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The Synthesis and Reaction of α,β-Unsaturated α-Nitrocarboxylic Esters[1)]

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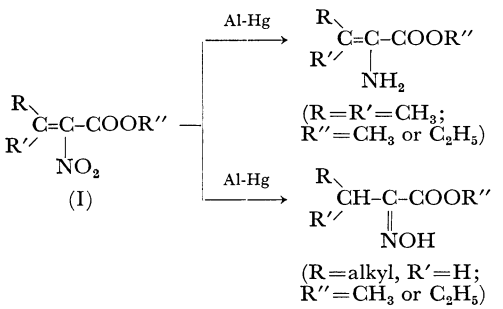
Synthetic studies of α,β-unsaturated α-nitrocarboxylic esters and the corresponding α-amino compounds are described. When α,β-unsaturated carboxylic ester was treated with fuming nitric acid, two products, α,β-unsaturated α-nitrocarboxylic ester and α-hydroxy-β-nitrocarboxylic ester, were formed. The former was converted into β-methoxy-α-nitrocarboxylic ester by treatment with methanol in the presence of a base such as sodium methoxide or sodium acetate. Reduction of β-methoxy-α-nitrocarboxylic esters with aluminum amalgam and the subsequent distillation of the products afforded α,β-unsaturated α-aminocarboxylic esters and α-hydroxyamino-β-methoxycarboxylic esters, which were confirmed by their *N*-phthaloylglycyl derivatives.

It was previously reported that the reduction of methyl and ethyl esters of β-methyl-α-nitrocrotonic acid (I: R=R′=CH_3) with aluminum amalgam gave the corresponding α-aminocarboxylic esters (enamines), while α-oximinocarboxylic esters were formed in the reduction of β-monosubstituted α,β-unsaturated α-nitrocarboxylic esters.[3,4)]



In the present paper, we report detailed studies on the preparation of α,β-unsaturated α-nitrocarboxylic esters (I), and the synthesis of α,β-unsaturated α-aminocarboxylic esters (VI) by the reduction of β-methoxy-α-nitrocarboxylic esters (III).

Nitration of α,β-unsaturated carboxylic esters with fuming nitric acid was reported by Bouveault[5)] and Tatsuoka.[6)] The reaction was reinvestigated under various conditions and it was found that two products were formed in the reaction. When methyl 4-methyl-2-pentenoate was treated with fuming nitric acid (sp.gr., 1.52) with vigorous stirring at about 30°C for more than 5 hr, methyl 4-methyl-2-nitro-2-pentenoate (Ie) and methyl 2-hydroxy-4-methyl-3-nitropentanoate (IIe) were obtained in 33 and 39% yields, respectively.

The nitroolefincarboxylic ester Ie was characterized by elementary analysis and infrared spectrum. The structure was also supported by the reduction with aluminum amalgam giving methyl 4-methyl-2-oximinopentanoate.[4)]

In place of methyl 2-hydroxy-4-methyl-3-nitro-

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3) C. Shin, M. Masaki and M. Ohta, This Bulletin, **39**, 858 (1966).

4) C. Shin, M. Masaki and M. Ohta, *J. Org. Chem.*, **32**, 1860 (1967).

5) L. Bouveault and A. Wahl, *C. R. Acad. Sci. Paris*, **131**, 687, 1212 (1900); L. Bouveault and A. Wahl, *Bull. Soc. Chim. Fr.*, **25**, 801, 913 (1901).

6) S. Tatsuoka, M. Murakami and T. Tamura, *Yakugaku Zasshi*, **70**, 230 (1950).

TABLE 1. α,β-UNSTATURATED α-NITRO- AND α-HYDROXY-β-NITROCARBOXYLIC ESTERS

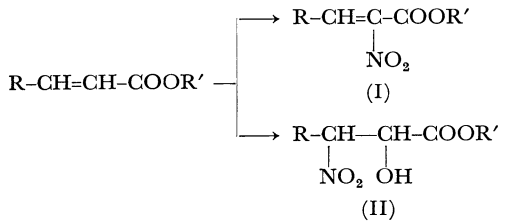
Compd	Yield (%)	Bp °C/mmHg	Formula	Found % C	Found % H	Found % N	Calcd % C	Calcd % H	Calcd % N	IR Spectrum[a] ν_{max}, cm^{-1}
Ia	32	88—92/4	$C_5H_7NO_4$	41.12	4.81	9.42	41.38	4.86	9.65	1740, 1640, 1560, 1350
Ib	39	85—87/3	$C_7H_{11}NO_4$			7.99			8.09	1735, 1650, 1540, 1370
Ic	31	91—107/4	$C_7H_{11}NO_4$	48.68	6.65	8.32	48.55	6.40	8.09	1740, 1660, 1540, 1380
Id	24	98—105/3[b]	$C_8H_{13}NO_4$	51.83	7.19	6.99	51.34	6.95	7.49	1740, 1665, 1560, 1380
Ie	33	84—86/4	$C_7H_{11}NO_4$	48.84	7.11	7.93	48.55	6.40	8.09	1740, 1660, 1540, 1380
If	38	91—95/2.5	$C_8H_{13}NO_4$	51.51	7.12	7.58	51.34	6.95	7.49	1740, 1660, 1560, 1380
IIb	18	108—109/3	$C_7H_{13}NO_5$	44.44	6.58	7.59	43.97	6.85	7.33	3450, 1740, 1560, 1375
IIc	27	104—110/5	$C_7H_{13}NO_5$	44.08	6.66	7.48	43.97	6.85	7.33	3450, 1740, 1560, 1370
IId	32.5	120—121/2	$C_8H_{15}NO_5$	46.51	6.99	6.76	46.82	7.37	6.83	3450, 1740, 1555, 1370
IIe	39	120—121/2	$C_7H_{13}NO_5$	44.21	6.67	7.21	43.97	6.85	7.33	3450, 1740, 1560, 1375
IIf	28	107—110/2	$C_8H_{15}NO_5$	46.61	7.08	7.18	46.82	7.37	6.83	3450, 1740, 1650, 1380

a) In NaCl. b) lit,[7] bp 72.5—79.5°C/0.7 mmHg.

pentanoate, an alternative 3-hydroxy-2-nitro structure might be also possible from elementary analysis and infrared spectrum. However, methyl 3-hydroxy-4-methyl-2-nitropentanoate prepared by an authentic method[7] showed bp 102—114°C/3 mmHg, while compound IIe obtained from the above nitration method has bp 120—121°C/2 mmHg.

Thus the most probable structure for IIe was concluded to be methyl 2-hydroxy-4-methyl-3-nitropentanoate.

Nitration of analogous olefinic carboxylic esters afforded the corresponding α-nitrocarboxylic esters (Ia—d and If) and 2-hydroxy-3-nitrocarboxylic esters (IIb—d and IIf) under similar experimental conditions; results of the elementary analyses and infrared spectra of the products are shown in Table 1.

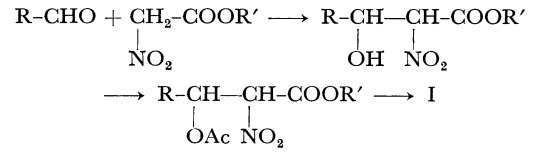


(I) (II)

a) $R=CH_3$, $R'=CH_3$
b) $R=C_2H_5$, $R'=C_2H_5$
c) $R=n\text{-}C_3H_7$, $R'=CH_3$
d) $R=n\text{-}C_3H_7$, $R'=C_2H_5$
e) $R=i\text{-}C_3H_7$, $R'=CH_3$
f) $R=i\text{-}C_3H_7$, $R'=C_2H_5$

Infrared spectrum of I showed bands of carbon-carbon double bond at 1640—1665 cm^{-1}, and of nitro group at 1540—1560 and 1350—1380 cm^{-1} regions. On the other hand, II showed infrared absorption bands of hydroxyl group at 3450 cm^{-1}, and of nitro group at 1555—1560 and 1370—1380 cm^{-1} regions.

The nitration method is useful for the preparation of α,β-unsaturated α-nitrocarboxylic esters (I), while Dornow and Menzel[8] and other workers[7,9] reported the preparation of I by a three-step reaction starting from aldehydes and nitroacetic ester *via* the route illustrated below.



When ethyl 4-methyl-2-nitro-2-pentenoate (If) was treated with methanol in the presence of sodium methoxide or sodium acetate below −10°C, ethyl 3-methoxy-4-methyl-2-nitropentanoate (IIIf) was obtained in a good yield. Other 3-methoxy-2-nitrocarboxylates (IIIb, IIIc and IIId) were also obtained from I under similar experimental conditions in good yields; the results are summarized in Table 2. When compounds III were heated at 150—160°C for 6 hr, the methoxyl group in the 3-position was eliminated to afford I.

Reduction of IIIf with aluminum amalgam in ether and the subsequently distillation of the resulting product under reduced pressure gave a small amount of ethyl 2-amino-4-methyl-2-pentenoate (VIf) as a lower boiling point fraction and ethyl 2-hydroxyamino-3-methoxy-4-methylpentanoate (IVf) as a higher boiling fraction in a 70% yield. The infrared spectrum of VIf exhibits two absorption bands at 1650 and 1735 cm^{-1} in carbonyl region and a broad band at 3350 cm^{-1} in amino region. The absorption pattern is essentially the

7) S. Umezawa and S. Zen, This Bulletin, **36**, 1143 (1963).

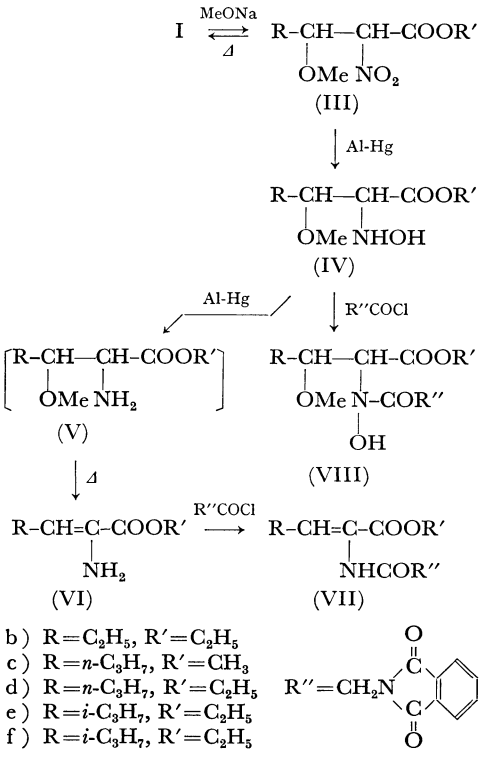
8) A. Dornow and H. Menzel, *Ann. Chem.*, **588**, 40 (1959).

9) I. S. Ivanova, Yu. V. Konnova and S. S. Novikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1962**, 1677.

TABLE 2. β-METHOXY-α-NITRO- AND β-METHOXY-α-HYDROXYAMINOCARBOXYLIC ESTERS

Compd	Yield (%)	Bp °C/mmHg	Formula	Found % C	Found % H	Found % N	Calcd % C	Calcd % H	Calcd % N	IR Spectrum[a] ν_{max}, cm^{-1}
IIIb	66	72—85/2	$C_8H_{15}NO_5$	46.13	7.34	6.97	46.82	7.37	6.83	1750, 1570, 1375, 1030
IIIc	92	95—97/2.5	$C_8H_{15}NO_5$	47.14	7.09	7.10	46.82	7.37	6.83	1750, 1565, 1370, 1100
IIId	70	99—103/3	$C_9H_{17}NO_5$	49.77	7.82	6.76	49.30	7.82	6.39	1750, 1570, 1380, 1100
IIIe	65	96—97/5	$C_8H_{15}NO_5$	47.50	7.02	7.27	46.82	7.37	6.83	1750, 1570, 1375, 1090
IIIf	78.4	88—93/2	$C_9H_{17}NO_5$	49.87	7.63	7.27	49.30	7.82	6.39	1750, 1570, 1380, 1100
IVb	87.8	105—110/4	$C_8H_{17}NO_4$	50.72	9.27	7.45	50.25	8.96	7.33	3350, 3250, 1735, 1075
IVc	52	96—101/4	$C_8H_{17}NO_4$			7.49			7.33	3350, 3250, 1735, 1080
IVd	59	105—108/2	$C_9H_{19}NO_4$			6.75			6.82	3400, 3250, 1735, 1095
IVe	50	109—111/4	$C_8H_{17}NO_4$			7.72			7.33	3400, 3250, 1735, 1095
IVf	74.5	98—100/4	$C_9H_{19}NO_4$			7.36			6.82	3350, 3250, 1735, 1095

a) In NaCl.



b) R=C_2H_5, R′=C_2H_5
c) R=n-C_3H_7, R′=CH_3
d) R=n-C_3H_7, R′=C_2H_5
e) R=i-C_3H_7, R′=C_2H_5
f) R=i-C_3H_7, R′=C_2H_5

same as that of α,β-unsaturated α-aminocarboxylic ester.[4] Reduction of other β-methoxy-α-nitro compounds (IIIb—e) afforded also enamines (VIb—e) as minor products and α-hydroxyamino-β-methoxycarboxylic esters (IVb—e) as main products. Formation of enamines could be explained by the fact that elimination of methoxyl group in the 3-position as methanol occurred during the distillation of α-amino-β-methoxycarboxylic esters (V) which were the further reduced products of the initially formed hydroxyamino esters (IV). Compounds VI were unstable and gradually polymerized at room temperature. In order to establish the structure, the new enamines were converted into their *N*-phthaloylglycyl derivatives. When ethyl 2-amino-2-pentenoate (VIb) was treated with phthaloylglycyl chloride in benzene in the presence of pyridine at room temperature, ethyl 2-(phthaloylglycyl)amino-2-pentenoate (VIIb) was obtained as a colorless crystalline product in a 9% yield. Analogous treatment of other enamines (VIc—f) with phthaloylglycyl chloride afforded (phthaloylglycyl)amino derivatives (VIIc—f); the results are summarized in Table 4. The structures of these phthaloylglycyl derivatives were confirmed by elementary analyses and their infrared absorption spectra which are very similar to alkyl esters of 3-methyl-2-(phthaloylglycyl)aminocrotonic acid.[3,4] On the other hand, treatment of IVf with phthaloylglycyl chloride under similar conditions, afforded ethyl 3-methoxy-4-methyl-2-*N*-(phthaloylglycyl)hydroxyaminopentanoate (VIIIf). Analogous acylation of other α-hydroxyaminocarboxylic esters (IVb and IVe) afforded the corresponding (phthaloylglycyl) hydroxyamino derivatives (VIIIb and VIIIe) in a poor yield; the results are summarized in Table 4. All these (phthaloylglycyl)hydroxyamino derivatives gave red coloration with methanolic ferric chloride. The structures of these esters were assigned on the basis of elementary analysis and infrared spectrum.

When methyl 2-hydroxyamino-3-methoxy-4-

TABLE 3. α,β-UNSATURATED α-AMINOCARBOXYLIC ESTERS

Compd	Yield (%)	Bp °C/mmHg	IR Spectrum[a] ν_{max}, cm^{-1}
VIb	16	62—66/4	3400, 1740, 1620
VIc	15.4	65—71/4	3300, 1730, 1650
VId	8.4	83—86/3	3350, 1740, 1650
VIe	18	57—65/4	3350, 1740, 1650
VIf	15.8	61—65/3	3350, 1735, 1650

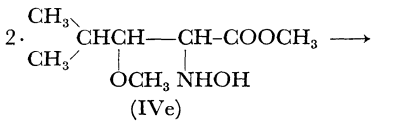
a) In NaCl.

TABLE 4. *N*-PHTHALOYLGLYCYL DERIVATIVES OF ENAMINE (VI) AND HYDROXYAMINOCARBOXYLATES (IV)

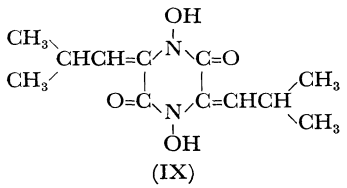
Compd	Yield (%)	Mp °C	Formula	Found %			Calcd %			IR Spectrum[d] ν_{max}, cm^{-1}		
				C	H	N	C	H	N			
VIIb	9	245—247	$C_{17}H_{18}N_2O_5$	61.48	5.66	8.62	61.81	5.49	8.48	3250,	1730,	1670
VIIc	13	202—203[a]	$C_{17}H_{18}N_2O_5$			7.84			8.48	3250,	1730,	1670
VIId	8.4	196—197[b]	$C_{18}H_{20}N_2O_5$			7.72			8.14	3250,	1720,	1660
VIIe	26	164—165	$C_{17}H_{18}N_2O_5$	61.45	5.70	8.64	61.81	5.49	8.48	3300,	1730,	1670
VIIIb	20.2	146—147	$C_{18}H_{22}N_2O_7$	57.06	6.02	7.67	57.13	5.86	7.40	3450,	1750,	1690
VIIIe	31	189—190[c]	$C_{18}H_{22}N_2O_7$			7.54			7.40	3500,	1720,	1660
VIIIf	52	119—120	$C_{19}H_{24}N_2O_7$	58.14	6.22	7.30	58.15	6.17	7.14	3470,	1730,	1670

a, b) Recrystallized from ethanol (colorless needles). c) Recrystallized from ligroin (colorless needles).
d) In KBr.

methylpentanoate (IVe) was allowed to stand at room temperature for two weeks, cyclic condensation took place and 1,4-dihydroxy-3,6-diisobutylidene-2,5-dioxopiperazine (IX) was obtained. Formation of the 2,5-dioxopiperazine ring supports 2-hydroxyamino structure of the reduction product and also the position of nitro group in the parent ester, methyl 4-methyl-2-nitro-2-pentenoate (Ie).



(IVe)



(IX)

Experimental

All melting and boiling points are uncorrected. The IR spectra were recorded with a Hitachi EPI-S2 Spectrometer.

Nitration of Methyl 4-Methyl-2-pentenoate with Fuming Nitric Acid. Methyl 4-methyl-2-pentenoate (20 g) was added drop by drop, with vigorous stirring, to fuming nitric acid (36 m*l*, sp.gr. 1.52) below 5°C. After addition of the ester had been completed, the mixture was stirred for several hr, while being allowed to warm to room temperature, and stirring was continued for additional 5 hr at 30°C. The mixture was added to ice water (200 m*l*) and then extracted several times with ether. The combined ethereal extracts were washed successively with water, saturated aqueous solution of sodium carbonate and finally with water. The extracts were dried over anhydrous sodium sulfate and then evaporated. Distillation of the residual oil afforded two fractions, as pale yellow oils, which were identified as methyl 4-methyl-2-nitro-2-pentenoate (Ie) and methyl 2-hydroxy-4-methyl-3-nitropentanoate (IIe).

Under analogous conditions, nitration of other olefinic carboxylic esters was performed and the corresponding α-nitro esters (Ia—d and If) and β-nitro esters (IIb—d and IIf) were obtained.

Ethyl 3-Methoxy-4-methyl-2-nitropentanoate (IIIf). The procedure was modified from the method of Yamagishi and Ishibiki.[10] A solution of ethyl 4-methyl-2-nitro-2-pentenoate (11 g) in methanol (70 m*l*) was added, with vigorous stirring, to 5% methanolic solution of sodium methoxide (from 4.8 g of sodium in methanol (70 m*l*)) cooled below −10°C. The temperature of the reaction mixture rose up to 15°C, at which stirring was continued for 20 min, and then a small amount of crushed dry ice was added portionwise. The cooled mixture was poured into water (500 m*l*), and the resulting solution was acidified with glacial acetic acid, whereby an oily product was separated out. The product was extracted several times with ether. The combined ethereal extracts were washed with water, dried over anhydrous magnesium sulfate, and then evaporated. Distillation of the residual oil afforded ethyl 3-methoxy-4-methyl-2-nitropentanoate as an almost colorless oil.

Analogous treatment of other α-nitroolefinic carboxylic esters with sodium methoxide afforded the corresponding β-methoxy-α-nitrocarboxylic esters (IIIb—e).

Reduction of Ethyl 3-Methoxy-4-methyl-2-nitropentanoate. A solution of IIIf (6 g) in ether (50 m*l*) was added drop by drop with vigorous stirring to a suspension of aluminum amalgam (from 4 g of aluminum) in ether (120 m*l*) at room temperature. In a few minutes ether began to reflux. During the addition of the above solution a few drops of water was added at 10-min intervals to maintain refluxing. After addition of the solution had been completed stirring was continued for additional 2 hr. The mixture was extracted thoroughly several times with ether. The combined ethereal extract was dried over anhydrous sodium sulfate and then evaporated. Distillation of the residual oil afforded two fractions, as pale yellow oils, which were identified as ethyl 2-amino-4-methyl-2-pentenoate (VIf) and ethyl 2-hydroxyamino-3-methoxy-4-methylpentanoate (IVf).

Analogous reduction of other α-nitrocarboxylic esters (III) afforded the corresponding enaminocarboxylic (VIb—e) and hydroxyaminocarboxylic esters (IVb—e).

Ethyl 2-(Phthaloylglycyl)amino-2-pentenoate (VII). Phthaloylglycyl chloride (0.65 g) was added

10) K. Yamagishi and Y. Ishibiki, *Nippon Kagaku Zasshi*, **81**, 971 (1960).

portionwise with vigorous stirring to ethyl 2-amino-2-pentenoate (VIb, 0.5 g) suspended in a solution of sodium hydrogencarbonate (0.3 g) in water (10 m*l*) at room temperature. After stirring for 30 min a syrup was precipitated. After one day the viscous syrup crystallized. The crystals were collected, washed well with water and recrystallized from a small quantity of ethanol to afford colorless needles. The product was characterized by the data given in Table 4.

Methyl 4-Methyl-2-(phthaloylglycyl)amino-2-pentenoate (VIIe). A solution of phthaloylglycyl chloride (2.5 g) in dry benzene (20 m*l*) was added drop by drop with vigorous stirring to a solution of methyl 4-methyl-2-amino-2-pentenoate (VIe, 1.8 g) at 20°C. After stirring for 3 hr, 30 m*l* of water was added to the resulting mixture and the insoluble substance was filtered off. The benzene layer was washed with water, dried over anhydrous sodium sulfate, and then evaporated. The residual viscous syrup crystallized gradually. Recrystallization from a small quantity of ethanol gave colorless needles, which were characterized as the expected phthaloylglycylamino compound by the data given in Table 4.

In an analogous manner, acylation of other α-aminocarboxylic esters (VIc and VId) was performed, and the corresponding α-phthaloylglycylamino esters (VIIc and VIId) were obtained in poor yields (Table 4).

Ethyl 3-Methoxy-2-*N*-(phthaloylglycyl)hydroxyaminopentanoate (VIIIb). Phthaloylglycyl chloride (0.65 g) was added portionwise with vigorous stirring to ethyl 2-hydroxyamino-3-methoxypentanoate (IVb, 0.6 g) suspended in a solution of sodium hydrogencarbonate (0.3 g) in water (10 m*l*) at room temperature. After stirring for 30 min, a viscous syrup began to separate. On being allowed to stand overnight at room temperature, the syrup became crystalline. The crystals were collected and washed with water. Recrystallization from ethanol afforded colorless prisms (Table 4).

Ethyl 3-Methoxy-4-methyl-2-*N*-(phthaloylglycyl)-hydroxyaminopentanoate (VIIIf). A solution of phthaloylglycyl chloride (1.1 g) in dry benzene (10 m*l*) was added drop by drop, with vigorous stirring, to a solution of ethyl 2-hydroxyamino-3-methoxy-4-methylpentanoate (IVf, 1 g) in dry benzene (10 m*l*) in the presence of pyridine (0.42 g) at room temperature. After stirring for 2 hr, 30 m*l* of water was added to the resulting mixture. The mixture was allowed to stand overnight at room temperature and the insoluble substance was filtered off. The benzene layer of the filtrate was washed with water, dried over anhydrous sodium sulfate, and then evaporated. The residual viscous syrup was crystallized by successive treatment of a small quantity of ether and di-*n*-butyl ether. Recrystallization from petroleum ether (bp 70—120°C) afforded the expected acylated compound as colorless needles.

In an analogous manner, α-hydroxyaminocarboxylic ester (IVe) was treated with phthaloylglycyl chloride to afford the corresponding α-(phthaloylglycyl)hydroxyaminocarboxylic ester (VIIIe) in a poor yield (Table 4).

1,4-Dihydroxy-3,6-diisobutylidene-2,5-dioxopiperazine (IX). Methyl 2-hydroxyamino-3-methoxy-4-methylpentanoate (IVe, 8 g) was allowed to stand for two weeks at room temperature, during which the ester became viscous, and then a small amount of crystals separated out gradually. The mixture was treated with ether and the crystalline product was collected. Recrystallization from a small quantity of methanol afforded colorless prismatic needles (2.1 g, 42%), mp 250—251°C (decomp.), which turned dark purple with methanolic ferric chloride. ν_{max}^{KBr} 3250, 1775, 1720, 1635 and 1610 cm^{-1}. λ_{max}^{EtOH} 221.5 mμ (ε=3500), 265.5 (4800) and 349 (9000).

Found: C, 56.29; H, 7.58; N, 11.09%. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02%.

The authors are indebted to Miss Toshiko Aoyagi for elementary analyses.