Synthetic Studies of the Derivatives of Nitroacetic Acid. II. The Synthesis of Isoxazolecarboxylic Acids from α, β-Unsaturated α-Nitroesters[1,2]

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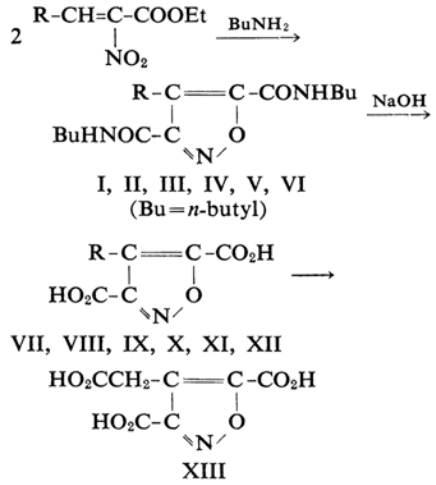
In a preliminary communication[3] we have shown that the treatment of α, β-unsaturated α-nitroesters with *n*-butylamine in ligroin or absolute ethanol gives derivatives of isoxazole-3, 5-dicarboxylic acid. In the present paper, we report a more detailed study of the new synthesis of isoxazole compounds.

When an excess of *n*-butylamine was added to a solution of diethyl α-nitroglutaconate,[4] it was found that considerable heat was evolved and, after the solution was allowed to stand at room temperature, crystals of 3, 5-bis(*n*-butylcarbamoyl)-4-(*n*-butylcarbamoylmethyl)-isoxazole (I) were deposited in almost a quantitative yield.

Moreover, we have found that the cyclization reaction is generally applicable to the synthesis of 4-substituted isoxazole-3, 5-dicarboxylic acids. The treatment of ethyl α-nitrocrotonate[4] with an excess of *n*-butylamine in absolute ethanol, followed by refluxing for several hours, gave 4-methyl-3, 5-bis(*n*-butylcarbamoyl)-isoxazole (II); 4-*n*-propyl-3, 5-bis(*n*-butylcarbamoyl)isoxazole (III), 4-phenyl-3, 5-bis(*n*-butylcarbamoyl)isoxazole (IV), 4-(*p*-chlorophenyl)-3, 5-bis(*n*-butylcarbamoyl)isoxazole (V) and 4-(*p*-nitrophenyl)-3, 5-bis(*n*-butylcarbamoyl)isoxazole (VI) have been obtained from ethyl 2-nitro-2-hexenoate,[4] ethyl α-nitrocinnamate,[5] ethyl *p*-chloro-α-nitrocinnamate[5] and ethyl 4, α-dinitrocinnamate[5] respectively by the same general procedure (Table I).



I, VII: R=BuHNOCCH$_2$; II, VIII: R=CH$_3$; III, IX: R=*n*-C$_3$H$_7$; IV, X: R=C$_6$H$_5$; V, XI: R=(*p*)Cl-C$_6$H$_4$; VI, XII: R=(*p*)NO$_2$-C$_6$H$_4$

Chart 1

By mild alkaline hydrolysis with 10% sodium hydroxide in 50% aqueous ethanol, the above-mentioned butylamides of isoxazolecarboxylic acids have been converted into the corresponding free acids of 4-substituted isoxazoles. Thus, 4-methylisoxazole-3, 5-dicarboxylic acid (VIII), 4-(*n*-propyl)isoxazole-3, 5-dicarboxylic acid (IX), 4-phenylisoxazole-3, 5-dicarboxylic acid (X), 4-(*p*-chlorophenyl)isoxazole-3, 5-dicarboxylic acid (XI) and 4-(*p*-nitrophenyl)isoxazole-3, 5-dicarboxylic acid (XII) have been obtained in high yields. The hydrolysis of 3, 5-bis(*n*-butylcarbamoyl)-4-(*n*-butylcarbamoylmethyl)isoxazole (I) at about 60°C gave 4-(*n*-butylcarbamoylmethyl)isoxazole-3, 5-dicarboxylic acid (VII), while more drastic hydrolysis achieved by refluxing for about seven hours with 10% sodium hydroxide in 50% aqueous ethanol afforded 3, 5-dicarboxyisoxazole-4-acetic acid (XIII) (Table II).

Evidence for the structures of the above-mentioned isoxazole derivatives could be deduced from the hydrolysis products. It has been known that isoxazoles are cleaved at the N–O and C=C bonds or C–C bond by drastic hydrolysis with alkali.[6] The drastic alkaline hydrolysis of 4-phenyl-3, 5-bis(*n*-butylcarbamoyl)isoxazole (IV) resulted in the formation of phenylacetic acid (IV′) and oxalic acid. Moreover, the hydrolysis of 4-(*p*-dimethylaminophenyl)-3, 5-bis(*n*-butylcarbamoyl)isoxazole (XIV)[7] by an analogous treatment afforded *p*-dimethylaminophenylacetic acid (XIV′) and oxalic acid. The above hydrolysis of IV and

1) Presented in part before the Division of Organic Chemistry of the Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1959.
2) Abstracted in part from the Ph. D. thesis presented to Keio University by Shonosuke Zen.
3) S. Umezawa and S. Zen, This Bulletin, 33, 1016 (1960).
4) S. Umezawa and S. Zen, ibid., 36, 1143 (1963).
5) A. Dornow and H. Menzel, *Ann.*, 580, 43 (1952).
6) L. Claisen, *Ber.*, 42, 65 (1909); C. Munsante, *Gazz. chim. ital.*, 72, 537 (1942); S. Takagi and H. Yasuda, *J. Pharm. Soc. Japan* (*Yakugaku Zassi*), 79, 467 (1959).
7) The synthesis of this isoxazole derivative will be described in the next paper.

TABLE I. 4-SUBSTITUTED 3,5-BIS(*n*-BUTYLCARBAMOYL)ISOXAZOLES

Compound	Procedure	M. p. °C	Solvent for recrystallization	Formula	Analysis Found C, %	Found H, %	Found N, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Yield %
I	—	179~179.5	a	$C_{19}H_{32}O_4N_4$	60.41	8.22	15.15	59.97	8.48	14.73	100 (nearly)
II	A B	84~86	b	$C_{14}H_{23}O_3N_3$	60.32	7.95	15.18	59.76	8.24	14.94	A: 5.5 B: 14.2
III	B	111.5~113	b	$C_{16}H_{27}O_3N_3$	61.63	8.61	13.60	62.11	8.80	13.58	34.1
IV	B	160~162	a	$C_{19}H_{25}O_3N_3$	66.86	6.90	12.55	66.43	7.34	12.24	64.6
V	B	125~127.5	c	$C_{19}H_{24}O_3N_3Cl$	60.60	6.27	11.23	60.39	6.41	11.12	50
VI	B	135	d	$C_{19}H_{24}O_5N_4$	58.52	6.34	14.66	58.75	6.23	14.43	40.3

a ethanol; b ligroin; c 70% ethanol; d *n*-propanol-petroleum ether

TABLE II. 4-SUBSTITUTED ISOXAZOLE-3,5-DICARBOXYLIC ACIDS

Compound	Procedure	M. p., °C (decomp.)	Solvent for recrystallization	Formula	Analysis Found C, %	Found H, %	Found N, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Yield %	Neutralization equivalent Found	Neutralization equivalent Calcd.
VII	C	156.5~157	e	$C_{11}H_{14}O_6N_2$	48.95	5.11	10.38	48.89	5.22	10.37	94	—	—
VIII	D	212~212.5	e	$C_6H_5O_5N$	42.25	3.11	7.97	42.11	2.95	8.19	94.8	85.3	85.6
IX	D	176~177	f	$C_8H_9O_5N$	47.98	4.81	6.96	48.24	4.57	7.03	99	100.9	99.5
X	C	183~183.5	g	$C_{11}H_7O_5N$	56.87	2.97	6.08	56.66	3.03	6.01	87.6	115.7	116.6
XI	C	187~187.5	g	$C_{11}H_6O_5NCl$	49.68	2.65	5.45	49.35	2.25	5.25	94	138.8	133.8
XII	C	172~174	g	$C_{11}H_6O_7N_2$	47.80	2.60	9.89	47.49	2.17	10.07	80	142.0	139.1
XIII	—	104~108 (m. p.)	e	$C_7H_5O_7N$	39.02	2.42	6.57	39.08	2.34	6.51	98	72.3	71.7

e dioxane-chloroform; f ethylene chloride; g dioxane-ethylene chloride-ligroin

TABL III. INFRARED SPECTRA OF 4-SUBSTITUTED ISOXAZOLE-3,5-DICARBOXYLIC ACIDS (Nujol, cm^{-1})

Compound	Crystalline water	Carboxyl OH	Carboxyl CO	Isoxazole[8] Ring stretching	Isoxazole[8] Ring breathing	Isoxazole[8] Ring deformation
VIII	3545~3478	2620~2530	1723	1622, 1492	1039	862
IX	3533, 3438	2640~2530	1717	1601, 1490	1072	904
X	3500~3334	2610~2520	1717	1610, 1505	1046	865
XI*	3511~3356	2586~2356	1720	1610, 1502	1042	862
XII*	—	2600~2300	1725	1608, 1508	1020	849
XIII	3480, 3342	2620~2540	1715	1623, 1488	1044	867

* KBr

XIV can be easily explained by the reaction sequence shown in Chart 2.

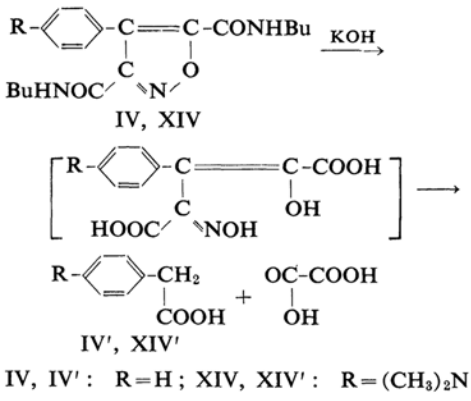


Chart 2

Reaction Mechanism.—The formation of isoxazole derivatives described above suggests that a key intermediate in the reaction sequence may be an addition compound (XIX) formed by the addition of nitroacetate to an α,β-unsaturated α-nitroester. Therefore, it seems reasonable to suggest that the initial step involves the base-catalyzed cleavage of α,β-unsaturated α-nitroester to liberate the nitroacetic ester moiety, which may be in equilibrium with the original unsaturated nitroester, followed by the addition of the former to the latter to give the above-mentioned key intermediate. It then cyclize to form an isoxazole derivative (XX) by the elimination of its water and nitrous acid.

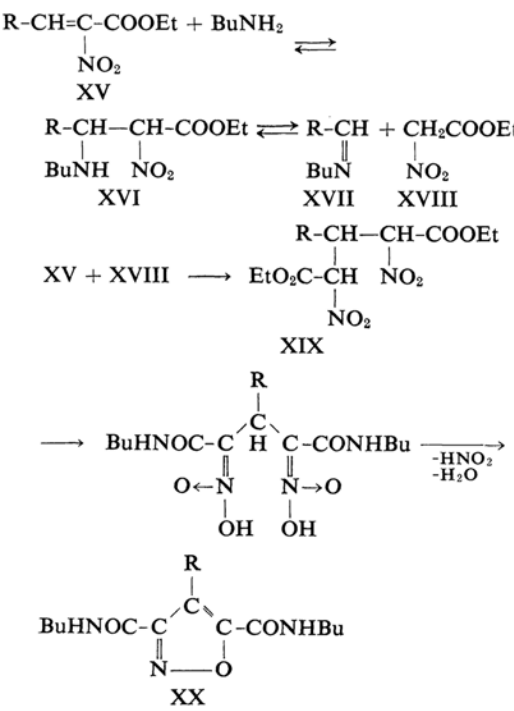


Chart 3

Fortunately, we could isolate a Schiff base (XVII), benzylidene-*n*-butylamine, from the mother liquor of the 4-phenyl-3, 5-bis(*n*-butylcarbamoyl)isoxazole (IV) which is obtained from ethyl α-nitrocinnamate by refluxing it with *n*-butylamine in absolute ethanol. Evidently, the initial reaction involves the addition of butylamine to an α,β-unsaturated α-nitroester (XV), while the adduct (XVI) generates nitroacetic ester (XVIII), which adds to the α,β-unsaturated α-nitroester in the presence of a basic catalyst (*n*-butylamine) in a way similar to that of the Michael reaction to give the key intermediate (XIX), as is outlined in Chart 3.

As was expected, the addition of ethyl nitroacetate to the above reaction-systems resulted in a significant increase in the yields of isoxazole derivatives.

Experimental

3, 5-Bis(*n*-butylcarbamoyl)-4-(*n*-butylcarbamoylmethyl)isoxazole (I). — Into a mixture of diethyl α-nitroglutaconate[4] (0.50 g., 0.0022 mol.) in ligroin (2 ml.) was added *n*-butylamine (1.0 g., 0.013 mol.) under stirring. During this period considerable heat was evolved, and the color of the solution changed to a yellowish brown. When the solution was left standing at room temperature, there were deposited crude crystals of I, which were then collected and washed with a small quantity of ethanol; m. p. 176~178°C, yield 0.41 g. (nearly quantitative). Recrystallization from ethanol gave an analytically pure sample.

4-Methyl-3, 5-bis(*n*-butylcarbamoyl)isoxazole (II). —(An example of procedure A) A mixture of ethyl α-nitrocrotonate[4] (1.0 g., 0.0063 mol.), absolute ethanol (2 ml.) and *n*-butylamine (2.75 g., 0.038 mol.) was refluxed for 3 hr. After standing at room temperature overnight, the solvent was removed by distillation to give a reddish brown sirup, which was then taken in hot ligroin, filtered, and cooled to give colorless needles of the title compound; m. p. 82~85°C; yield 0.035 g. (5.5%). Recrystallization from ligroin gave an analytically pure sample.

(An example of procedure B) By the addition of ethyl nitroacetate.—A mixture of ethyl α-nitrocrotonate (1.06 g., 0.0066 mol.), ethyl nitroacetate (0.88 g., 0.0066 mol.) and *n*-butylamine in absolute ethanol was refluxed for 10.5 hr. After the solution had been left standing at room temperature overnight, the solvent was removed by distillation to give a deep yellow residue, which was then recrystallized from ligroin (yield, 0.19 g.). The product was found to be identical with the product prepared by procedure (A) above by undepressed m. p. and infrared spectra.

8) A. R. Katritzky and A. J. Boulton, *Spectrochimica Acta*, **17**, 238 (1961).

4-(*n*-Butylcarbamoylmethyl)isoxazole-3,5-dicarboxylic Acid (VII).—(An example of procedure C) A mixture of 3,5-bis(*n*-butylcarbamoyl)-4-(*n*-butylcarbamoylmethyl)isoxazole (1.14 g.) and 10% sodium hydroxide in 50% aqueous ethanol (110 ml.) was warmed at 50~55°C for 2 hr. while being stirring. After the removal of the ethanol by distillation under reduced pressure, the aqueous solution was acidified with hydrochloric acid and then extracted with ether. The extract was dried over anhydrous sodium sulfate, filtered, and evaporated to give a powdery residue (yield 0.74 g.). Recrystallization gave colorless needles of the title compound.

3,5-Dicarboxyisoxazole-4-acetic Acid (XIII).—A mixture of 3,5-bis(*n*-butylcarbamoyl)-4-(*n*-butylcarbamoylmethyl)isoxazole (I) (0.80 g.) and 10% sodium hydroxide in 50% aqueous ethanol (25 ml.) was refluxed for 7 hr. After the removal of the ethanol by distillation, aqueous solution was acidified with hydrochloric acid and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate, filtered and evaporated to give a pale-yellow powder (yield 0.44 g.). Recrystallization gave colorles needles of the titlec ompound.

4-Methylisoxazole-3,5-dicarboxylic Acid (VIII).—(An example of procedure D) A mixture of 4-methyl-3,5-bis(*n*-butylcarbamoyl)isoxazole (II) (0.82 g.) and 10% sodium hydroxide in 50% aqueous ethanol (33 ml.) was refluxed for 2 hr. and worked up as has been described in the preparation of XIII (yield, 0.47 g.).

The Ring Opening of 4-Phenyl-3,5-bis(*n*-butylcarbamoyl)isoxazole.—A mixture of 4-pheny-3,5-bis(*n*-butylcarbamoyl)isoxazole (1.0 g.) and 28.5% potassium hydroxide in 50% aqueous ethanol (55 ml.) was refluxed for about 4 hr. After the ethanol had been removed by distillation, the aqueous solution was cooled to about 5°C, acidified with hydrochloric acid, and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate, filtered, and evaporated to give a crystalline residue (yield 0.55 g.). The product was then extracted with benzene.

The soluble part obtained by the evaporation of the benzene extract was washed with petroleum ether to give crystals of phenylacetic acid, m. p. 74~77°C; yield 0.25 g. (64%). Mixed m. p. with an authentic specimen of phenylacetic acid was undepressed.

The insoluble part in benzene was recrystallized from dioxane-chloroform to give colorless crystals of oxalic acid dihydrate, m. p. 97.5~99°C; yield 16 mg. Mixed m. p. with an authentic sample of oxalic acid dihydrate was undepressed.

The Ring Opening of 4-(*p*-dimethylaminophenyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole.—A mixture of 4-(*p*-dimethylaminophenyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole[7] (0.5 g.) and 10% sodium hydroxide in 50% aqueous ethanol (10 ml.) was refluxed for 2 hr. After the ethanol had been removed by distillation, the aqueous solution was acidified to pH 5.4~5.6 with hydrochloric acid and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate, filtered and evaporated to give a crystalline residue, yield 0.12 g. (51.6%). Recrystallization from ligroin gave colorless plates of *p*-(dimethylamino)phenylacetic acid, m. p. 109.5~110.5°C.[9]

Found: C, 67.46; H, 7.21; N, 7.50. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82%.

Paperchromatography of the mother-liquor which remained after extraction with ether showed the presence of oxalic acid.

The Isolation of Benzylidene-*n*-butylamine from the Reaction Mixture Obtained from Ethyl α-Nitrocinnamate and *n*-Butylamine.—A mixture of ethyl α-nitrocinnamate (1.0 g., 0.0048 mol.), *n*-butylamine 1.32 g., 0.019 mol.) and absolute ethanol (4 ml.) was refluxed for 8 hr. After the solution had been left standing at room temperature, the resulting crystals of 4-phenyl-3,5-bis(*n*-butylcarbamoyl)-isoxazole (IV) was collected by filtration. Concentration of the filtrate gave the second crop; the total yield of IV was 0.187 g. (23.5%). The mother liquor which separated from the second crop was distilled under reduced pressure to give a colorless liquid boiling at 95~112°C/12 mmHg.

The product was extracted with benzene. The removal of benzene by evaporation, followed by vacuum distillation, gave benzylidene-*n*-butylamine, b, p. 110~111°C/13 mmHg., yield 92 mg., which was found by infrared spectra to be identical with an authentic specimen.

Summary

1) α,β-Unsaturated α-nitroesters react with *n*-butylamine to give 4-substituted isoxazole-3,5-carboxylic butylamides. This is a new synthesis of isoxazole derivatives.

2) The mechanistic features of the above reaction have been explained.

3) The mild alkaline hydrolysis of the above butylamides gave 4-substituted isoxazole-3,5-dicarboxylic acids.

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9) Reported m. p. 112~113°C. M. Okubo and R. Goto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **82**, 261 (1961).