Synthesis of 4-Substituted Isoxazole-3,5-dicarboxylic Acids from 2-Substituted-1,3-dinitroglutarates and the Reaction Mechanism therefrom[1,2]

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A solution of 1 mol of 2-substituted-1,3-dinitroglutarates[3] (**1**) in absolute ethanol was added to about 10 mol of a primary amine, such as *n*-butylamine or *n*-propylamine. The reaction mixture was refluxed for several hours, and upon concentration crude 4-substituted bis-carbamoylisoxazoles (**5**) were obtained as oils, which were crystallized after washing, digesting or extracting with suitable solvents. Compounds **5**, listed in Table 1 were identified by comparison with authentic samples[4] (except 5-E and 5-F). They were hydrolysed with aqueous sodium hydroxide to give free acids[5] (**6**).

1 was decomposed in the presence of the amines. After liberation of nitrous acid, it gave isoxazoline-*N*-oxide (**3**) which might be produced *via* an olefin intermediate (**2**), followed by the intramolecular addition as suggested by Nielsen and Archibalt.[6]

Since compound (**3**) is also classified as "*Cyclic Nitronic Esters*,"[7,8] the following mechanism seems to be reasonable. (a) Compound **3** is decomposed into an oximino-ketone (**4**), and (**4a**), the enol-form of **4** yields a dehydrated product, an isoxazole (**5**) as observed by Worrall.[9] (b) Two ester groups of (**4a**) form diamide of the corresponding primary amine in the final step.

The mechanism was confirmed by the following results. (i). An isoxazoline-*N*-oxide (**3a**, $R^1=C_6H_5$, $R^3=CO_2CH_3$ of **3**), mp 94.5—96°C; IR (KBr), 1730 (ester CO), 1610 (phenyl), 1340 cm^{-1} (*N*-oxide); NMR ($CDCl_3$), 2.61 (s. 5H phenyl), 5.02 (d, 1H ring), 5.12 (d, 1H ring), 6.06 (s. 3H methyl), 6.24 τ (s. 3H methyl), could be obtained from a solution of a diethylamine salt of 2-phenyl-1,3-dinitroglutarate in methanol at room temperature. (ii). When an excess of *n*-butylamine was added to an ethanol solution of **3a**, it was converted into isoxazole (**5**, $R^1=C_6H_5$, $R^2=C_4H_9$) in a 97% yield. As emphasized in previous papers,[4,5] compound **1** should be regarded as a key compound for the reaction of α,β-unsaturated α-nitroesters with *n*-butylamine to give **5**.

The postulated mechanism is shown in Chart 1.

All new compounds reported above (**3a**, 5-B($R^2=n\text{-}C_3H_7$), 5-E, and 5-F) gave satisfactory results in C, H, and N analyses.

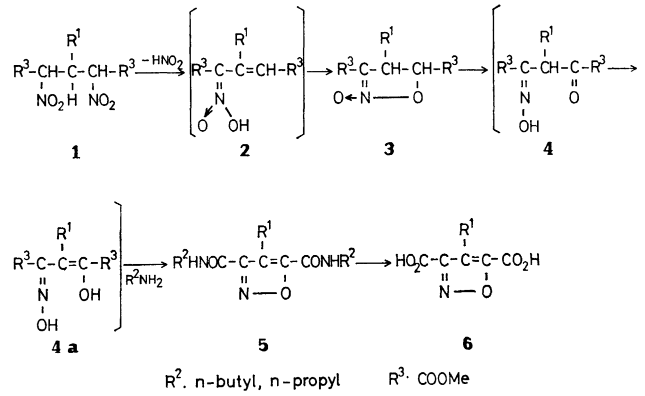
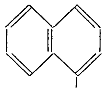
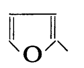
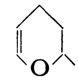
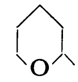


Chart 1.

Table 1. 4-Substituted 3,5-bis(*n*-butylcarbamoyl)isoxazoles (**5**) from 2-substituted 1,3-dinitroglutarates (**1**)

5, R^1:	*n*-C_3H_7 (5-A)[a]	C_6H_5 (5-B)[b]	 (5-C)[a]	 (5-D)[a]	 (5-E)[c]	 (5-F)[d]	 (5-G)[a]
Yield, %	39	80	76	56	41	48	50

a) Ref. 4 b) Ref. 5; $R^2=n\text{-}C_3H_7$: mp 165—166°C (ethanol-water) c) mp 81—84°C (*n*-hexane) d) mp 83—85°C (*n*-hexane)

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[1] Part VI in the series, "The Synthetic Reactions of Aliphatic Nitro Compounds," Part V: S. Zen, M. Koyama, and S. Koto, *Kogyo Kagaku Zasshi*, **74**, 70 (1971).

[2] This work was presented in part at the 91st Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April, 1971; Abstracts of Presentation, p. 689 (1971).

[3] Prepared by the methods described by A. Dornow and G. Wiehler (*Ann.*, **578**, 113 (1952)) and A. Dornow and A. Frese, (*Ann.*, **581**, 211 (1953)). Monodiethylamine salts were employed because of their better stability than the free acids.

[4] S. Zen and S. Umezawa, This Bulletin, **34**, 890 (1961); **36**, 1146 (1963); **36**, 1150 (1963).

[5] S. Umezawa and S. Zen, *ibid.*, **33**, 1016 (1960).

[6] A. T. Nielsen and T. G. Archibalt, *J. Org. Chem.*, **34**, 984 (1969).

[7] A. T. Nielsen, *Tetrahedron Lett.*, **1968**, 3375: *Tetrahedron*, **26**, 3475 (1970); H. Feuer, "The Chemistry of the Nitro and Nitroso Groups," Part 1, Interscience Publishers, New York (1969), p. 417.

[8] Generally, nitronic ester is given as *O*-alkylated product by the reaction of metallic salts of nitroparaffins with alkyl halides. This acyclic nitronic ester decomposes readily to form an oxime and an aldehyde or ketone as shown by

$$R^1R^2\cdot C{=}NO_2^-Na^+ + XCHR^3R^4 \longrightarrow R^1R^2\cdot C{=}N(\rightarrow O)OCHR^3R^4 \longrightarrow$$

(*acyclic nitronic ester*)

$$R^1R^2\cdot C{=}N\text{-}OH + R^3R^4\cdot C{=}O$$

[9] Dibenzoyl phenyl monoxime is readily converted into triphenylisoxazole (D. E. Worrall, *J. Amer. Chem. Soc.*, **57**, 2299 (1935)).