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140. Hideo Kano, Ikuo Adachi, and Eiko Yamazaki: Isoxazoles. XVI.[*1] The Reaction of Nitrous Acid on 5-Amino-3,4-dialkylisoxazoles.

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As described in a previous paper[1] of this series, it has been shown that the reaction of nitrous acid on 3-aminoisoxazoles gives 1,3-bis(3-isoxazolyl)triazenes. The behavior of nitrous acid on 5-aminoisoxazoles has not been thoroughly investigated. Although the reaction of 3-ethyl-4-methyl-5-aminoisoxazole (Ic) with nitrous acid was reported by Hanriot[2] and the structure 3,3′-diethyl-4,4′-dimethyl-5,5′-azoxyisoxazole (II) was assigned to the reaction product, our present investigation has revealed this assignment is in error.

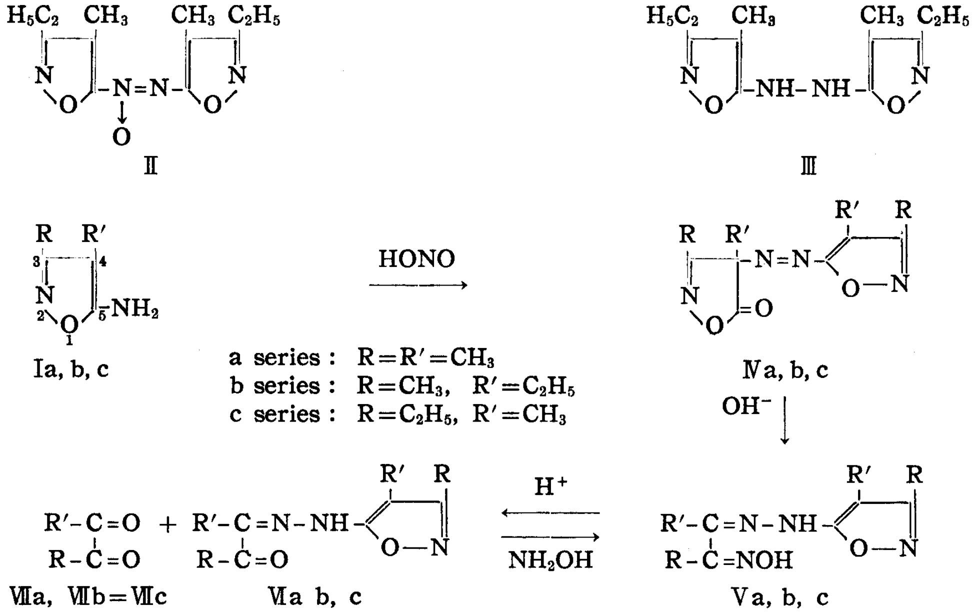

Chart 1.

When Ic was treated with one half equivalent amounts of sodium nitrite in 20% hydrochloric acid, it gave yellow crystals, m.p. 63.5～64° in good yield. The molecular formula and melting point of this product (IVc) are in good agreement with those of the compound formulated as II by Hanriot.[2] However, its infrared spectrum showed a strong absorption band at 1800 cm^{-1}. Analogous reaction products (IVa and IVc) obtained from 3,4-dimethyl- and 3-methyl-4-ethyl-5-aminoisoxazoles (Ia and Ib) also exhibited strong absorption bands at 1800 cm^{-1}. These spectral data cannot be reconciled with the azoxy structure such as II.

It was reported by Boulton and Katritzky[3] that the infrared spectra of 5(4*H*)-isoxazolones exhibit characteristic carbonyl absorption bands at 1793～1808 cm^{-1}, which suggests the structure of IVa, b, c would insolve the 5(4*H*)-isoxazolone ring. Further

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[*1] Part XV: Tetrahedron, **20**, 159 (1964).

[*2] Fukushima-ku, Osaka (加納日出夫, 足達郁夫, 山崎瑛子).

1) H. Kano, E. Yamazaki: Tetrahedron, **20**, 261 (1954).

2) M. Hanriot: Compt. rend., **112**, 798; Bull. soc. chim. France, (3) **5**, 776 (1891).

3) A. J. Boulton, A. R. Katritzky: Tetrahedron, **12**, 41 (1961).

information available for assignment of the structure can be obtained by the fact[4] that 3-methyl-5-aminoisoxazole couples with aryldiazonium salts giving the corresponding 4-arylazo derivatives. Based on these considerations, the product (IVa, IVb, and IVc) should be formulated as 4-(3,4-dialkyl-5-isoxazolyl)azo-3,4-dialkyl-5(4*H*)-isoxazolones.

When the compounds (IVa, IVb, and IVc) were warmed with aqueous ammonia for a few minutes, hydrolytic ring cleavage and decarboxylation occurred to give the corresponding 3,4-dialkyl-5-isoxazolylhydrazones of α,β-diketone monooximes (Va, Vb, and Vc), the infrared spectra of which showed the presence of -NH-, -OH, and -C=N- groups. Treatment of IVc with hydrogen sulfide in alcoholic ammonia also produced Vc, which seems to have been erroneously formulated as 1,2-bis(3-ethyl-4-methyl-5-isoxazolyl)-hydrazine (III)[*3] by Hanriot.[2] Further hydrolysis of Va, b, c with sulfuric acid gave mixtures of simple diketones (VIIa, VIIb, and VIIc) and their 3,4-dialkyl-5-isoxazolylhydrazones (VIa, VIb, and VIc), respectively. Reaction of VIa, b, c with hydroxylamine hydrochloride reproduced the corresponding oximes (Va, Vb, and Vc). These decomposition reactions provide further evidence in support of the present assignment for the compounds (IVa, IVb, and IVc).

The formation of IVa, b, c would involve initial diazotization of one half amounts of amines (Ia, Ib, and Ic), followed by coupling of the resultant diazonium salts with the other half amounts of amines in their tautomeric imide form, and subsequent hydrolysis of the imino group. The following experiment was carried out to gain insight into this reaction mechanism.

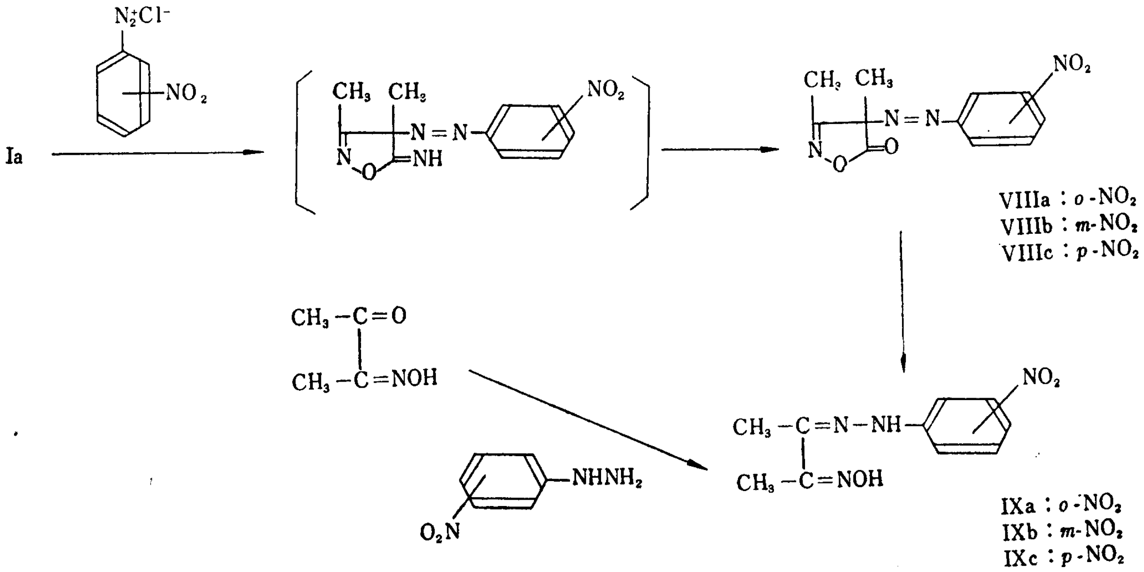

Chart 2.

Reaction of Ia with *o*-, *m*-, and *p*-nitrobenzenediazonium chloride gave 4-nitrophenylazo-3,4-dimethyl-5(4*H*)-isoxazolones (VIIIa, VIIIb, and VIIIc), the infrared spectra of which showed the characteristic strong carbonyl bands near 1800 cm^{-1}. VIIIa, b, c were hydrolyzed with ethanolic ammonia to give the corresponding nitrophenylhydrazones of 2,3-butanedione monooxime (IXa, IXb, and IXc),[5] which were proved to be identical with samples prepared from 2,3-butanedione monooxime[6] and *o*-, *m*-, or *p*-nitrophenylhydrazone, respectively. This unequivocal sequence of reactions which is apparently analogous

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[*3] The melting point (ca. 150°) reported by Hanriot as that of III is nearly identical with that of Vc.

4) E. v. Meyer : J. prakt. Chem., [2], 58, 146 (1898).

5) P. C. Guha, N. K. De : J. Indian Chem. Soc., 3, 46 (1926).

6) O. Diels, H. Jost : Ber., 35, 3290 (1902).

to the reaction sequence in Chart 1, provides support for the mechanism proposed to explain the formation of IVa, b, c.

Experimental[*4]

Reaction of Nitrous Acid on 5-Amino-3,4-dimethylisoxazole (Ia)——To a solution of Ia (20 g.) in 20% HCl (70 ml.) was added an aqueous solution of $NaNO_2$ (7 g.) with stirring below 5°. The resulting precipitate was filtered, washed with H_2O and dried to give 19.3 g. (78%) of 4-(3,4-dimethyl-5-isoxazolyl)azo-3,4-dimethyl-5(4*H*)-isoxazolone (IVa). Recrystallization from dil. EtOH gave yellow crystals, m.p. 85°, IR cm^{-1} : $\nu_{C=O}$ 1800 (Nujol). *Anal.* Calcd. for $C_{10}H_{12}O_3N_4$: C, 50.84; H, 5.12; N, 23.72. Found : C, 50.66; H, 5.19; N, 23.28.

Reaction of Nitrous Acid on 3-Methyl-4-ethyl-5-aminoisoxazole (Ib)——To a solution of Ib (5 g.) in 10% HCl was added an aqueous solution of $NaNO_2$ (1.4 g.) with stirring below 5°. The resulting solution was extracted with $CHCl_3$, and the extract was dried over anhyd. Na_2SO_4 and evaporated to yield 5.1 g. of yellow liquid. IR cm^{-1} : $\nu_{C=O}$ 1800 (Nujol).

Reaction of Nitrous Acid on 3-Ethyl-4-methyl-5-aminoisoxazole (Ic)——By the above procedure, 4.55 g. (60%) of 3-ethyl-4-methyl-4-(3-ethyl-4-methyl-5-isoxazolyl)azo-5(4*H*)-isoxazolone (IVc) was obtained from Ic (8 g.) and $NaNO_2$ (2.3 g.). Recrystallization from dil. EtOH gave yellow crystals, m.p. 63.5~64°, IR cm^{-1} : $\nu_{C=O}$ 1800 ($CHCl_3$). *Anal.* Calcd. for $C_{12}H_{16}O_3N_4$: C, 54.55; H, 6.10; N, 21.20. Found : C, 54.84; H, 6.27; N, 21.45.

Hydrolysis of 5-Isoxazolones (IVa,b,c) with Aqueous Ammonia——As a typical procedure the hydrolysis of IVa was carried out as follows. When a solution of IVa (2 g.) in 10% NH_4OH (20 ml.) was heated on a water bath for 5 min., an exothermic reaction occurred. The solution was acidified with HCl to precipitate 1.7 g. (85%) of 3,4-dimethyl-5-isoxazolylhydrazone of 2,3-butanedione monooxime (Va). Recrystallization from EtOH gave colorless crystals, m.p. 202~203°, IR cm^{-1} : $\nu_{-NH-, -OH}$ 3330, 3260; $\nu_{C=N}$ 1145 (Nujol). *Anal.* Calcd. for $C_9H_{16}O_2N_4$: C, 50.93; H, 7.60; N, 26.40. Found : C, 51.58; H, 7.02; N, 26.25.

3-(3-Methyl-4-ethyl-5-isoxazolyl)hydrazone of 2,3-pentanedione 2-oxime (Vb) : Colorless prisms (dil. EtOH), m.p. 203.5~205°. Yield, 61.7%. *Anal.* Calcd. for $C_{11}H_{18}O_2N_4$: C, 55.44; H, 7.61; N, 23.52. Found : C, 55.06; H, 7.85; N, 23.56.

2-(3-Ethyl-4-methyl-5-isoxazolyl)hydrazone of 2,3-pentanedione 3-oxime (Vc) : Colorless prisms (dil. EtOH), m.p. 149~150°. Yield, 100%. *Anal.* Calcd. for $C_{11}H_{18}O_2N_4$: C, 55.44; H, 7.61; N, 23.52. Found : C, 55.25; H, 7.85; N, 23.96. Vc was proved to be identical with a sample prepared by treating IVc with H_2S in alcoholic ammonia. This product was erroneously formulated as III by Hanriot.[2)]

Hydrolysis of Hydrazones (Va,b,c) with Sulfuric Acid——Va, Vb or Vc was dissolved in 30~40% H_2SO_4. After cooling, the solution was diluted with H_2O, then extracted with benzene. Evaporation of the solvent gave the corresponding isoxazolylhydrazone of 2,3-butanedione.

2-(3,4-Dimethyl-5-isoxazolyl)hydrazone of 2,3-butanedione (VIa) : Pale yellow needles (from benzene), m.p. 113~114.5°. Yield, 75%. *Anal.* Calcd. for $C_9H_{15}O_3N_3$: C, 50.69; H, 7.09; N, 19.71. Found : C, 50.85; H, 7.31; N, 19.33.

3-(3-Methyl-4-ethyl-5-isoxazolyl)hydrazone of 2,3-butanedione (VIb) : Colorless needles (ligroin), m.p. 95~97°. *Anal.* Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.17; H, 7.68; N, 18.82. Found : C, 58.76; H, 7.71; N, 18.96.

2-(3-Ethyl-4-methyl-5-isoxazolyl)hydrazone of 2,3-pentanedione (IVc) : Colorless needles (ligroin), m.p. 102~104°. *Anal.* Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.17; H, 7.68; N, 18.82. Found : C, 58.81; H, 7.80; N, 18.92.

VIa, VIb, or VIc was treated with $NH_2OH \cdot HCl$ in EtOH to reproduce Va, Vb, or Vc, respectively.

The hydrolytic aqueous solutions of Va, b, c after extraction with $CHCl_3$, were submitted to steam destillation to give the known diketones : 2,3-butanedione from Va and 2,3-pentanedione from Vb or Vc. These were characterized as their bissemicarbazones, which were identified with authentic samples.[7)]

4-(*o*-Nitrophenylazo)-3,4-dimethyl-5(4*H*)-isoxazolone (VIIa)——To a solution of Ia (5.6 g.) in 10% HCl was added equimolar amounts of *o*-nitrobenzenediazonium chloride. The oily product was extracted with $CHCl_3$ and the extract was dried over anhyd. Na_2SO_4 and evaporated to give VIIIa as yellow liquid (9.4 g.).

4-(*m*-Nitrophenylazo)-3,4-dimethyl-5(4*H*)-isoxazolone (VIIIb)——By the same procedure as for VIIIa, VIIIb (11.4 g.) was obtained from Ia (5.6 g.) and *m*-nitrobenzenediazonium chloride. Recrystallization from

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[*4] All melting points were taken on a Kofler-Block "Monoscope IV" and are uncorrected. Infrared spectra were recorded with a Kōken Infrared Spectrophotometer Model IK-S.

7) T. Posner : Ber., 34, 3978 (1901).

dil. EtOH gave yellow crystals (11.4 g.), m.p. 72~74°, IR cm^{-1} : $\nu_{C=O}$ 1800 ($CHCl_3$). *Anal.* Calcd. for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84; N, 21.37. Found : C, 50.86; H, 4.00; N, 21.00.

4-(*p*-Nitrophenylazo)-3,4-dimethyl-5(4*H*)-isoxazolone (VIIIc)——By the same procedure as for Ⅷa, Ⅷc (10.7 g.) was obtained from Ia (5.6 g.) and *p*-nitrobenzenediazonium chloride. Recrystallization from EtOH gave greenish yellow crystals, m.p. 91~93°, IR cm^{-1} : $\nu_{C=O}$ 1800 ($CHCl_3$). *Anal.* Calcd. for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84; N, 21.37. Found : C, 49.70; H, 4.05; N, 20.95.

***o*-, *m*-, and *p*-Nitrophenylhydrazone of 2,3-Butanedione Monooximes (IXa, b, c)**——The solution of Ⅷa, Ⅷb, or Ⅷc in 10% NH_4OH and EtOH (1:1) was heated on a water bath for a few minutes. After cooling, the corresponding oxime was precipitated.

o-Nitrophenylhydrazone of 2,3-butanedione monooxime (Ⅸa) : Colorless needles (Me_2CO), m.p. 221° (decomp.). *Anal.* Calcd. for $C_{10}H_{12}O_3N_4$: C, 50.84; H, 5.12; N, 23.72. Found : C, 50.96; H, 5.34; N, 23.61. Ⅸa was identified with the sample prepared from 2,3-butanedione monooxime and *o*-nitrophenylhydrazine.

m-Nitrophenylhydrazone of 2,3-butanedione monooxime (Ⅸb) : Colorless needles (Me_2CO), m.p. 257~258°. *Anal.* Calcd. for $C_{10}H_{12}O_3N_4$: C, 50.84; H, 5.12; N, 23.72. Found : C, 50.83; H, 5.33; N, 23.18. Ⅸb was identical with a sample prepared from 2,3-butanedione monooxime and *m*-nitrophenylhydrazine.

p-Nitrophenylhydrazone of 2,3-butanedione monooxime (Ⅸc) : Colorless needles (dil. EtOH), m.p. 251~252°. *Anal.* Calcd. for $C_{10}H_{12}O_3N_4$: C, 50.84; H, 5.12; N, 23.72. Found : C, 51.11; H, 5.32; N, 23.40. Ⅸc was identified with an authentic sample.5)

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Summary

The reaction products of nitrous acid on 5-amino-3,4-dialkylisoxazoles (Ia, b, c) has been formulated as 4-(3,4-dialkyl-5-isoxazolyl)azo-3,4-dialkyl-5(4*H*)-isoxazolones (Ⅳa, b, c) rather than the azoxy structure (II) which was originally proposed by Hanriot. To gain insight into this reaction mechanism, the behavior of *o*-, *m*-, and *p*-nitrobenzenediazonium chlorides on Ia has been also investigated.

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141. Kuniyoshi Tanaka, Toshio Sugawa, Ritsuo Nakamori, Yasushi Sanno, Yasuo Ando, and Kin-ichi Imai : Studies on Nucleic Acid Antagonists. VI. Synthesis of 1,4,6-Triazaindenes(5*H*-Pyrrolo[3,2-*d*]pyrimidines).[*1]

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1,4,6-Triazaindene is a condensed heterobicyclic ring isosteric to both purine and indole, and therefore its properties, especially its behaviors to various chemical reactions intrigued us. Besides, purine and indole are the basic substances of a number of important metabolites, and it may well be that some triazaindene compounds might be active as

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[*1] Part V : K. Tanaka, T. Sugawa, Y. Kuwada, K. Imai, M. Morinaga, J. Watanabe, T. Komeda, T. Usui, H. Yokotani, H. Ito, S. Hemmi, M. Kato, H. Mima, K. Kaziwara : Ann. Rept. Takeda Res. Lab., 22, 192 (1963).

[*2] Juso-nishino-cho, Higashiyodogawa-ku, Osaka (田中邦喜, 須川利男, 中守律夫, 三野 安, 安藤康雄, 今井欣一).