Synthetic Studies of the Derivatives of Nitroacetic Acid. III. The Synthesis of Isoxazole-3, 5-dicarboxylic Acids from Schiff Bases and Nitroacetic Ester[1)]

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The authors have previously reported[2)] that dibutylamides of 4-substituted isoxazole-3, 5-dicarboxylic acids were obtained when α, β-unsaturated α-nitrocarboxylates were treated with an excess of *n*-butylamine in an anhydrous solvent; they also presented the reaction mechanism of the new synthesis.

If the mechanism presented by the authors is valid, one should be able to obtain the derivatives of isoxazole-3, 5-dicarboxylic acids by the reaction of Schiff bases (1) with nitroacetic ester (2) in the presence of basic catalysts by means of the scheme outlined in Chart 1.

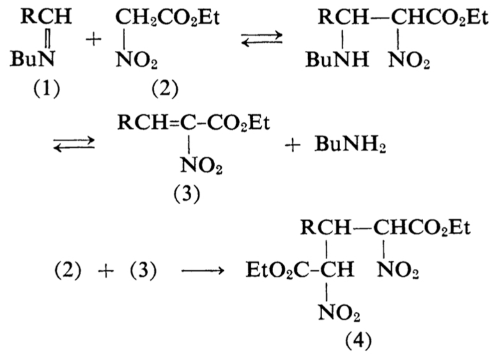
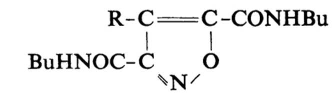


Chart 1

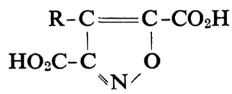
The authors have already mentioned, in a previous paper,[2)] the sequel of the path from (4) to the isoxazole derivatives.

This expectation has now been realized. When an excess of *n*-butylamine (about five moles) was added to a mixture of Schiff base (one mole) and ethyl nitroacetate (two moles) in absolute ethanol, an exothermic reaction occurred. After refluxing for several hours, the mixture was concentrated to give a crystalline solid of 3, 5-bis(*n*-butylcarbamoyl) derivatives of isoxazole.

By this general procedure the following compounds, I—XVII, have been prepared from the corresponding Schiff bases and ethyl nitroacetate:



I—XVII



VI', IX'*, XI', XIII'*, XIV', XVII'

Aliphatic series:

	R
I:	CH_3
II:	*n*-C_3H_7
III:	$(CH_3)_2C{=}CH(CH_2)_2{-}CH(CH_3)CH_2$

Aromatic series:

IV:	C_6H_5
V:	$(p)Cl{-}C_6H_4$
VI, VI':	$(2,4)Cl_2C_6H_3$
VII:	$(p)NO_2{-}C_6H_4$
VIII:	$(m)NO_2{-}C_6H_4$
IX:	$(p)CH_3CONH{-}C_6H_4$
IX'*:	$H_2N{-}C_6H_4$
X:	$(p)(CH_3)_2NC_6H_4$
XI, XI':	1-Naphthyl
XII:	9-Anthryl

Heterocyclic series:

XIII, XIII'*:	2-Furyl
XIV, XIV':	2-Thienyl
XV:	2-Pyrrolyl
XVI:	2-Pyridyl
XVII, XVII':	3-Indolyl

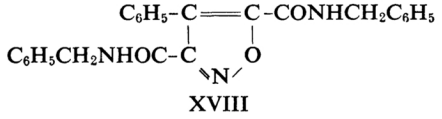
Citronellylidene-*n*-butylamine failed to give isoxazole compounds, whereas citronellylidenebenzylamine gave 4-(2, 6-dimethyl-2-octenyl)-3, 5-bis(benzylcarbamoyl)isoxazole (III) by means of a reaction with ethyl nitroacetate in the presence of an excess of benzylamine. Indole-3-aldehyde and *n*-butylamine failed to give a Schiff base; however, 3-indolylidenaniline could be used to give 4-(3-indolyl)-3, 5-bis-(*n*-butylcarbamoyl)isoxazole (XVII) by means of the general procedure.

1) Presented in part before the Division of Organic Chemistry of the 14th and 15th Annual Meetings of the Chemical Society of Japan, Tokyo, April, 1961, and Kyoto, April, 1962. Preliminary communication: S. Zen and S. Umezawa, This Bulletin, 34, 890 (1961).

2) S. Zen and S. Umezawa, This Bulletin, 36, 1146 (1963).

* Dimethyl ester were caused to crystallize.

As an example using a primary amine other than *n*-butylamine the treatment of benzylidenebenzylamine with ethyl nitroacetate in the presence of an excess of benzylamine by analogous reaction conditions gave 4-phenyl-3,5-bis(benzylcarbamoyl)isoxazole (XVIII) in 84% yield.



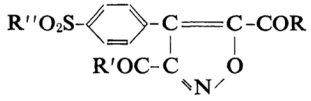
XVIII

XIX

The di-*n*-butylamine Schiff base of terephthalaldehyde, namely, *p*-xylylidene-di(*n*-butylamine), also gave a diisoxazolyl derivative of benzene (XIX) upon the treatment of one mole of the Schiff base with four moles of ethyl nitroacetate and an excess of *n*-butylamine.

An alternative method, in which aldehydes and an primary amine are used instead of a Schiff base, also gave a 4-substituted isoxazole-3,5-dicarboxylic acid. However, the yield by this alternative method have been found to be generally lower than corresponding yields by the first-mentioned method.

4-(*p*-Sulfamoylphenyl)-3(or 5)-(*n*-butylcarbamoyl)-5(or 3)-(ethoxycarbonyl)isoxazole (XX) was obtained by the alternative procedure in good yield.



XX: R, R'=BuHN, C_2H_5O or vice versa; R''=NH_2

XX': R, R', R''=OH

The above amide derivatives of isoxazole-3,5-dicarboxylic acid have been hydrolyzed mildly with sodium hydroxide in aqueous ethanol by the procedure described in a proceding paper[2] to give the corresponding 4-substituted isoxazole-3,5-dicarboxylic acids. In general, the derivatives substituted for aliphatic groups at the 4-position gave better yields when the reaction mixture was refluxed, while the derivatives substituted by aromatic or heterocyclic groups at the same position gave better yields when the reaction mixture was warmed at 50~60°C for several hours.

The hydrolysis of 4-(*p*-acetamidophenyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (IX) and 4-(2-furyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (XIII) failed to give crystalline products of free acids; their methyl ester have, however, been crystallized.

Experimental

4-Methyl-3,5-bis(*n*-butylcarbamoyl)isoxazole (I).—(A typical example of the general method).—Into a solution of ethylidene-*n*-butylamine[3] (1.50 g., 0.015 mol.) in absolute ethanol (5 ml.) was added ethyl nitroacetate (4.03 g., 0.03 mol.) under stirring. During this period considerable heat was evolved; the temperature of the reaction mixture rose to 60°C from 18°C. *n*-Butylamine (5.53 g., 0.076 mol.) was then added to the mixture. When the exothermic reaction had subsided, the reaction mixture was gently refluxed for 5 hr. After the solution had been left standing at room temperature, the solvent was removed by distillation to give a reddish brown sirup, which was allowed to stand in a refrigerator to give crystals of the title compound, yield 0.46 g. (10.9%) which were then recrystallized from ligroin to give feathery crystals, m. p. 84~86°C. The product was found by undepressed mixed melting point and infrared spectra to be identical with the authentic specimen[2] prepared from ethyl α-nitrocrotonate.

II–XI, XIV, XVI and XIX were prepared by the general procedure (Tables I and II).

4-(9-Anthryl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (XII).—The reaction mixture obtained from 9-anthrylidene-*n*-butylamine (2.09 g.), ethyl nitroacetate (2.31 g.) and *n*-butylamine (2.92 g.) was refluxed for 9 hr. After the mixture had cooled to room temperature, water (about 10 ml.) was added to give a crude crystalline solid. The product was dissolved in ethanol (11 ml.), and the solution was diluted with water (6 ml.) to give a crystalline solid. This was again dissolved in benzene (7.3 ml.) and diluted with ligroin, whereupon there separated analytically pure crystals of the title compound (yield 0.34 g.); UV (methanol): 255 mμ (ε, 235000).

4-(2-Furyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (XIII).—The reaction mixture obtained by the general method from 2-furylidene-*n*-butylamine[5] (7.55 g.), ethyl nitroacetate (13.3 g.) and *n*-butylamine (18.5 g.) was refluxed for 9 hr. and allowed to stand, whereupon it gave a crude solid (yield 5.60 g.) The mother liquor was concentrated, and the residue was extracted with hot cyclohexane. When the cyclohexane extract was cooled, the second crop was obtained; (yield 3.64 g.; total 55.5%). Recrystallization from cyclohexane gave colorless feathery crystals (UV (methanol): a shoulder at 246 mμ (ε, 16000), 308 mμ (ε, 10700)).

4-(2-Pyrrolyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (XV).—The reaction mixture obtained by the general procedure from 2-pyrrolylidene-*n*-butylamine (1.0 g.), ethyl nitroacetate (1.8 g.) and *n*-butylamine

3) L. Kahorec, *Acta Phys. Austrica*, **1**, 307 (1948).
4) A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta*, **17**, 238 (1961).
5) J. E. Beatty and J. R. Stevens, *J. Am. Chem. Soc.*, **71**, 703 (1949).

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

Compound	M. p. °C	Solvent for recrystallization	Formula	Analysis						Yield %
				Found			Calcd.			
				C, %	H, %	N, %	C, %	H, %	N, %	
III	126~128	a	$C_{28}H_{33}O_3N_3$	72.44	7.03	9.52	73.17	7.27	9.14	19.8
VI	139~140.5	b	$C_{19}H_{23}O_3N_3Cl_2$	55.41	5.77	10.44	55.34	5.63	10.19	51.5
VIII	168~169	b	$C_{19}H_{24}O_5N_4$	58.80	6.11	14.51	58.75	6.23	14.43	57
IX	159~160	c	$C_{21}H_{28}O_4N_4$	63.13	6.92	13.19	62.98	7.05	13.99	48
X	117.5~118.5	b	$C_{21}H_{30}O_3N_4$	65.74	7.95	14.80	65.26	7.82	14.50	30.8
XI	181.5~183	a	$C_{23}H_{27}O_3N_3$	70.61	6.68	10.64	70.20	6.92	10.68	52.5
XII	159~162	d	$C_{27}H_{29}O_3N_3$	73.43	6.33	9.56	73.11	6.59	9.47	9.6
XIII	127~127.5	e	$C_{17}H_{23}O_4N_3$	61.15	7.02	12.76	61.24	6.95	12.61	55.5
XIV	120~123	a	$C_{17}H_{23}O_3N_3S$	58.55	6.56	12.06	58.44	6.64	12.03	50
XV	180~182	f	$C_{17}H_{24}O_3N_4$	61.56	7.41	17.03	61.42	7.28	16.86	4.8
XVI	128~129	b	$C_{18}H_{24}O_3N_4$	62.90	6.83	16.46	62.77	7.02	16.27	21.4
XVII	184.5~185.5	b	$C_{21}H_{26}O_3N_4$	66.00	7.01	14.38	65.95	6.85	14.65	44
XIX	255~257	a	$C_{32}H_{44}O_6N_6$	63.28	7.02	13.89	63.14	7.29	13.81	45.4

a ethanol; b ethanol-water; c *n*-propanol-ligroin; d benzene-ligroin; e cyclohexane f *n*-hexane

(2.45 g.) was refluxed for 14 hr., and the solvent was removed by distillation to give a tarry residue, which was then extracted with benzene. The benzene solution was evaporated to give again a tarry residue. This residue was again extracted with hot *n*-hexane (30 ml.), and the hexane extract was cooled to give crystals of the title compound; yield 0.072 g.; recrystallized from *n*-hexane to give slightly violet needles; UV (methanol): 247~255 mμ (ε, 7900).

4-(3-Indolyl)-3, 5-bis(*n*-butylcarbamoyl)isoxazole (XVII). — The reaction mixture obtained by the general procedure from indolylidenaniline[6] (1.0 g.), ethyl nitroacetate (1.2 g.) and *n*-butylamine (1.7 g.). was refluxed for 6.5 hr. and evaporated to give a dark red tar, which was then caused to crystallize by treatment with aqueous ethanol (yield 0.77 g.) Repeated recrystallization from 50% ethanol gave yellow needles (UV (methanol) : a shoulder at 281 mμ (ε, 8510) and 288 mμ (ε, 7400)).

4-Phenyl-3, 5-bis(benzylcarbamoyl)isoxazole (XVIII).—To a mixture of benzylidenebenzylamine (1.95 g.) and ethyl nitroacetate (2.66 g.) benzylamine (5.35 g.) was added, and the mixture was refluxed for 2 hr. After the mixture had stood at room temperature, the resulting solid was collected by filtration; yield 3.46 g. (84%) recrystallized from ethanol to give colorless needles of the title compound, m. p. 199.5~200°C.

Found: C, 72.98; H, 4.99; N, 10.30. Calcd. for $C_{25}H_{21}O_3N_3$: C, 72.98; H, 5.14; N, 10.21%.

The hydrolysis of the product with 10% sodium hydroxide in 50% ethanol at 50~60°C for 2 hr. gave 4-phenylisoxazole-3,5-dicarboxylic acid[2] in 69% yield.

The Alternative Method Using Aldehydes and Primary Amine Instead of Schiff Bases. — To a mixture of an aldehyde (1.0 mol.) and ethyl nitroacetate (2.0 mol.) in absolute ethanol *n*-butylamine (6 mol.) was added; the mixture was refluxed for 5 hr. and worked up in a manner similar to that described in the preparation of the above-described 4-substituted isoxazole-3,5-dicarboxylic dibutylamides. Yields by the alternative method are shown in comparison with those obtained through Schiff bases in Table II.

TABLE II. THE YIELD OF 4-SUBSTITUTED ISOXAZOLE-3,5-DICARBOXYLIC DIBUTYLAMIDES

Compound	Yield, %*	
	Through Schiff bases	By the alternative method
I	10.9	24.0
II	29.5	22.9
IV	66.5	38
V	47.5	42.4
VI	51.5	21.4
VIII	57.0	36
XX	—	68.2

* Crude products

4-(*p*-Sulfamoylphenyl)-3(or 5)-(*n*-butylcarbamoyl)-5(or 3)-(ethoxycarbonyl)isoxazole (XX).—Prepared by the alternative method from *p*-sulfamoylbenzaldehyde[7] (1.0 g.), ethyl nitroacetate (1.45 g.), *n*-butylamine (2.37 g.) and absolute ethanol (1.6 ml.); yield 1.47 g. (68.2%); recrystallized from *n*-butanol as colorless feathery crystals, m. p. 120~123°C; UV: 243 mμ (ε, 16400); IR (Nujol): 3340, 3260, 1750, 1674, 1549, 1329, 1195 (-SO_2N=), 1618, 1500, 1014 and 851 cm^{-2}.

Found: C, 51.52; H, 5.48; N, 10.28. Calcd. for $C_{17}H_{21}O_6N_3S$: C, 51.63; H, 5.35; N, 10.63%.

4-(2, 4-Dichlorophenyl)isoxazole-3, 5-dicarboxylic Acid (VI').—Prepared from 4-(2,4-dichlorophenyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (VI) (1.2 g.) by

6) M. p. 133~135°C. Reported m. p. 126~127°C by R. Majima and M. Kotake, *Ber.*, **58B**, 2039 (1925).

7) T. P. Sycheva and M. N. Shchukina, *Chem. Abstr.*, **49**, 932 (1955).

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

Compound	M. p., °C (decomp.)	Solvent for recrystallization	Formula	Analysis Found C, %	Found H, %	Found N, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Yield %	Neutrarization equivalent Found	Neutrarization equivalent Calcd.
VI′	183~186	a	$C_{11}H_5O_5NCl_2$	44.10	1.97	4.85	43.75	1.65	4.64	59.5	155.4	151.0
XI′	198.5~199.5	b	$C_{15}H_9O_5N$	63.42	3.30	5.06	63.61	3.20	4.96	35.3	140.4	141.6
XIV′	158~159	c	$C_9H_5O_5NS$	46.00	2.25	5.41	45.20	2.11	5.86	67.9	114.5	119.6
XVII′	211~213	d	$C_{13}H_8O_5N_2$	56.90	3.53	9.98	57.36	2.96	10.29	56.5	138.3	136.1
XX′	143~145	d	$C_{11}H_7O_8NS$	42.20	2.96	4.79	42.17	2.26	4.48	87	104.5	104.4

a ether-ligroin; b water; c dioxane-ligroin; d dioxane-chloroform

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

Compound	Crystalline water	Carboxyl OH	Carboxyl CO	Isoxazole[4] Ring stretching	Isoxazole[4] Ring breathing	Isoxazole[4] Ring deformation
VI′	3350	2650~2550	1733	1610, 1495	1040	866
XIV′	3517~3350	2595~2350	1751, 1724	1612, 1465	1044	862
XVII′	3425	2666~2380	1717	1605, 1420	1015	844
XX′	3345~3230	2660~2520	1722	1600, 1496	1017	901

TABLE V. SCHIFF BASES OF *n*-BUTYLAMINE

No.	Compound	Formula	B. p., °C/mmHg	M. p., °C	Analysis Found N, %	Analysis Calcd. N, %	Yield %
1	2,4-Dichlorobenzylidene-*n*-butylamine	$C_{11}H_{13}NCl_2$	127~130/2.5	—	—	—	70.1
2	*p*-Acetamidobenzylidene-*n*-butylamine	$C_{13}H_{18}ON_2$	—	108~110*	12.79	12.83	94.5
3	*p*-(Dimethylamino)benzylidene-*n*-butylamine	$C_{13}H_{20}N_2$	131~135/3	—	—	—	77
4	1-Naphthylidene-*n*-butylamine	$C_{15}H_{17}N$	167~169/7	—	6.43	6.63	81.5
5	9-Anthrylidene-*n*-butylamine	$C_{19}H_{19}N$	—	64~ 65**	5.24	5.36	91.6
6	2-Pyrrolylidene-*n*-butylamine	$C_9H_{14}N_2$	91~92.5/3	—	18.69	18.65	79.5
7	2-Pyridylidene-*n*-butylamine	$C_{10}H_{14}N_2$	81~82.5/3	—	—	—	76
8	*p*-Xylylidene-di(*n*-butylamine)	$C_{16}H_{24}N_2$	159~160/3	—	—	—	84
9	Citronellylidene-*n*-butylamine	$C_{14}H_{27}N$	93~95.5/3	—	6.64	6.69	65.5

* Recrystallized from benzene; colorless plates

** Recrystallized from aqueous ethanol; yellow needles

a procedure similar to that described in the preceding paper.[2] Hydrolysis was carried out at 50~60°C for 2 hr.; yield 0.52 g.; recrystallized from ether-ligroin to give colorless plates.

A sample free from crystalline water was analyzed.

XI' XIV' and XVII' were prepared by a similar procedure (Tables III and IV).

Dimethyl 4-(*p*-Aminophenyl)isoxazole-3, 5-dicarboxylate (IX').—A mixture of 4-(*p*-acetamidophenyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (IX) (10.6 g.) and 10% sodium hydroxyde in 50% aqueous ethanol (430 ml.) was refluxed for 2 hr. After the mixture had stood at room temperature, a small quantity of an insoluble matter was removed by filtration, and then ethanol (1.0 l.) was added to the filtrate to give disodium salt of the title compound; yield 5.27 g. (68.1%); m. p.>300°C. A sample of the salt (0.36 g.) was suspended in absolute methanol (11 ml.), and the mixture was saturated with hydrogen chloride gas while being cooled. After standing at room temperature overnight, the solution was evaporated to dryness. The residue was dissolved in water, and the solution was made alkaline with a 5% sodium carbonate solution to pH 8.7~9.0, followed by extraction with methylene chloride.

The extract was dried over anhydrous sodium carbonate and evaporated to give an yellow solid yield 0.10 g. (28%); recrystallization from ethyl acetate-ligroin gave yellow needles of the title compound, m. p. 163~166°C.

Found: C, 57.01; H, 4.10; N, 10.27. Calcd. for $C_{15}H_{12}O_5N_2$: C, 56.52; H, 4.38; N, 10.14%.

Dimethyl 4-(2-Furyl)isoxazole-3, 5-dicarboxylate (XIII').—A mixture of 4-(2-furyl)-3,5-bis(*n*-butylcarbamoyl)isoxazole (1.67 g.) and 10% sodium hydroxide in 50% ethanol (20 ml.) was warmed at 55~60°C for 1 hr. The dark brown mixture thereby obtained was evaporated under reduced pressure to remove the ethanol, acidified with hydrochloric acid, and extracted with ether. Evaporation of the ethereal extract gave a dark brown sirup (1.22 g.) which failed to crystallize. A part of the residue (0.9 g.) was dissolved in absolute methanol (40 ml.); the solution was then saturated with dry hydrogen chloride gas and left to stand at room temperature. After the removal of the methanol by distillation, the resulting sirup with dissolved in chloroform (30 ml.) and washed with a 5% sodium carbonate solution and water. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to give a dark brown sirup, which was caused to crystallize, giving needles yield, 0.1 g. (10%); recrystallized from *n*-hexane; colorless needles, m. p. 63~64.5°C.

Found: C, 52.44; H, 3.62; N, 5.80. Calcd. for $C_{11}H_9O_6N$: C, 52.59; H, 3.61; N, 5.58%.

4-(*p*-Sulfophenyl)isoxazole-3, 5-dicarboxylic Acid (XX'). — A mixture of 4-(*p*-sulfamoylphenyl)-3(or 5)-(*n*-butylcarbamoyl)-5(or 3)-(ethoxycarbonyl)isoxazole (XX) (0.30 g.) and 10% sodium hydroxide in 50% aqueous ethanol (20 ml.) was warmed at about 60°C for 2 hr. while being stirred. After removal of the ethanol, the aqueous solution was acidified with hydrochloric acid to pH 2.0 and extracted with ether. The extract was dried over anhydrous sodium sulfate, filtered, and evaporated to give a yellow powder (0.22 g.), which was a partially hydrolized product. A part (0.1 g.) of the product was dissolved in 10% aqueous sodium hydroxide (2.0 ml.), and the solution was refluxed for 1 hr. After acidified with hydrochloric acid to pH 4.0, the solution was extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate, filtered, and evaporated to give a yellow powder (0.1 g.). Recrystallization from dioxane-chloroform gave colorless needles.

Schiff Base (Table V). — Prepared by a general procedure illustrated by the following examples.

n-Butylidene-n-butylamine.—A mixture of *n*-butylaldehyde (5.04 g., 0.07 mol.) and *n*-butylamine (5.11 g., 0.07 mol.) in benzene (15 ml.) was refluxed for 30 min. After the mixture had been dried over anhydrous sodium sulfate, the benzene was removed and the residue was distilled under reduced pressure to give the Schiff base, b. p. 113.5~114°C/20 mmHg, yield 4.10 g. (46.1%).

Citronellylidene-n-benzylamine. — A mixture of citronellal (5.0 g.) and benzylamine (3.8 g.) in benzene (30 ml.) was stirred and allowed to stand for 1 hr. The benzene layer was then separated and dried over anhydrous sodium sulfate. After the removal of the benzene, the residue was distilled under reduced pressure to give the Schiff base, b. p. 150~151.5°C/5.5 mmHg, yield 4.76 g. (60.3%).

Found: N, 5.86. Calcd. for $C_{17}H_{25}N$: 5.76%.

Summary

1) Schiff bases react with ethyl nitroacetate in the presence of *n*-butylamine or benzylamine to give 4-substituted isoxazole-3, 5-dicarboxylic amides. This is a new synthesis of isoxazole derivatives.

2) Twenty kinds of 4-substituted isoxazole-3, 5-dicarboxylic amides, including aliphatic, aromatic and heterocyclic derivatives, have been prepared.

3) Seven of the above-mentioned amides have been hydrolyzed to give the corresponding 4-substituted isoxazole-3, 5-dicarboxylic acids.

4) Some Schiff bases have been described.

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