BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 1826—1829 (1973)

Studies of the Synthesis of Furan Compounds. XXIX.[1] Syntheses of 2-(5-Nitro-2-furyl)vinyl-1,8-naphthyridines[2]

Ichiro HIRAO, Yasuhiko KATO, Yoshimasa FUKANO, and Shinpei YANAI

Laboratory of Organic Synthesis, Department of Industrial Chemistry, Kyushu Institute of Technology, Tobata-ku, Kita-Kyushu 804

(Received December 16, 1972)

In continuing our study of the relationship between structures and antibacterial activity, 2-[2-(5-nitro-2-furyl)vinyl]-5-hydroxy- and 4-[2-(5-nitro-2-furyl)vinyl]-2,7-dihydroxy-1,8-naphthyridine and their related derivatives have been synthesized. In these compounds, 2-[2-(5-nitro-2-furyl)vinyl]-5-hydroxy- (I) and 2-[2-(5-nitro-2-furyl)vinyl]-5-hydroxy-6-ethoxycarbonyl-1,8-naphthyridine (II) showed broad spectra of antibacterial activity, and the activity of I was greater than that of II. Other compounds exhibit a strong antibacterial activity against *Diplococcus pneumoniae*, *Streptococcus hemolyticus*, and *Staphilococcus aureus*, but they show a weak activity against the other microorganisms tested.

In 1,8-naphthyridine compounds, nalidixic acid (1-ethyl-4-oxo-7-methyl-1,8-naphthyridine-3-carboxylic acid) has been known as an effective chemotherapeutic drug for Gram-negative infections. Nishigaki *et al.* reported that the derivatives of nalidixic acid and its related methyl-1,8-naphthyridines, whose methyl groups were condensed with 5-nitrofurfural, showed a broad spectrum of antibacterial activity greater than that of the parent nalidixic acid; another excellence of these compounds is that the nalidixic acid resistant-strain of *Escherichia coli* K-12 and *Shigella dysenteriae* Hanabusa are still as susceptible to these compounds as the original strains.[3,4] Several patents concerning the syntheses and the use of 2-(5-nitro-2-furyl)vinyl-1,8-naphthyridines have been granted.[5–10]

In order to compare the antibacterial activity, 2-[2-(5-nitro-2-furyl)vinyl]- and 4-[2-(5-nitro-2-furyl)-vinyl]-1,8-naphthyridine derivatives were prepared.

Results and Discussion

2-[2-(5-Nitro-2-furyl)vinyl]-5-hydroxy-1,8-naphthyridine (I) was obtained by the condensation of 2-methyl-5-hydroxy-1,8-naphthyridine[11] with 5-nitrofurfural in refluxing acetic anhydride. In a similar manner, 2-[2-(5-nitro-2-furyl)vinyl]-5-hydroxy-6-ethoxycarbonyl-1,8-naphthyridine[4] (II) was obtained from the corresponding 2-methyl-1,8-naphthyridine. I and II were converted into the corresponding 5-chloro derivatives (Ia and IIa respectively) by being heated in phosphoryl chloride. On the other hand, Ia was also obtained from 2-methyl-5-chloro-1,8-naphthyridine[11] and 5-nitrofurfural. When Ia or IIa was heated with phenol, the 5-chlorine atom was replaced by a phenoxy group to give 2-[2-(5-nitro-2-furyl)vinyl]-5-

1) Part XXVIII of this series: Y. Kato, T. Kuboyama, and I. Hirao, This Bulletin, **45**, 3165 (1972).

2) Presented at the 24th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1971.

3) S. Nishigaki, F. Yoneda, K. Ogiwara, T. Naito, R. Domori, S. Kadoya, Y. Tanaka, and I. Takamura, *Chem. Pharm. Bull.*, (Tokyo), **17**, 1827 (1969); F. Yoneda, S. Nishigaki, N. Mizushima, and H. Takahashi, *J. Med. Chem.*, **14**, 638 (1971).

4) S. Nishigaki, T. Naito, Y. Oshima, R. Domori, and S. Nagasaki, Japan Pat. 69 13950; 69 13951; 69 13952, June 21, 1969.

5) S. Nishigaki, T. Naito, Y. Oshima, R. Domori, S. Nagasaki, S. Kadoya, and I. Takamura, Japan Pat. 69 13949, June 21, 1969.

6) B. Herbert, S. Kurt, D. Otto, V. Wolfgang, and S. Winfriede, S. African Pat. 69 02496, October 15, 1969.

7) T. Naito, Y. Oshima, R. Domori, S. Nagasaki, Y. Tanaka, and R. Yoshimura, Japan Pat. 70 30337, October 10, 1970.

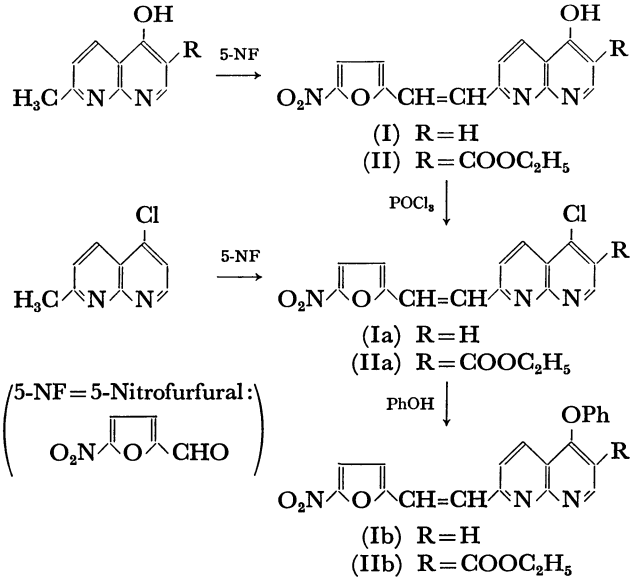
8) R. Domori, R. Yoshimura, and T. Naito, Japan Pat. 70 39096, December 9, 1970.

9) R. Ueno and W. Kashihara, Japan Pat. 71 15632, April 27, 1971.

10) B. Herbert, G. Rudi, T. Max, V. Wolfgang, and S. Winfriede, Ger. Offen. 2030581, December 30, 1971.

11) E. V. Brown, *J. Org. Chem.*, **30**, 1607 (1965).

phenoxy-1,8-naphthyridine (Ib) and 2-[2-(5-nitro-2-furyl)vinyl]-5-phenoxy-6-ethoxycarbonyl-1,8-naphthyridine (IIb) (Scheme 1).



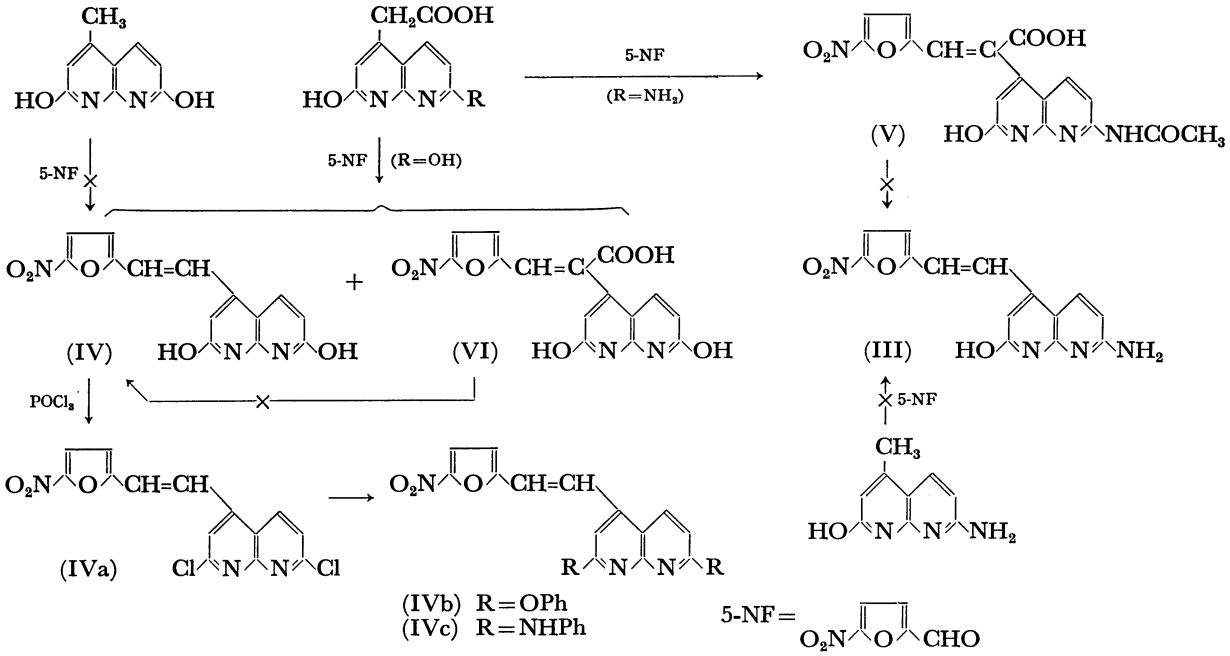
Scheme 1

It was found that the reactivity of the methyl group at the γ-position on the 1,8-naphthyridine nucleus is smaller than that at the α-position. An attempt to prepare 2-hydroxy-7-amino- (III) or 2,7-dihydroxy-4-[2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridine (IV) from the corresponding 4-methyl-1,8-naphthyridines and 5-nitrofurfural was unsuccessful, although Herbert *et al.*[6] have described the preparation of the same compounds (III and IV) by this method. In our results, the raw materials were recovered as 5-nitrofurfural diacetate and 2-hydroxy-7-acetamido- or 2,7-dihydroxy-4-methyl-1,8-naphthyridine themselves in place of the desired III or IV. Another method for preparation of III and IV is the decarboxylation of 3-(5-nitro-2-furyl)-2-(2-hydroxy-7-acetamido-1,8-naphthyridin-4-yl)acrylic acid (V) and 3-(5-nitro-2-furyl)-2-(2,7-dihydroxy-1,8-naphthyridin-4-yl)acrylic acid (VI), which had themselves been prepared by the reaction of 2-hydroxy-7-amino- and 2,7-dihydroxy-1,8-naphthyridine-4-acetic acid[12] respectively with 5-nitrofurfural. While the decarboxylation of V and VI did not occur in the presence of copper bichromate in hot quinoline or in the presence of benzoyl peroxide in dimethylformamide, IV was produced as the main product in the preparation of VI. It can be assumed that IV was formed by condensation of 2,7-dihydroxy-1,8-naphthyridine-4-acetic acid with 5-nitrofurfural involved in the decarboxylation.

When IV was heated with phosphoryl chloride, the corresponding 2,7-dichloro derivative (IVa) was obtained. IVa gave 2,7-diphenoxy (IVb) and 2,7-dianilino (IVc) compounds when heated with phenol and aniline respectively.

In the IR spectra of I, II, IV, V, and VI, the C=O stretching absorption band was observed in the 1660—1650 cm^{-1} region, while it disappeared in the corresponding chloro derivatives (Ia, IIa, and IVa); this suggests that the hydroxy-naphthyridine part takes the keto structure in the solid state. The *trans*-configuration of I, Ia, b, II, IIa, b, IV, and IVa—c is supported by the presence of a C–H out-of-plane deformation vibration band in the 960—950 cm^{-1} region.

Microbiological Assays.[13] The antibacterial activities of these compounds in response to ten microorganisms were examined. The minimum amount of



Scheme 2

12) S. Carboni, A. Da Settimo, and G. Pirisino, *Ann. Chim.* (Rome), **54**, 883 (1964).

13) The authors are indebted to Dr. R. Ueno and his staff of the Ueno Pharmaceutical Company, Ltd., for the assay.

TABLE 1. INHIBITORY ACTIVITY OF TEN COMPOUNDS ON MICROORGANISMS
Minimum inhibitory concentration, μg/ml

Compound	*Diplococcus pneumoniae* Dp-1	*Streptococcus hemolyticus* Group A 089	*Staphylococcus aureus* 209 P	*Bacillus subtilis* pcl 219	*Salmonella enteritidis* 1891	*Salmonella pullorum* Chuyu 114	*Escherichia coli* 0-55	*Klebsiella pneumoniae* ST-101	*Proteus vulgaris* HX 19	*Pseudomonus aeruginosa* 347
Type A										
I	<0.10	<0.10	0.39	—	0.39	0.78	0.39	0.39	0.39	3.13
II	0.78	0.19	0.78	—	3.13	6.25	1.56	1.56	3.13	>25
Ib	1.56	1.56	0.78	1.56	3.13	>3.13	>3.13	>3.13	1.56	>3.13
IIa	1.56	<0.19	1.56	<0.19	3.13	25	3.13	3.13	>25	>25
Type B										
IV	3.13	0.78	3.13	3.13	>25	>25	>25	>25	>25	>25
IVa	1.56	1.56	0.78	0.78	—	>25	>25	>25	1.56	>25
IVb	>25	>25	12.5	25	—	>25	>25	>25	>25	>25
IVc	1.56	—	0.78	1.56	—	>25	>25	>25	>25	>25
Type C										
V	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25
VI	>12.5	0.19	>12.5	>12.5	>12.5	>12.5	>12.5	>12.5	>12.5	>12.5
Contrast[a)]	12.5	0.39	1.56	1.56	0.78	1.56	1.56	3.13	6.25	25

a) 3-(5-Nitro-2-furyl)-2-(2-furyl)acrylic amide was used in the test.

each compound necessary for the complete inhibition of growth was determined by the dilution method, using the usual bouillon agar medium (pH 6.8—7.0); some of the results are shown in Table 1. The compounds employed in this test consist of three types (Table 1). I, Ib, II, and IIa are the compounds substituted by the 5-nitro-2-furylvinyl group at the 2-position on the 1,8-naphthyridine nucleus (type A), IV and IVa—c are those substituted at the 4-position (type B), and V and VI are acrylic acid derivatives (type C). The three types of compounds showed a decreasing tendency of activity in the order: type A> type B>type C.

All the compounds of type A, except for Ib, showed broad spectra of antibacterial activity; I was the most active antibacterial against all the microorganisms employed. All the compounds of type B, except IVb, showed a strong activity against *Diplococcus pneumoniae*, *Streptococcus hemolyticus*, *Staphilococcus aureus*, and *Bacillus subtilis*, but they exhibited no activity against the other microorganisms. The lack of activity in Ib and IVb may be due to the substituent (phenoxy group). The compounds of type C include almost no active antibacterial.

Experimental[14)]

2-[2-(5-Nitro-2-furyl)vinyl]-5-hydroxy-1,8-naphthyridine (I). A mixture of 2-methyl-5-hydroxy-1,8-naphthyridine[11)] (1.6 g, 10 mmol), 5-nitrofurfural (1.6 g, 11 mmol), and acetic anhydride (10 ml) was refluxed for 5 hr. Cooling provided 1.8 g of a crude product; when the mother filtrate was then allowed to stand for several days at room temperature, an additional 0.2 g of the product was obtained. Recrystallization from ethylene glycol monomethyl ether afforded 1.8 g (63.6%) of I as pale yellow needles; mp 316—317 °C (decomp.). IR (KBr) cm^{-1}: 1650 (ν C=O), 965 (δ C–H; *trans*).

Found: C, 59.19; H, 3.07; N, 14.60%. Calcd for $C_{14}H_9N_3O_4$: C, 59.36; H, 3.20; N, 14.83%.

2-[2-(5-Nitro-2-furyl)vinyl]-5-hydroxy-6-ethoxycarbonyl-1,8-naphthyridine (II). 2-Methyl-5-hydroxy-6-ethoxycarbonyl-1,8-naphthyridine[15)] (2.6 g, 12.2 mmol) and 5-nitrofurfural (1.8 g, 12.5 mmol) were heated in acetic anhydride (10 ml) under reflux for 1.5 hr. On cooling, the precipitated product was collected and washed with ether and methanol. Crystallization from ethylene glycol monomethyl ether gave 3 g (76.5%) of II as pale yellow needles which melted, with decomposition, at 285 °C. IR (KBr) cm^{-1}: 1730 and 1710 (shoulder) (ν C=O), 960 (δ C–H; *trans*).

Found: C, 57.42; H, 3.85; N, 11.53%. Calcd for $C_{17}H_{13}N_3O_6$: C, 57.47; H, 3.69; N, 11.83%.

2-[2-(5-Nitro-2-furyl)vinyl]-5-chloro-1,8-naphthyridine (Ia).

Procedure A: Compound I (0.4 g, 1.7 mmol) was heated in phosphoryl chloride (5 ml) for 4 hr under reflux. The reaction mixture was then poured into cold water, and the product was collected, washed with water, and then dried. Recrystallization from ethylene glycol monomethyl ether gave 0.23 g (54%) of Ia as pale yellow needles; mp 231—232 °C (decomp.). IR (KBr) cm^{-1}: 960 (δ C–H; *trans*).

Found: C, 55.76; H, 2.53; N, 13.54%. Calcd for $C_{14}H_8N_3O_3Cl$: C, 55.74; H, 2.67; N, 13.93%.

Procedure B: 2-Methyl-5-chloro-1,8-naphthyridine[11)] (1 g, 5.6 mmol) and 5-nitrofurfural (0.9 g, 6.4 mmol) were heated in acetic anhydride (5 ml) under reflux for 1.5 hr. Cooling provided 1.2 g of the crude product. Work-up as above afforded 0.8 g (58.9%) of Ia; mp 231—232 °C (decomp.), undepressed on admixture with a sample prepared by *Procedure A* as has been described above for Ia.

2-[2-(5-Nitro-2-furyl)vinyl]-5-chloro-6-ethoxycarbonyl-1,8-naphthyridine (IIa). II (0.6 g, 2.12 mmol) was covered with phosphoryl chloride (*ca.* 10 ml) and refluxed for 1 hr. After cooling the reaction mixture was poured into ice water and neutralized with aqueous ammonia. The precipitated product was filtered and washed with water. Crystallization from pyridine gave 0.3 g (47.5%) of IIa as pale yellow needles

14) All the melting and decomposition points are uncorrected. The elemental analyses were carried out with a Yanagimoto CHN Corder, MT-2 type. The infrared absorption spectra (IR) were recorded with a JASCO Model IRA-2 grating infrared spectrophotometer.

15) G. R. Lappin, *J. Amer. Chem. Soc.*, **70**, 3348 (1948).

which did not melt below 300 °C. IR (KBr) cm^{-1}: 1730 (ν C=O), 960 (δ C–H; *trans*).

Found: C, 54.95; H, 3.24; N, 11.14%. Calcd for $C_{17}H_{12}N_3O_5Cl$: C, 54.63; H, 3.24; N, 11.24%.

2-[2-(5-Nitro-2-furyl)vinyl]-5-phenoxy-1,8-naphthyridine (Ib). A mixture of Ia (0.5 g, 1.7 mmol) and phenol (5 ml) was refluxed for 15—20 min. After cooling, aqueous sodium carbonate was added to the reaction mixture, and the precipitated product was filtered. Recrystallization from tetrahydrofuran afforded 0.45 g (76.5%) of Ib as a pale yellow powder which melted at 223—224 °C. IR (KBr) cm^{-1}: 950 (δ C–H; *trans*), 734 and 690 (δ C–H; mono-substituted benzene).

Found: C, 66.92; H, 3.70; N, 11.56%. Calcd for $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.65; N, 11.69%.

2-[2-(5-Nitro-2-furyl)vinyl]-5-phenoxy-6-ethoxycarbonyl-1,8-naphthyridine (IIb). The chloro compound, IIa (0.15 g, 4 mmol), was heated in 2 ml of phenol under reflux for 40 min. Aqueous sodium carbonate was then added to the reaction mixture, and the precipitates were filtered. They were subsequently crystallized from ethylene glycol monomethyl ether to afford 0.08 g (63.8%) of IIb as pale yellow granules; mp>300 °C. IR (KBr) cm^{-1}: 1730 (ν C=O), 955 (δ C–H; *trans*), 730 and 690 (δ C–H; mono-substituted benzene).

Found: C, 64.72; H, 3.98; N, 9.51%. Calcd for $C_{23}H_{16}N_3O_6$: C, 64.88; H, 3.75; N, 9.76%.

4-[2-(5-Nitro-2-furyl)vinyl]-2,7-dihydroxy-1,8-naphthyridine (IV) and 3-(5-Nitro-2-furyl)-2-(2,7-dihydroxy-1,8-naphthyridin-4-yl)acrylic Acid (VI). A mixture of potassium salt of 2,7-dihydroxy-1,8-naphthyridine-4-acetic acid[12] (4.2 g, 16.3 mmol), 5-nitrofurfural (2.6 g, 18.4 mmol), and acetic anhydride (40 ml) was heated at 66—70 °C for 4 hr. After cooling, 40 ml of glacial acetic acid was added to the reaction mixture, and then this was poured into cold water. The precipitated product was filtered and recrystallized from dimethyl sulfoxide to give 2.3 g (42%) of IV as a yellow powder; mp 317 °C (decomp.). IR (KBr) cm^{-1}: 3100—2800 (ν O–H; associated), 1663 (ν C=O), 957 (δ C–H; *trans*).

Found: C, 55.97; H, 3.24; N, 13.98%. Calcd for $C_{14}H_9N_3O_5$ (IV): C, 56.19; H, 3.03; N, 14.04%.

The mother filtrate was concentrated under reduced pressure, after which the precipitated product was collected on a filter and washed with water. Recrystallization from aqeuous acetic acid afforded 1.5 g (24%) of VI as a yellow powder; mp>320 °C. IR (KBr) cm^{-1}: 3140—2800 (ν O–H; associated), 1706 and 1658 (ν C=O).

Found: C, 52.33; H, 2.67; N, 12.45%. Calcd for $C_{15}H_9N_3O_7$ (VI): C, 52.48; H, 2.64; N, 12.24%.

4-[2-(5-Nitro-2-furyl)vinyl]-2,7-dichloro-1,8-naphthyridine (IVa). IV (1 g, 3.3 mmol) was heated in phosphoryl chloride (20 ml) under reflux for 3 hr. After cooling, the reaction mixture was poured into ice water and the precipitated product was filtered. This product was recrystallized from ethylene glycol monomethyl ether to give 0.83 g (75%) of IVa as a yellow powder which melted at 259—260 °C. IR (KBr) cm^{-1}: 957 (δ C–H; *trans*).

Found: C, 50.28; H, 2.40; N, 12.49%. Calcd for $C_{14}H_7N_3O_3Cl$: C, 50.00; H, 2.08; N, 12.50%.

4-[2-(5-Nitro-2-furyl)vinyl]-2,7-diphenoxy-1,8-naphthyridine (IVb). IVa (1 g, 3 mmol) was heated in phenol (10 ml) under reflux for 30 min. After cooling, the reaction mixture was diluted with ether, and the precipitates were collected and washed with ether. Subsequent crystallization from ethylene glycol monomethyl ether gave 0.5 g (33%) of IVb as yellow needles; mp 216—217 °C. IR (KBr) cm^{-1}: 953 (δ C–H); *trans*), 750 and 690 (δ C–H; mono-substituted benzene).

Found: C, 69.24; H, 3.64; N, 9.45%. Calcd for $C_{26}H_{17}N_3O_5$: C, 69.18; H, 3.77; N, 9.31%.

4-[2-(5-Nitro-2-furyl)vinyl]-2,7-dianilino-1,8-naphthyridine Monohydrochloride (IVc). Aniline (0.3 g, 3.2 mmol), IVa (0.5 g, 1.5 mmol), and ethylene glycol monomethyl ether (10 ml) were refluxed for 1 hr. After cooling, concentrated hydrochloric acid was added to the reaction mixture. The isolated product was then collected and washed with water. Recrystallization from aqueous methanol afforded 0.35 g (48.5%) of IVc as a crimson-colored powder; mp 147—148 °C. IR (KBr) cm^{-1}: 959 (δ C–H; *trans*), 755 and 690 (δ C–H; mono-substituted benzene).

Found: C, 64.91; H, 3.98; N, 14.04%. Calcd for $C_{26}H_{19}N_5O_3 \cdot HCl$: C, 64.26; H, 4.12; N, 14.41%.

3-(5-Nitro-2-furyl)-2-(2-hydroxy-7-acetamido-1,8-naphthyridin-4-yl)acrylic Acid (V). A mixture of potassium salt of 2-hydroxy-7-amino-1,8-naphthyridine-4-acetic acid[12] (11.7g, 45 mmol), 5-nitrofurfural (7.1 g, 50 mmol), and acetic anhydride (10 ml) was heated at 50—55 °C for 4 hr. The reaction mixture was then poured into ice water, and the separated product was filtered and washed with water. Recrystallization from glacial acetic acid gave 11.5 g (62.5%) of V as a yellow powder; mp>320 °C. IR (KBr) cm^{-1}: 3230 (ν N–H), 2925 (ν CH_3), 1707, 1693, and 1660 (ν C=O).

Found: C, 53.26; H, 3.38; N, 15.06%. Calcd for $C_{17}H_{12}N_4O_7$: C, 53.13; H, 3.13; N, 14.58%.