Tetrahedron 1964, Vol. 20, pp. 461 to 464. Pergamon Press Ltd. Printed in Northern Ireland

ISOXAZOLES—XIV*

A NEW CONVERSION OF 3-DIAZOAMINOISOXAZOLES INTO TETRAZOLES

H. Kano and E. Yamazaki
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku,
Osaka, Japan

(*Received* 3 *September*; *in revised form* 28 *October* 1963)

Abstract—In the course of our studies on the isoxazole series, a new base-induced conversion of 1,3-bis(5'-methyl-3'-isoxazolyl)triazene (IIa) into 2-(5'-methyl-3'-isoxazolyl)-5-acetonyltetrazole (IIIa) has been encountered. This reaction has been extended to 3-(*m*- and *p*-nitrophenyldiazoamino)-5-methylisoxazoles (IIb and IIc), which undergo similar conversion into 2-(*m*- and *p*-nitrophenyl)-5-acetonyltetrazoles (IIIb and IIIc), respectively. These 5-acetonyltetrazoles have been oxidized to the corresponding 5-tetrazolecarboxylic acids (IVa, IVb and IVc).

Reaction of 5-methyl-3-aminoisoxazole[1] (I) with one half equivalent amounts of sodium nitrite in 10% hydrochloric acid gave a yellow crystalline compound, which was assigned the structure 1,3-bis-(5'-methyl-3'-isoxazolyl)triazene (IIa). Confirmation of the structure assigned to IIa was obtained by stannous chloride–hydrochloric acid reduction of IIa, which gave a mixture of I and 3-hydrazino-5-methylisoxazole. The latter was isolated as an oil by means of chromatography on alumina and converted to its benzylidene derivative for characterization.

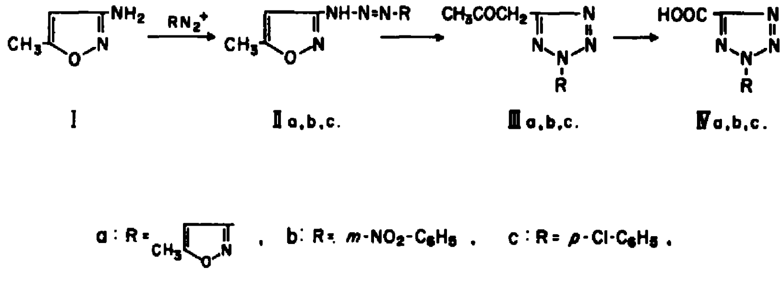

Chart I

When the triazene IIa was dissolved by warming in an alkaline medium, an exothermic reaction occurred and an isomer of IIa was obtained in good yield. In this reaction aqueous acetone containing ammonia was found to be a preferable medium.

The IR spectrum of this product exhibited characteristic absorption bands due to the carbonyl group at 1730 cm^{-1} and a series of bands attributable to isoxazole ring

---

* A brief report of this work was published as a Communication to the Editor in *Chem. Pharm. Bull.* **10**, 993 (1962).

[1] H. Kano and K. Ogata, *Ann. Rept. Shionogi Res. Lab.* 7 (1), 1 (1957).

stretching[2] at 1617 cm^{-1}, 1463 cm^{-1} and 1413 cm^{-1}. The presence of a ketone group in the product was confirmed by the formation of an oxime. Therefore the structure of 2-(5′-methyl-3′-isoxazolyl)-5-acetonyltetrazole (IIIa) was assigned to this compound. Oxidation of IIIa with potassium permanganate in aqueous acetone yielded a carboxylic acid which is best represented by the structure of 2-(5′-methyl-3′-isoxazolyl)-5-tetrazolecarboxylic acid (IVa). Further evidence concerning the structure of these products was obtained by the following analogous reactions.

3-(*m*- and *p*-nitrophenyldiazoamino)-5-methylisoxazoles (IIb and IIc) were prepared by the action of equimolar amounts of *m*- and *p*-nitrobenzenediazonium chloride on I, respectively; IIb and IIc underwent conversion to the corresponding isomers by the same treatment as for IIa. The products were assigned the structures 2-*m*- and 2-*p*-nitrophenyl-5-acetonyltetrazoles (IIIb and IIIc), respectively, by their elementary analyses and IR spectra which indicated the presence of ketone groups (1730 cm^{-1} and 1732 cm^{-1}, respectively). Oxidation of IIIb and IIIc with potassium permanganate gave the corresponding 2-substituted 5-tetrazolecarboxylic acids (IVb and IVc). Definite proof for the tetrazole structure was obtained by identifying IVc and its methyl ester with authentic samples prepared by the method of Bladin.[3]

Only one example has been reported by Woodward and Olofson,[4] for conversion of the isoxazole derivative into the tetrazole derivative. N-methyl-5-phenylisoxazolium salt (IV) undergoes conversion into 1-methyl-5-benzoylmethyltetrazole (VII) by rapid combination with azide ion in aqueous solution followed by treatment with methanol–water. The intermediate of this reaction is isolated and formulated as the iminoazide (VI). This reaction seems to have a feature closely resembling the present new type of conversion of isoxazoles.

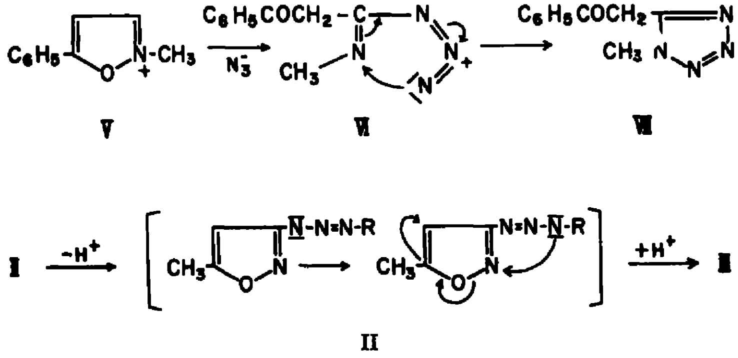

Chart 2

In consequence, a tentative mechanism for the formation of the 2-substituted 5-acetonyltetrazole (III) from the 3-diazoaminoisoxazole derivative (II) is proposed. Abstraction of a proton from II by the attack of base on the acidic amino group lends the hybride anion (II′), which induces rupture of the N—O bond in the isoxazole ring. Subsequent or synchronous recyclization between two nitrogens in a similar manner as in VI affords the tetrazole derivative III.

---

[2] A. R. Katritzky and A. Boulton, *Spectrochim. Acta* **17**, 258 (1961); *Tetrahedron* **12**, 41 (1961).

[3] J. A. Bladin, *Chem. Ber.* **25**, 1411 (1892).

[4] R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.* **83**, 1007 (1961).

EXPERIMENTAL

M.p.s. were determined on a Kofler-Block "Monoscop IV" and are uncorrected, UV absorption spectra were recorded on a Hitachi Recording UV Spectrophotometer EPS-2, and IR spectra were taken on a Ko-Ken IR Spectrophotometer, Model DS 301.

1,3-*Bis(5′-methyl-3′-isoxazolyl)triazene* (IIa)

To a solution of 10 g 5-methyl-3-aminoisoxazole (I) in 30 ml 10% HCl, 35 ml 10% sodium nitrite solution was added with stirring below 5°. The resulting precipitate was collected by filtration, yield 9 g (87%). Recrystallization from ethanol gave pale yellow crystals, m.p. 146–147°, λ_{max}^{EtOH} 291 mμ (log ε 4·25), $\nu_{max}^{CHCl_3}$ 3300 cm^{-1} (—NH—), 1550 cm^{-1} (—N=N—). (Found: C, 46·35; H, 4·61; N, 33·80; $C_8H_9O_2N_5$ requires: C, 46·37; H, 4·38; N, 33·80%).

Stannous chloride–hydrochloric acid reduction of IIa

To a solution of 10 g IIa in 120 ml conc. HCl, 21·8 g $SnCl_2 \cdot 2H_2O$ was added in small portions at 30–40°. After the addition, stirring was continued for 30 min and the solution was then allowed to stand for 3 hr. Under ice cooling and stirring the solution was basified (NaOH aq.), followed by repeated extractions of the reaction mixture with chloroform. The chloroform extract was concentrated, dried over Na_2SO_4 and chromatographed on alumina. Elution with chloroform gave 3·15 g I and further elution with ethanol gave 0·65 g *5-methyl-3-hydrazinoisoxazole* (oil), which on treatment with benzaldehyde in ethanol gave its *benzylidene derivative*. Recrystallization from ethanol gave pale yellow crystals, m.p. 149° (Found: C, 65·93; H, 5·55; N, 20·45; $C_{11}H_{11}ON_3$ requires: C, 65·67; H, 5·51; N, 20·88%).

3-(m-*Nitrophenyldiazoamino*)-*5-methylisoxazole* (IIb)

To a solution of 20 g I and 56 g of sodium acetate in 1000 ml water, a solution of *m*-nitrobenzendiazonium chloride (prepared from 28 g of *m*-nitroaniline, 14 g of sodium nitrite and 220 ml of 10% HCl) was added with stirring below 5°. After the addition, a small amount of red brown by-product was filtered off. The filtrate was allowed to stand for 2 days, giving 40·5 g pale yellow solid (82%). Recrystallization from acetone gave pale yellow crystals, m.p. 131·5–133·5°, λ_{max}^{EtOH} 250 mμ (log ε 4·36), $\nu_{max}^{CHCl_3}$ 3265 cm^{-1} (—NH—), 1545 cm^{-1} (—N=N—). (Found: C, 48·45; H, 3·93; N, 28·20; $C_{10}H_9O_3N_5$ requires: C, 48·58; H, 3·65; N, 28·33%).

3-(p-*Nitrophenyldiazoamino*)-*5-methylisoxazole* (IIc)

This compound was obtained by the same procedure as for IIb in 62% yield. Recrystallization from acetone gave pale yellow crystals, m.p. 169–171°, λ_{max}^{EtOH} 286 mμ (log ε 4·3), $\nu_{max}^{CHCl_3}$ 3200 cm^{-1} (—NH—), 1550 cm^{-1} (—N=N—). (Found: C, 48·22; H, 3·71; N, 28·22; $C_{10}H_9O_3N_5$ requires: C, 48·58; H, 3·65; N, 28·33%).

2-(*5′-Methyl-3′-isoxazolyl*)-*5-acetonyltetrazole* (IIIa)

A solution of 2·1 g IIa in aqueous acetone containing 5% ammonia (sufficient amount to dissolve the solid) was heated on a water bath for about 5 min. An exothermic reaction occurred and a crystalline product precipitated. Water was added to the reaction mixture and the precipitate removed by filtration, yield, 1·7 g (81%). Recrystallization from ethyl acetate gave colorless plates, m.p. 147–149°. (Found: C, 46·64; H, 4·66; N, 33·48; $C_8H_9O_2N_5$ requires: C, 46·35; H, 4·38; N, 33·80%).

Oxime of IIIa

To a solution of 0·5 g IIIa in 5 ml ethanol, 0·2 g $NH_2OH \cdot HCl$ and 0·3 g Na_2CO_3 were added. The solution was refluxed for 10 min on a water bath, then diluted with 5 ml water to precipitate crystals. Recrystallization from ethanol gave 0·3 g VI, m.p. 134–136°. (Found: C, 43·52; H, 4·99; N, 37·54; $C_8H_{10}O_2N_6$ requires; C, 43·24; H, 4·54; N, 37·83%).

2-(m-*Nitrophenyl*)-*5-acetonyltetrazole* (IIIb)

By the above procedure 38·2 g (94·5%) IIIb was obtained from 40·5 g IIb. Recrystallization from alcohol gave pale yellow prisms, m.p. 113–114°. (Found: C, 48·82; H, 4·04; N, 28·08; $C_{10}H_9O_3N_5$ requires: C, 48·58; H, 3·65; N, 28·33%).

2-(p-*Nitrophenyl*)-*5-acetonyltetrazole* (IIIc)

By the above procedure 2·6 g (56%) IIIc was obtained from 4·6 g IIc. Recrystallization from ethyl acetate gave colorless plates, m.p. 132–134°. (Found: C, 48·76; H, 3·94; N, 28·08. $C_{10}H_9O_3N_5$ requires: C, 48·58; H, 3·65; N, 28·33%).

2-(5′-*Methyl-3′-isoxazolyl*)-*5-tetrazolecarboxylic acid* (IVa)

To a solution of 0·1 mole IIIa in 300 ml acetone and 100 ml water, 32 g $KMnO_4$ was added in small portions at 60° with stirring. Heating and stirring was continued until the color of permanganate had disappeared, and the resulting hot mixture was filtered. After cooling, the filtrate was acidified with 10% HCl. Most of the acetone was removed to precipitate the acid; yield, 50%. Recrystallization from water gave colorless plates, m.p. 150° (dec.). (Found: C, 36·86; H, 2·83; N, 36·06; $C_6H_5O_3N_5$ requires: C, 36·93; H, 2·58; N, 35·89%).

2-(m-*Nitrophenyl*)-*5-tetrazolecarboxylic acid* (IVb) was obtained from IIIb by the same procedure as for IVa in 80% yield. Recrystallization from water gave colorless plates, m.p. 144–147° (dec.). (Found: C, 39·46; H, 2·64; N, 28·58; $C_8H_5O_4N_5 \cdot \frac{1}{2}H_2O$ requires: C, 39·34; H, 2·46; N, 28·69%).

2-(p-*Nitrophenyl*)-*5-tetrazolecarboxylic acid* (IVc) was obtained from IIIc by the same procedure as for IVa in 58% yield. Recrystallization from acetone–water gave colorless plates, m.p. 172–174° (dec.), which was identified by mixed m.p. and comparison of IR spectra with an authentic sample.[8] (Found: C, 40·89; H, 2·36; N, 29·40; Calc. for $C_8H_5O_4N_5$: C, 40·86; H, 2·14; N, 29·78%).

Methylester of IVc was prepared by refluxing of 8 g IVc in 50 ml ethanol containing of 2 ml H_2SO_4 for 3 hr. Recrystallization from ethyl acetate gave crystals, m.p. 167·5–169·5°, which was undepressed by admixture with an authentic sample.[8] (Found: C, 43·39; H, 3·02; N, 27·76; Calc. for $C_9H_7O_4N_5$: C, 43·38; H, 2·83; N, 28·11%).

Acknowledgements—The authors are greatly indebted to Prof. Emeritus E. Ochiai of Tokyo University and Dr. K. Takeda of this laboratory for their helpful advice and continued encouragement. Thanks are also due to Dr. Y. Matsui, Mr. I. Tanaka and Mr. M. Takasuka for ultraviolet and infrared spectral measurements, and to the members of the Analysis Room of this laboratory for elemental analysis.