160 ml) by heating. To this hot solution was added crystalline NBS (freshly recrystallized and finely powdered) (27.6 g: 0.0738×2.1 mole) and α,α′-azobisisobutyronitrile (100 mg). The reaction mixture was heated under reflux by irradiation with an UV lamp for 26 hr. The solid substance was filtered off, washed with $CHCl_3$. The combined filtrate was evaporated under reduced pressure. To the residue was added $CHCl_3$ and insoluble substance was removed by filtration, washed with $CHCl_3$. The filtrate was again evaporated under reduced pressure to give a red oil (38.7 g). This oil was dissolved in dry tetrahydrofuran (200 ml) and to this solution was dropwise added Et_3N (31.4 g: 0.0738×4.2 mole) in tetrahydrofuran (50 ml) under ice–water cooling. After stirring at room temperature for 12 hr the reaction mixture was heated under reflux for 2.5 hr. The cooled mixture was diluted with benzene and washed successively with H_2O, 10% HCl solution, $NaHCO_3$ solution and finally with H_2O until neutral to litmus, dried over Na_2SO_4 and evaporated to give an oil (23 g). This oil was chromatographed on silica gel (500 g) impregnated with 5% $AgNO_3$ solution (dried at 115°). Elution with benzene and $CHCl_3$ gave crystalline diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (5.45 g). Recrystallization from *n*-hexane–EtOH afforded pure IV as prisms, mp 94—95° (2.30 g), which was identical in all respects with a sample obtained from 1,4-pentadiyne and ethyl chloroximino acetate. *Anal.* Calcd. for $C_{13}H_{14}O_6N_2$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.75; H, 4.65; N, 9.70.

5,5′-Methylenebisisoxazole-3,3′-dicarboxylic Acid (X)——Diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (50 mg) was dissolved in dioxane (6 ml) and to this solution was added aqueous 20% HCl solution (6 ml). The reaction mixture was heated on a water bath (40°) for 40 hr. The solution was evaporated under reduced pressure to give a white crystalline substance, mp 155—158° with previous softening (43 mg). Recrystallization from CH_3COOEt–benzene gave 5,5′-methylenebisisoxazole-3,3′-dicarboxylic acid (X) as prisms, mp 173—175° (decomp.) (30 mg). Two more recrystallization from the same solvents afforded a sample melting at 183—185° (decomp.). *Anal.* Calcd. for $C_9H_6O_6N_2$: C, 45.39; H, 2.54; N, 11.76. Found: C, 45.46; H, 2.55; N, 11.68. UV λ_{max}^{EtOH} mμ (log ε): 234.5 (3.92). IR ν_{max}^{Nujol} cm^{-1}: 3070—2500 (COOH), 1709 (CO), 1590 (isoxazole).

Decarboxylation Reaction of 5,5′-Methylenebisisoxazole-3,3′-dicarboxylic Acid (X)——5,5′-Methylenebisisoxazole-3,3′-dicarboxylic acid (X) (399 mg) in DMSO (25 ml) and Et_3N (2.5 ml) was heated on an oil bath (125°) for 30 minutes. After 20 minutes heating, the evolution of CO_2 gas ceased. The solution was evaporated under reduced pressure on a water-bath (60—65°) to dryness to give a crystalline substance (319 mg) mp 250—270°. Recrystallization from EtOH gave black crystalls, mp 242—245° with previous softening (50 mg). From the filtrate, further black crystalls, mp 240° (with previous softening) was obtained (37 mg). IR ν_{max}^{Nujol} cm^{-1}: 2220 (C≡N). IR spectrum of the recrystallized sample was almost same as that of non-recrystallized sample.

2,2-Bis(3-carbethoxy-5-isoxazolyl)-1,3-diphenylpropane (XVII)——Sodium (57 mg: 2.47 mmole) was dissolved in absolute EtOH (12 ml) and to this solution was added crystalline diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (729 mg: 2.47 mmole) and dimethylsulfoxide (4 ml). After stirring at room temperature for 30 minutes, benzyl bromide (424 mg: 2.47 mmole) in absolute EtOH (2 ml) was added and the reaction mixture was heated on a water bath (80—85°) for 5.5 hr. The mixture was poured into ice–water and extracted with ether. The combined extracts were washed three times with H_2O, dried over Na_2SO_4 and evaporated to give an oil (818 mg). This oil was chromatographed on silica gel (40 g). Elution with benzene–$CHCl_3$ (20:1) and evaporation afforded an oil (156 mg), which crystallized on standing. Recrystallization from EtOH gave 2,2-bis(3-carbethoxy-5-isoxazolyl)-1,3-diphenylpropane (XVII) as leaflets, mp 159—160° (130 mg). *Anal.* Calcd. for $C_{27}H_{26}O_6N_2$: C, 68.34; H, 5.52; N, 5.90. Found: C, 68.21; H, 5.64; N, 5.93. UV ν_{max}^{EtOH} mμ (log ε): 238.5 (3.89). IR ν_{max}^{Nujol} cm^{-1}: 1732 (CO), 1588 (isoxazole). NMR (10% solution in $CDCl_3$) δ ppm: 1.41 (6H, triplet, $J=7.0$ Hz, $2\times COOCH_2CH_3$), 3.64 (4H, singlet, $2\times C_6H_5-CH_2-$), 4.46 (4H, quartet, $J=7.0$ Hz, $2\times COOCH_2CH_3$), 6.34 (2H, singlet, isoxazole H at 4 position), 6.60—7.30 (10H, multiplet, aromatic hydrogens).

Further elution with $CHCl_3$ gave a crystalline substance (295 mg), which was rechromatographed on silica gel (7.0 g). Elution with benzene and benzene–$CHCl_3$ (1:1) afforded the starting material, diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (93 mg).

2,2-Bis(3-carbethoxy-5-isoxazolyl)styrene (XIX) and 1,1-Bis(3-carbethoxy-5-isoxazolyl)-1-propenyl-2-acetate (XX)——A mixture of diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (2.50 g: 8.5 mmole),

benzaldehyde (0.90 g: 8.5 mmole), Et_3N (0.86 g: 8.5 mmole) and acetic anhydride (20 ml) was heated on a water-bath (80—85°) for 16 hr. The cooled solution was poured into ice-water (300 ml) and extracted with ether. The combined extracts were washed with $NaHCO_3$ solution and saturated NaCl solution, dried over Na_2SO_4 and evaporated to give an oil (3.0 g). This oil was chromatographed on silica gel (30 g). Elution with benzene and evaporation gave 2,2-bis(3-carbethoxy-5-isoxazolyl)styrene (XIX) as an oil, which was distilled under high vacuum to give pure XIX, bp 230—240° (bath temperature) (0.0001 mmHg). *Anal.* Calcd. for $C_{20}H_{18}O_6N_2$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.77; H, 4.78; N, 7.45. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.06) (plateau), 259.5 (3.97) (plateau), 314 (4.35). IR ν_{max}^{liquid} cm^{-1}: 3140 (isoxazole H at 4 position), 1732 (C=O), 1630, 1575. NMR (10% solution in $CDCl_3$) δ ppm: 1.41 (3H, triplet, J=7.3 Hz, -COOCH$_2$C$\underline{H}_3$), 1.45 (3H, triplet, J=7.3 Hz, -COOC$\underline{H}_2$CH$_3$), 4.48 (2H, quartet, J=7.3 Hz, -COOC$\underline{H}_2$CH$_3$), 4.50 (2H, quartet, J=7.3 Hz, -COOC$\underline{H}_2$CH$_3$), 6.57 (1H, singlet, isoxazole H at 4 position), 6.76 (1H, singlet, isoxazole H at 4 position), 7.00—7.60 (5H, multiplet, aromatic hydrogens), 7.83 (1H, singlet, C_6H_5-C$\underline{H}$-C<).

Further elution with benzene afforded 1,1-bis(3-carbethoxy-5-isoxazolyl)-1-propenyl-2-acetate (XX) as an oil. High vacuum distillation gave pure XX, bp 200—205° (bath temperature) (0.0001 mmHg) (500 mg), which solidified on standing. Recrystallization from cyclohexane gave needles, mp 66—67°. *Anal.* Calcd. for $C_{17}H_{18}O_8N_2$: C, 53.97; H, 4.80; N, 7.41. Found: C, 53.80; H, 4.87; N, 7.45. UV λ_{max}^{EtOH} mμ (log ε): 240 (4.05) (shoulder), 263 (4.17). IR ν_{max}^{Nujol} cm^{-1}: 3160 (isoxazole H at 4 position), 1775, 1732 (C=O), 1658, 1588. NMR (10% solution in $CDCl_3$) δ ppm: 1.42 (3H, triplet, J=7.2 Hz, -COOCH$_2$C$\underline{H}_3$), 1.44 (3H, triplet, J=7.2 Hz, -COOCH$_2$C$\underline{H}_3$), 2.28 (3H, singlet, -CH$_3$), 2.33 (3H, singlet, -CH$_3$), 4.46 (2H, quartet, J=7.2 Hz, -COOC$\underline{H}_2$-CH$_3$), 4.48 (2H, quartet, J=7.2 Hz, -COOC$\underline{H}_2$CH$_3$), 6.63 (1H, singlet), 6.78 (1H, singlet).

1,1-Bis(3-carbethoxy-5-isoxazolyl)-1-propenyl-2-acetate (XX) from Diethyl 5,5′-Methylenebisisoxazole-3,3′-dicarboxylate (IV) and Acetic Anhydride——A mixture of diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (200 mg), Et_3N (200 mg) and acetic anhydride (4 ml) was heated on an oil bath (115°) for 9 hr. The cooled solution was poured into ice-water and stirred for 2 hr after addition of ether in order to decompose the excess of acetic anhydride. Ethereal layer was separated and washed with $NaHCO_3$ solution, and then with H_2O until neutral to litmus. After drying over Na_2SO_4 ether was evaporated to give an oil (254 mg), which was chromatographed on silica gel (12 g). Elution with benzene–$CHCl_3$ (7:3) and evaporation afforded 1,1-bis(3-carbethoxy-5-isoxazolyl)-1-propenyl-2-acetate (XX) as an oil (180 mg), which crystallized on standing for a long time. Recrystallization from cyclohexane gave tufts of needles, mp 65—66° with previous softening (104 mg). An analytical sample melted at 66—67°, which was identical in all respects with a sample obtained in the reaction of IV with benzaldehyde and acetic anhydride. *Anal.* Calcd. for $C_{17}H_{18}O_8N_2$: C, 53.97; H, 4.80; N, 7.41. Found: C, 54.16; H, 5.02; N, 7.67.

Ethyl 4-Bis(3-carbethoxy-5-isoxazoyl)-3-phenylbutyrate (XXII)——Sodium (13 mg) was dissolved in absolute EtOH (1 ml) and to this solution was added crystalline diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (294 mg: 1 mmole) and then, ethyl cinnamate (XXI) (176 mg: 1 mmole) in absolute EtOH (1.3 ml) was added at room temperature. The reaction mixture was heated under reflux for 6 hr. To the cooled mixture were added AcOH (34 mg) and H_2O and extracted with ethyl acetate (the aqueous solution was saturated with NaCl). The combined extracts were washed once with saturated NaCl solution, dried over Na_2SO_4 and evaporated to give an oil (455 mg). This oil was chromatographed on silica gel (10 g). Elution with benzene and benzene–$CHCl_3$ (2:1) gave ethyl 4-bis(3-carbethoxy-5-isoxazolyl)-3-phenylbutyrate (XXII) as an oil (213 mg), which could not be distilled even in high vacuum (0.0001 mmHg). *Anal.* Calcd. for $C_{24}H_{26}O_8N_2$: C, 61.27; H, 5.57; N, 5.96. Found: C, 62.15; H, 5.80; N, 5.97. UV λ_{max}^{EtOH} mμ (log ε): 237 (4.02). IR ν_{max}^{liquid} cm^{-1}: 3135 (isoxazole H at 4 position), 1725 (CO), 1593 (isoxazole). NMR (10% solution in $CDCl_3$) δ ppm: 1.10 (3H, triplet, J=7.3 Hz, -COOCH$_2$C$\underline{H}_3$), 1.39 (3H, triplet, J=7.3 Hz, -COOCH$_2$C$\underline{H}_3$), 1.44 (3H, triplet, J=7.3 Hz, -COOCH$_2$C$\underline{H}_3$), 2.75 (2H, doublet, J=7.5 Hz, -CH$_2$-COO-), 4.01 (2H, quartet, J=7.3 Hz, -COOC$\underline{H}_2$CH$_3$), 4.06 [1H, multiplet (obscure), J_1=7.5 Hz, J_2=9.5 Hz, C_6H_5-C$\underline{H}$<], 4.42 (2H, quartet, J=7.3 Hz, -COOC$\underline{H}_2$CH$_3$), 4.48 (2H, quartet, J=7.3 Hz, -COOC$\underline{H}_2$CH$_3$), 5.00 (1H, doublet, J=9.5 Hz, methine between two isoxazole rings), 6.43 (1H, singlet, isoxazole ring H at 4 position), 6.68 (1H, singlet, isoxazole ring H at 4 position), 7.00—7.40 (5H, multiplet, aromatic hydrogens).

Triethylamine Salt of Ethyl 5-Benzoylamino-7-(3-carbethoxy-5-isoxazoyl)-4,7-dihydro-4-oxo-1,2-benzisoxazol-3-carboxylate (XXIV)——To a mixture of diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (1.0 g: 0.0034 mole) and 4-ethoxymethylene-2-phenyl-2-oxazoline-5-one (738 mg: 0.0034 mole) in dimethyl sulfoxide (11 ml) was added Et_3N (378 mg: 0.0034 × 1.1 mole) in dimethyl sulfoxide (2 ml) at room temperature. The reaction mixture was allowed to stand at room temperature for 48 hr. The solution was poured into ice-water and the appeared precipitate was collected by centrifugation, dried *in vacuo* to give a red crystalline substance (1.36 g), mp 146—150°. Recrystallization from dioxane gave pure triethylamine salt of ethyl 5-benzoylamino-7-(3-carbethoxy-5-isoxazolyl)-4,7-dihydro-4-oxo-1,2-benzisoxazol-3-carboxylate (XXIV) as needles, mp 152—154° (870 mg). An analytical sample melted at 153—155° after recrystallization from ethyl acetate. *Anal.* Calcd. for $C_{29}H_{34}O_8N_4$: C, 61.47; H, 6.05; N, 9.89. Found: C, 61.84; H, 6.19; N, 9.76. UV ν_{max}^{EtOH} mμ (log ε): 255 (4.16), 338 (3.95), 354 (3.96), 477 (4.58). IR ν_{max}^{Nujol} cm^{-1}: 2640, 2520, 1743, 1730, 1648, 1608, 1597, 1585, 1566, 1528, 1271, 1253, 1232. NMR (10% solution in CD_3-SOCD_3) δ ppm (100 Mc): 1.21 (9H, triplet, J=7 Hz, >N-CH$_2$C$\underline{H}_3$), 1.36 (3H, triplet, J=7 Hz, -COOCH$_2$C$\underline{H}_3$), 1.43 (3H, triplet, J=7 Hz, -COOCH$_2$C$\underline{H}_3$), 3.10 (6H, quartet, J=7 Hz, -N-C$\underline{H}_2$CH$_3$), 4.39 (2H, quartet,

J=7 Hz, -COOC$\underline{H}_2$CH$_3$), 4.45 (2H, quartet, J=7 Hz, -COOC$\underline{H}_2$CH$_3$), 6.55 (1H, singlet, isoxazole H at 4 position), 7.32 (1H, singlet, $\underline{H}$-C=C-NHCOC$_6$H$_5$), 8.04 (1H, broad singlet, -NH), 7.35—7.88 (5H, multiplet, aromatic hydrogens).

Ethyl 5-Benzoylamino-7-(3-carbethoxy-5-isoxazolyl)-6-phenyl-5,6-dihydro-1,2-benzisoxazol-4(3aH)-oxo-3-carboxylate (XXVI)——To a mixture of diethyl 5,5′-methylenebisisoxazole-3,3′-dicarboxylate (IV) (100 mg: 0.34 mmole) and 4-benzal-2-phenyl-2-oxazoline-5-one (XXV) (84.8 mg: 0.34 mmole) in dimethylformamide (1 ml) was dropwise added Et_3N (37.8 mg; 0.34×1.1 mmole) in dimethylformamide (1 ml). The reaction mixture was allowed to stand at room temperature for 40 hr. The yellow clear solution was poured into ice–water and extracted three times with $CHCl_3$. The combined extracts were evaporated under reduced pressure to give an oil (188 mg), which was chromatographed on silica gel (6.5 g). Elution with benzene–$CHCl_3$ (1:1) and evaporation gave an oil (86 mg), which crystallized when dissolved in small amount of benzene and left overnight. Recrystallization from EtOH gave ethyl 5-benzoylamino-7-(3-carbethoxy-5-isoxazolyl)-6-phenyl-5,6-dihydro-1,2-benzisoxazol-4(3aH)-oxo-3-carboxylate (XXVI) as flakes, mp 166—168° (57 mg). One more recrystallization from the same solvent gave a sample melting at 175—177° (33 mg). *Anal.* Calcd. for $C_{29}H_{25}O_8N_3$: C, 64.08; H, 4.64; N, 7.73. Found: C, 63.66; H, 4.75; N, 7.80. UV λ_{max}^{EtOH} mμ (log ε): 237.5 (4.42). IR ν_{max}^{Nujol} cm^{-1}: 3280, 3160, 1732, 1687, 1604, 1588, 1514, 1269, 1244. NMR (10% solution in $CDCl_3$) δ ppm: 1.35 (3H, triplet, J=7 Hz, -COOCH$_2$C$\underline{H}_3$), 1.37 (3H, triplet, J=7 Hz, -COOCH$_2$-C$\underline{H}_3$), 4.38 (2H, quartet, J=7 Hz, -COOC$\underline{H}_2$CH$_3$), 4.43 (2H, quartet, J=7 Hz, -COOC$\underline{H}_2$CH$_3$), 5.57 (1H, doublet, J=11.5 Hz, C$_6$H$_5$C$\underline{H}$<), 5.96 (1H, doublet, J=11.5 Hz, C$_6$H$_5$CONH-C$\underline{H}$<), 6.46 (1H, singlet, -CO-C$\underline{H}$< or isoxazole H at 4 position), 6.82 (1H, singlet, isoxazole H at 4 position or -CO-CH<), 7.20—8.00 (10H, multiplet, aromatic hydrogens), 9.13 (1H, broad singlet, NH).

Acknowledgement The authors are very grateful to Mr. T. Miyamura for his technical assistance. They also wish to express their thanks to Mr. H. Kuwano for measuring 100 Mc NMR. Thier thanks are also due to the members of physical chemistry laboratory for the spectroscopic measurement and microanalyses.