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Synthesis of 1-Substituted 1,4-Dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine Derivatives. I[1]

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In order to test of antimicrobial activity, 1-ethyl-1,4-dihydro-7-[2-(5-nitro-2-furyl)-vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (V) which contained nalidixic acid and 5-nitro-2-furaldehyde was prepared and a convenient method for the synthesis of its derivatives was studied.

Nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) (II) was synthesized by Lesher *et al.*[3] in 1962 and has been well known as a peculiar chemotherapeutic agent against various gram-negative bacteria. It has previously been reported that nitrofuran agents with nitrofuran rings and various heterocyclic moieties have potent antibacterial activities.[4]

As a part of investigation of new chemotherapeutic agents, we studied synthetic methods for 1-ethyl-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic acid (V) which contained nalidixic acid (II) and 5-nitro-2-furaldehyde, and examined its antimicrobial activity.

The first attempt to prepare V by the direct condensation of II with 5-nitro-2-furaldehyde was unsuccessful. V was detected by paper chromatography but could not be isolated. Examination was then made on the condensation of ethyl 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate[5] (I), derived from II, with 5-nitro-2-furaldehyde. By this reaction in polyphosphoric acid or in a mixture of acetic anhydride and acetic acid, ethyl 1-ethyl-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (IV) was obtained in a poor yield as yellow crystals, and this compound (IV) was hydrolyzed in a mixture of hydrochloric acid and acetic acid to give the desired compound (V) in a good yield.

The structure of V was confirmed by elementary analysis, and from its UV, IR, and NMR spectra. Fig. 1 shows the NMR spectrum of V. It was concluded that the configuration of the double bond combining the furan ring with the naphthyridine ring was in the *trans* form due to the fact the coupling constant of two protons was 15.6 cps in the NMR spectrum measured in trifluoroacetic acid.[6] Though various crystals of V which differ in the IR spectra

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3) G.Y. Lesher, E.J. Froelich, M.D. Gruett, J.H. Bailey and R.P. Brundage, *J. Med. Pharm. Chem.*, **5**, 1063 (1962).
4) K. Miura and H.K. Reckendorf, "Progress in Medicinal Chemistry," Vol. 5, ed. by G.P. Ellis and G.B. West, Butterworths & Co. (Publishers) Ltd. London, 1967, pp. 320—381.
5) G.Y. Lesher and M.D. Gruett, U.S. Patent 3149104 (1964).
6) J.W. Emsley, J. Feeney and L.H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Ltd., Oxford, London, 1966, p. 1137; A. Fujita, M. Nakata, S, Minami and H, Takamatsu, *Yakugaku Zasshi*, **86**, 1014 (1966); M. Ito, *ibid.*, **87**, 279 (1967); H. Saikachi and S. Nakamura, *ibid.*, **88**, 110 (1968); K. Harada and S. Emoto, *Chem. Pharm. Bull.* (Tokyo) **14**, 1300 (1966).

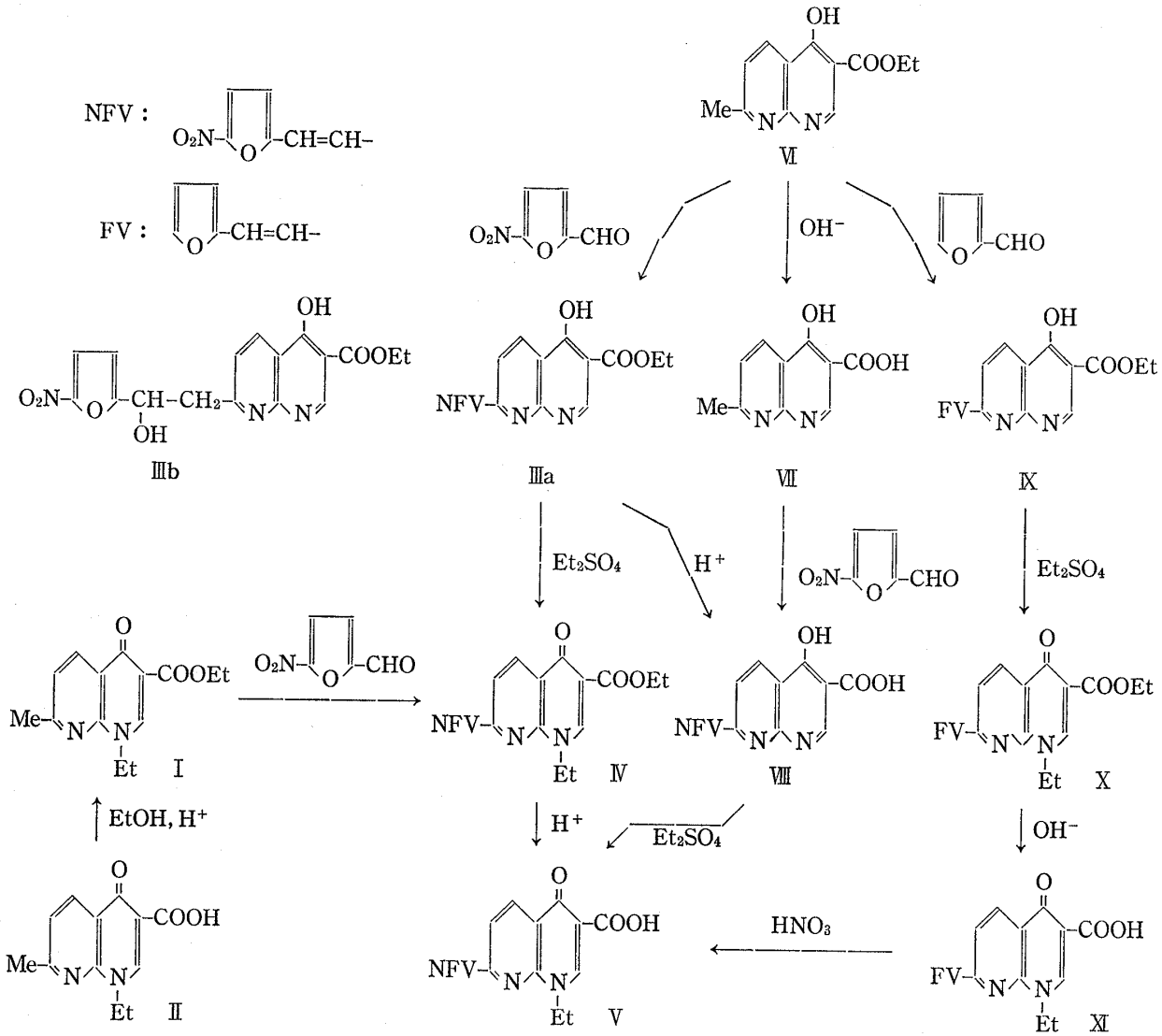

Chart 1

(1728, 1718, and 1736 cm^{-1} for $\nu_{C=O}$ of α, β, and γ-form, respectively, measured by KBr disk method) were obtained on recrystallization under various conditions, they seemed to be polymorphs because their elementary analysis, and UV, NMR, and IR (in $CHBr_3$ solution) spectra were identical.

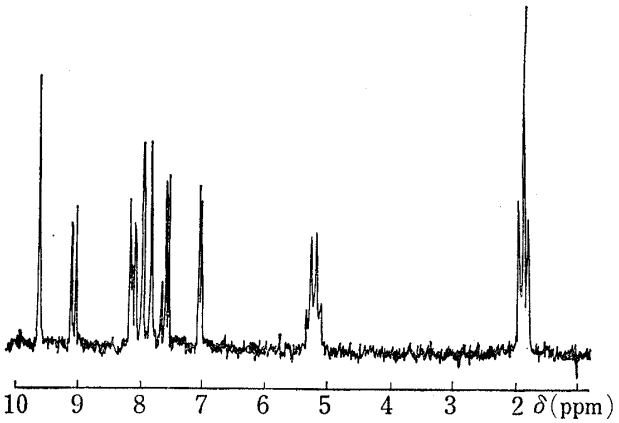

Fig. 1. Nuclear Magnetic Resonance Spectrum of V in CF_3COOH (TMS)[9b]

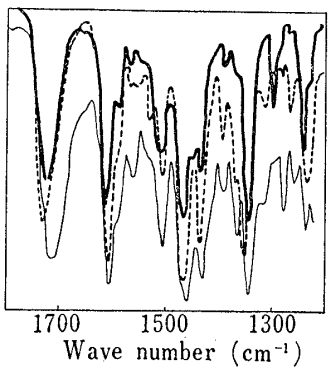

Fig. 2. Infrared Absorption Spectra of V in KBr Disk

——: α-form ——: β-form
------: γ-form

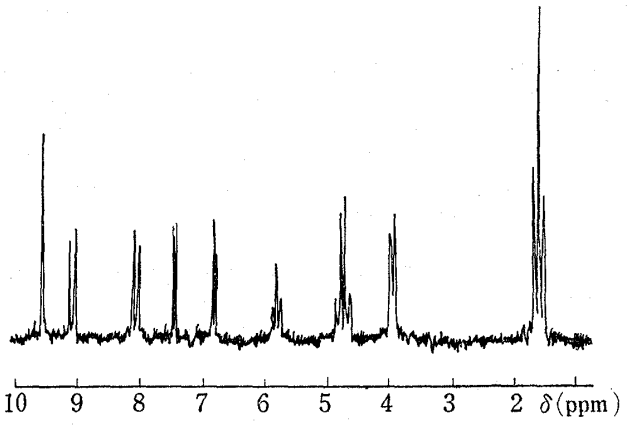

Fig. 3. Nuclear Magnetic Resonance Spectrum of IIIb in CF_3COOH (TMS)[9b,10]

Since V showed a potent antibacterial activity against various gram-positive and gram-negative bacteria *in vitro*, a better synthetic method for V was desired. The method described above, that is, I→IV→V, gave a poor yield and unsuitable for the synthesis of derivatives of V, so that the following alternative methods were examined in which ethyl 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate[7] (VI) was used as the starting material.

Heating of VI with 5-nitro-2-furaldehyde in a mixture of acetic anhydride and acetic acid gave ethyl 4-hydroxy-7-[2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridine-3-carboxylate (IIIa) in a good yield showing absorption maximum (in MeOH) at 388 mμ. From this mother liquor of IIIa a small quantity of colorless crystals were obtained which did not show absorption maximum at 388 mμ. This compound, which was convertible into IIIa by treatment with an acid, seemed to be the intermediate of this condensation reaction,[8] that is, ethyl 4-hydroxy-7-[2-hydroxy-2-(5-nitro-2-furyl)ethyl]-1,8-naphthyridine-3-carboxylate (IIIb), whose NMR spectrum is shown in Fig. 3. Ethylation of IIIa gave 1-ethyl derivative which was identical with the above-mentioned compound (IV) derived from I. On the other hand, condensation of 4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid[7] (VII), obtainable from VI with 5-nitro-2-furaldehyde, gave 4-hydroxy-7-[2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridine-3-carboxylic acid (VIII) which was also obtained by the hydrolysis of IIIa. Ethylation of VIII gave the desired compound (V) in a good yield.

The other alternative method to prepare V was also examined. Condensation of VI with 2-furaldehyde gave ethyl 7-[2-(2-furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylate (IX), whose ethylation gave ethyl 1-ethyl-7-[2-(2-furyl)vinyl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (X). Hydrolysis of X with a solution of potassium hydroxide in methanol gave 1-ethyl-7-[2-(2-furyl)vinyl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (XI) and its nitration with nitric acid gave the desired compound (V). The yield of the nitration process was so poor that this method could not be chosen as the preparative method for V.

In the synthetic methods for V described above, it is evident that ethylation occurred at N-1 position, considering that V obtained by these methods were identical with the product (V) derived from nalidixic acid (II).

The best method which gives a good yield and is suitable for the synthesis of derivatives, which will be reported in the following paper, may be the route of VI→III_a→IV→V or VI→III_a→VIII→V.

Details on the antimicrobial activities of these compounds synthesized in the present work will be reported in near future.

Experimental[9]

Ethyl 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate (I)[5]——A suspension of nalidixic acid (7.0 g) in EtOH (140 ml) containing conc. H_2SO_4 (1.8 ml) was refluxed for 23 hr. After evapora-

7) G.R. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).
8) A. Fujita, J. Aritomi, S. Minami and H. Takamatsu, *Yakugaku Zasshi*, **86**, 427 (1966).
9) *a*) All melting points were uncorrected; *b*) NMR spectra were measured at 100 Mcps on JNM-4H-100 (Japan Electron Optics Lab. Tokyo Japan). Tetramethylsilane as internal standard.

tion, the residue was washed with 10% NaOH and recrystallized from AcOEt to give I (3.5 g, 45%) as colorless needles, mp 118°.

Condensation of Ethyl 4-Hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (VI) with 5-Nitro-2-furaldehyde——To a mixture of AcOH (23.6 ml) and Ac_2O (23.6 ml) were added V (5.5 g, 24 mmoles) and 5-nitro-2-furaldehyde (3.7 g, 26 mmoles), and the mixture was heated at 110—130° for one hour. The resulting precipitate was collected by filtration, washed with warm AcOH and then with ether to give the crude product as a yellow powder. Recrystallization from dimethyl sulfoxide (DMSO) gave IIIa as a yellow powder (6.7 g, 80%), mp>300°. *Anal.* Calcd. for $C_{17}H_{13}O_6N_3$: C, 57.46; H, 3.69; N, 11.83. Found: C, 57.08; H, 3.95; N, 11.71.

The mother liquor of the recrystallization containing IIIa and IIIb was concentrated to about half of its original volume and cooled to remove IIIa by filtration. The fitrate was treated in the same way several times. The last filtrate was evaporated to dryness and the residue was recrystallized from dimethylformamide (DMF) to give IIIb, as a colorless powder (0.45 g, 5.0%), mp>280°. *Anal.* Calcd. for $C_{17}H_{15}O_7N_3$: C, 54.69; H, 4.05; N, 11.26. Found: C, 54.58; H, 4.13; N, 11.27. NMR (10% solution in CF_3COOH)[10] δ (ppm): 1.57 (3H, triplet, $J=7.5$ cps, $CH_2C\underline{H}_3$), 3.94 (2H, doublet, $J=6.9$ cps, $C\underline{H}_2CH(OH)$), 4.74 (2H, quartet, $J=7.5$ cps, $C\underline{H}_2CH_3$), 5.80 (H, triplet, $J=6.7$ cps, $C\underline{H}(OH)-CH_2$), 6.81 and 7.44 (2H, each doublet, $J=3.5$ cps, furan–C_3– and –C_4–H), 8.07 and 9.12 (2H, each doublet, $J=9.0$ cps, naphthyridine–C_5– and –C_6–H), 9.59 (H, singlet, naphthyridine–C_2–H).

A suspension of IIIb (0.50 g) in AcOH (15 ml) was refluxed for 2 hr. The resulting precipitate was filtered and recrystallized from DMSO to give IIIa (0.28 g) as a yellow powder, mp>300°.

Ethyl 1-Ethyl-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate (IV)——a) A mixture of I (1.3 g, 5 mmoles), 5-nitro-2-furaldehyde (0.8 g, 5.5 mmoles), AcOH (2 ml) and Ac_2O (3.4 ml) was heated at 145—150° for 29 hr and then allowed to stand at room temperature over 6 days. The resulting precipitate was filtered and recrystallized from DMF to give IV (0.25 g, 13%) as a yellow powder, mp 267—269° (decomp.). *Anal.* Calcd. for $C_{19}H_{17}O_6N_3$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.49; H, 4.71; N, 11.00. IR ν_{max}^{KBr} cm^{-1}: 1720 (ester C=O), 1355 (NO_2).

b) A mixture of I (5.2 g, 20 mmoles), 5-nitro-2-furaldehyde (2.8 g, 20 mmoles) and polyphosphoric acid (50 g) was heated at 100° (bath temperature) for 1.5 hr, and poured into ice–water and then neutralized with K_2CO_3. The resulting precipitate was collected, dried and extracted with $CHCl_3$ (500 ml). After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (80 ml) and passed through an Al_2O_3 column and then eluted with $CHCl_3$. The eluate was concentrated to give a brown residue (2 g) decomposing at 240—250°. Recrystallization from $CHCl_3$–EtOH gave yellow crystals (1.3 g, 17%), mp 262—264° (decomp.).

c) A mixture of IIIa (7.1 g, 0.02 mole), diethyl sulfate (15.6 g, 0.1 mole), K_2CO_3 (5.5 g, 0.04 mole) and DMF (71 ml) was heated at 75—85° for 0.5 hr. After cooling, the resulting precipitate was filtered and washed with H_2O to give the crude product as a yellow powder (4.46 g, 60.8%), mp 255—268° (decomp.). Recrystallization from DMF gave IV as yellow flakes, mp 267—269° (decomp.), which was identified by IR spectra.

4-Hydroxy-7-[2-(5-nitro-2-furyl)vinyl]-1,8-naphthyridine-3-carboxylic Acid (VIII)——a) A suspension of IIIa (21.3 g) in conc. HCl–90% AcOH (1:11 in volume) (320 ml) was refluxed for 2 hr. After cooling the precipitate was filtered off, washed with H_2O and then with MeOH. Recrystallization from DMF gave VIII as yellow needles (13.0 g, 66.4%), mp>300°. *Anal.* Calcd. for $C_{15}H_9O_6N_3$: C, 55.05; H, 2.77; N, 12.84. Found: C, 54.80; H, 3.04; N, 12.98. IR ν_{max}^{KBr} cm^{-1}: 1716 (COOH), 1350 (NO_2).

b) A mixture of VII (0.20 g, 1.0 mmole), 5-nitro-2-furaldehyde (0.32 g, 2.3 mmoles), AcOH (4 ml) and conc. H_2SO_4 (7—10 drops) was heated at 70° for 20 hr. After cooling, the resulting precipitate was filtered off, washed with MeOH and recrystallized from DMF to give VIII as a yellow powder (0.16 g, 48%), mp>300°, which was identified by IR spectra.

Ethyl 7-[2-(2-Furyl)vinyl]-4-hydroxy-1,8-naphthyridine-3-carboxylate (IX)——To Ac_2O (48 ml) were added VI (9.6 g, 44 mmoles) and 2-furaldehyde (5.1 g, 53 mmoles) and the mixture was refluxed for 48 hr. After cooling, the resulting precipitate was collected by filtration, washed with pyridine, then with ether to give dark yellow crystals of IX (5.38 g, 39.1%) decomposing at 288°. Recrystallization from DMF gave an analytical sample as yellow plates, mp 288° (decomp.). *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.95; H, 4.50; N, 9.38.

Ethyl 1-Ethyl-7-[2-(2-furyl)vinyl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (X)——To a stirred suspension of IX (4.03 g, 13 mmoles) and K_2CO_3 (3.58 g, 26 mmoles) in DMF (40 ml) was added diethyl sulfate (10.0 g, 65 mmoles) and the mixture was stirred for 75 min at 60—70°. The reaction mixture was poured into ice and water. The precipitate was collected, washed with H_2O, and dried to give X (4.28 g, 97.3%) melting at 183—185°. Recrystallization from $CHCl_3$–ether gave yellow needles melting at 187—187.5°. *Anal.* Calcd. for $C_{19}H_{18}O_4N_2$: C, 67.44; H, 5.36; N, 8.28. Found :C, 67.94; H, 5.44; N, 8.43.

1-Ethyl-7-[2-(2-furyl)vinyl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (XI)——X (6.30 g, 19 mmoles) was refluxed in 0.2 N KOH–95% MeOH for one hour. After removal of the solvent, the residue

10) Measured immediately after dissolving in CF_3COOH.

was treated with H_2O and acidified with HCl to give XI (5.51 g, 95.7%) as a yellow powder decomposing at 245—248°. Recrystallization from $CHCl_3$–ether gave XI as yellow prisms decomposing at 245—247°. *Anal.* Calcd. for $C_{17}H_{14}O_4N_2$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.35; H, 4.43; N, 9.15.

1-Ethyl-1,4-dihydro-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (V)——a) A solution of IV (7.7 g, 20 mmoles) in conc. HCl–90% AcOH (1:11) (77 ml) was refluxed for 2 hr. After cooling, the precipitate was filtered off, and washed with MeOH to give the crude product as a yellow powder (6.1 g, 86%). Recrystallization from DMSO, DMF and AcOH gave V as α, β and γ-forms respectively. mp (α-form) 279—280° (decomp.); (β-form) 278—282° (decomp.); (γ-form) 280—284° (decomp.). *Anal.* Calcd. for $C_{17}H_{13}O_6N_3$: C, 57.46; H, 3.69; N, 11.83. Found (α-form): C, 56.98; H, 3.93; N, 11.52. Found (β-form): C, 57.14; H, 3.97; N, 11.63. Found (γ-form): C, 57.23; H, 3.65; N, 11.62. IR ν_{max}^{KBr} cm^{-1} (COOH) : α-form, 1728; β-form, 1718; γ-form, 1736. NMR (10% solution in CF_3COOH) δ (ppm) : 1.80 (3H, triplet, J=7.5 cps, $CH_2\underline{CH_3}$), 5.14 (2H, quartet, J=7.5 cps, $\underline{CH_2}CH_3$), 7.00 and 7.54 (2H, each doublet, J=3.9 cps, furan-C_3- and -C_4–H), 7.73 and 7.98 (2H, each doublet, J=15.6 cps, –CH=CH–), 8.07 and 9.00 (2H, each doublet, J=8.8 cps, naphthyridine–C_5– and –C_6–H), 9.55 (1H, singlet, naphthyridine–C_2–H).

b) To a stirred suspension of VIII (19.6 g, 0.06 mole) and K_2CO_3 (9.9 g, 0.072 mole) in DMF (392 ml) was added dropwise diethyl sulfate (18.5 g, 0.12 mole) at 110° and the reaction mixture was stirred for 2 hr. After cooling the yellow precipitate was filtered off, washed with H_2O and then with MeOH, to give the crude product (V) (18.0 g, 84.5%). Recrystallization from DMF gave V as yellow needles (16.3 g, 76.5%), mp 280° (decomp.), which was identified by IR spectra.

c) To conc. HNO_3 (d 1.38) (20 ml) stirred and cooled to −10° was added portionwise finely powdered XI (0.93 g, 3 mmoles), and the mixture was stirred for 10 min at the same temperature. The resulting solution was poured into ice water and the precipitate was collected by filtration, washed with H_2O and dried *in vacuo*. The crude product was extracted with $CHCl_3$ and the extract was passed through a silica gel column to remove polar colored material. Elution with $CHCl_3$ gave upon evaporation a yellow powder (83 mg, 8.3%) decomposing at 258—267°. Recrystallization from DMSO afforded a yellow powder (V) (43 mg, 4.3%) decomposing at 279—280°, which was identical with the one (α-form) described above in all respects.