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Synthesis of Furan Derivatives. LVII.[1] The Reaction of Keto Acetylenic Esters with Carbonyl Reagents[2]

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Methyl (ethyl) 5-(2′-furyl) isoxazole-3-carboxylate (**3a** and **3b**) were prepared from methyl (ethyl) 2-furoylpropiolates with hydroxylamine, respectively. Methyl (ethyl) 5-(2′-furyl) pyrzaole-3-carboxylates (**10a** and **10b**) were formed by the condensation of methyl (ethyl) 2-furoylpropiolates with hydrazine hydrate. The corresponding 5′-nitro furan derivatives (**4a** and **11b**) were obtained in usual manner, and the each position of nitro group of the furan rings was confirmed by the nuclear magnetic resoance and infrared spectral data.

In our previous paper,[4] our concern was focused mostly on the synthetic studies of the ethynyl carbinols from 2-furyl- and 2-(5-nitrofuryl)-(*p*-substituted aryl) ketones with lithium acetylide (or lithiumacetylide–ethylenediamine) as a starting material for the object of the formation of heterocyclic ring at 2-position of furan ring. Furthermore, for the same object, we[1] carried out the synthesis of methyl 2-furoyl-propiolate and ethyl 2-furoylpropiolate by the reaction of furfural with the corresponding Grignard reagents of methyl propiolate and ethyl propiolate, respectively (Chart 1).

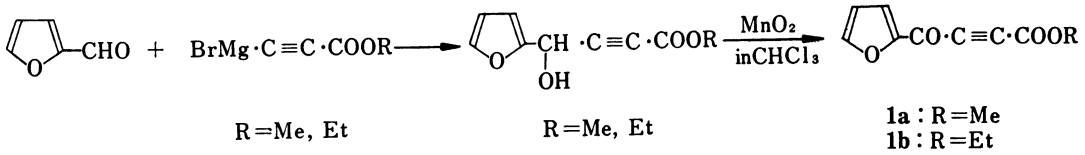

Chart 1

In the present paper, these furoyl acetylenic esters (**1a** and **1b**) obtained thus were used as starting material for isoxazole and pyrazole ring formation with hyroxylamine or hydrazine hydrate, respectively.

Hence, the cyclization of isoxazole and pyrazole ring attached to 2′-position of furan ring was undertaken by the modification of Jones's method.[5] In the reaction of the furoyl acetylenic esters (**1a** and **1b**) with hydroxylamine, two possible pathways at least may be considered for the formation of the isoxazole ring substituted by 2′-furyl group at 3- or 5-position of the isoxazole ring[6] (Chart 2). Accordingly, in order to determine whether intermediary oxime of the 2′-furoyl group adjacent to the acetylenic bond with hydroxylamine may first

1) Part LVI: H. Saikachi and T. Kitagawa, *Yakugaku Zasshi*, **91**, 454, (1971).
2) Some parts of this work presented at the 90th Annual Meeting of te Pharmaceutical Society of Japan at Sapporo, July 1970.
3) Location: *1276, Katakasu, Fukuoka.*
4) H. Saikachi and T. Kitagawa, *Yakugaku Zasshi*, **89**, 1626 (1969).
5) *a*) K. Bowden, E.A. Braude, E.R.H. Jones, and B.C. Weedon, *J. Chem. Soc.*, **1946**, 45; *b*) K. Bowden and E.R.H. Jones, *ibid.*, **1946**, 953; *c*) E.R.H. Jones, T.Y. Shen, and M.C. Whitting, *ibid.*, **1950**, 236.
6) C. Claisen, *Ber.*, **44**, 1161 (1912).

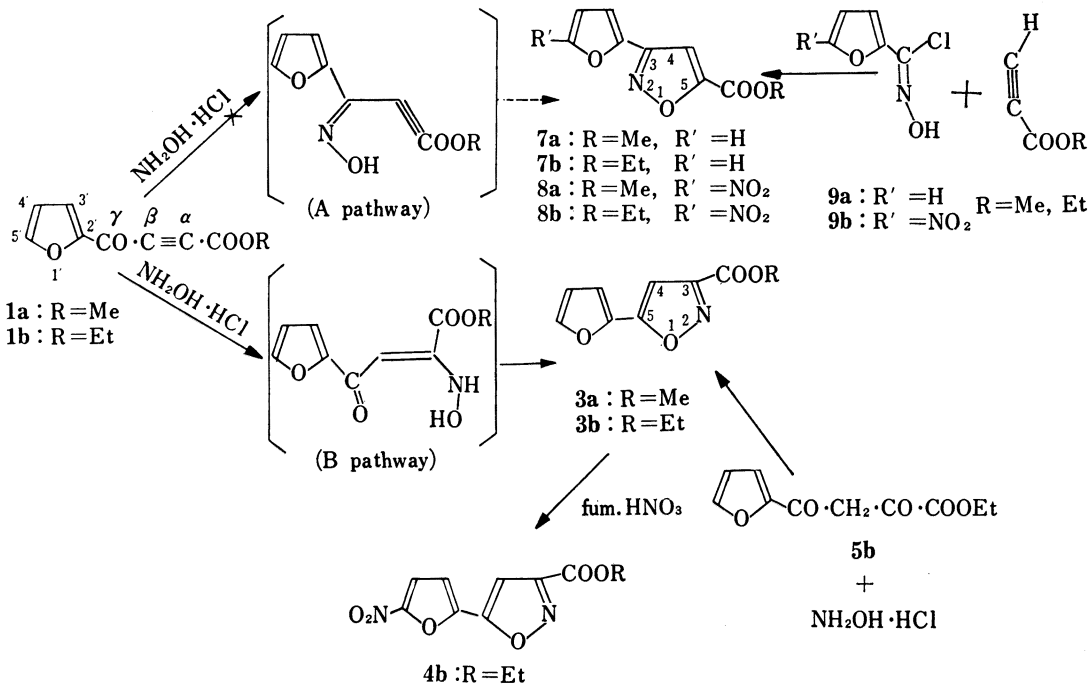

Chart 2

be formed or nucleophilic addition of hydroxylamine may preferentially occur at α-position carbon atom of acetylenic bond in **1a** and **1b**, the following procedures were taken. Namely, infrared (IR), ultraviolet (UV) and nucelar magnetic resonance (NMR) spectral observations on the final products (**3a** and **3b**) obtained were carried out, because neither hydroxyamino-ethylenic ketones[5c] (in B pathway) nor oximes (in A pathway) which might be assumed to be intermediate were isolable in the course of this reaction. On the basis of the IR: 1735 cm^{-1} (-COOEt), UV: 290 mμ (13700) and NMR: δ 6.82 (1H, singlet, a proton of 4-position of isoxazole ring), the formation of ethyl 5-(2′-furyl)isoxazole-3-carboxylate (**3b**), mp 52—53°, was virtually made clear. Consequently the above results supported that the B reaction pathway might be more preferable for the cyclization of the keto-acetylenic esters with hydroxylamine. Separately isomeric ethyl 3-(2′-furyl)isoxazole-5-carboxylate(**7b**), mp 94—95°, the IR: *ca.* 1740 cm^{-1} (-COOEt), was also prepared by the condensation[7] of ethyl propiolate[8] with 2-furohydroximoylchloride(**9a**)[9] in the presence of a catalytic amount of triethylamine in benzene.

The condensation of methyl furoylpropiolate (**1a**) and ethyl furoylpropiolate (**1b**) with hydrazine hydrate, respectively, was carried out in alcohol to obtain the corresponding pyrazole derivatives (**10a**, mp 139—140° and **10b**, mp 135—136°). And also authentic ethyl 3(5)-(2′-furyl)pyrazole-5(3)-carboxylate, mp 136—137°, was separately prepared from ethyl furoylpyruvate (**5b**)[10] with hydrazine hydrate in usual manner[11] (Chart 3). No mixed melting point determination of **10b** with the above authentic sample did show any depression. Additional observations of IR, UV and NMR spectra of both **10b** and the authentic sample

7) H. Kano, I. Adachi, R. Kido, and K. Hirose, *J. Med. Chem.*, **10**, 411 (1967).
8) E.H. Ingold, *J. Chem. Soc.*, **1925**, 1199.
9) H. Rheinbolt, *Ann.*, **451**, 166 (1927).
10) F. Kipnis, I. Lery, and J. Ornfelt, *J. Am. Chem. Soc.*, **70**, 4265 (1948).
11) A. Angeli, *Ber.*, **23**, 2159 (1891).

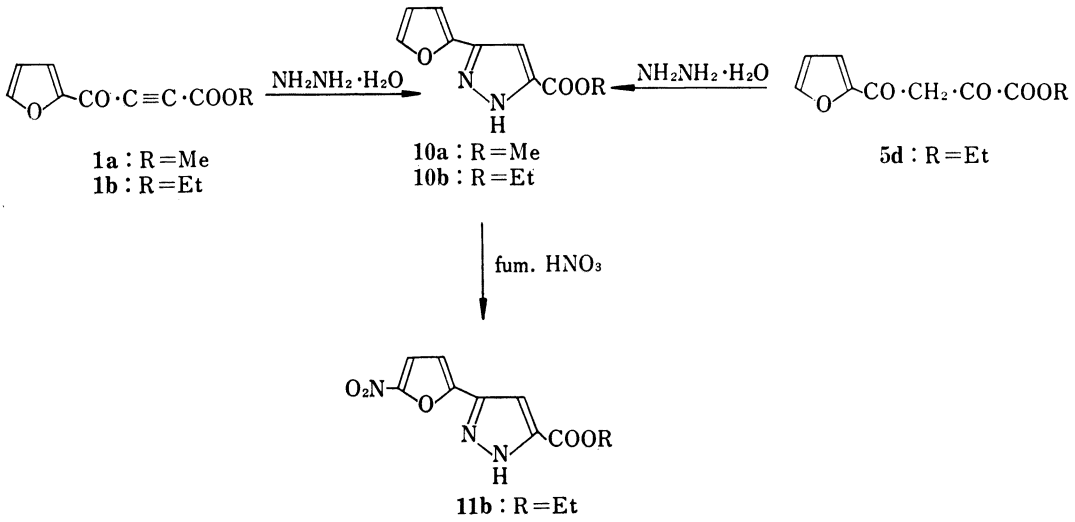

Chart 3

resulted in evidences as follows; IR: 1740 cm^{-1} (γ-COOEt), UV: 259 mμ (12000), NMR: δ 11.89 (1H, singlet, a proton of 1-position) and δ 6.98 (1H, singlet, a proton of 4-position) of both pyrazole ring. From the above facts, **10b** was confirmed to be quite identical with the authentic sample: (ethyl 3(5)-(2'-furyl)pyrazole-5(3)-carboxylate). In conclusion, it can possibly be said that the γ-ketone group of γ-keto-α:β-acetylenic esters (**1a** and **1b**) was not reactive toward usual carbonyl reagents, but nucleophilic addition of carbonyl reagents predominantly might occur to the α-carbon atom.

On the occasion, the careful nitration of ethyl furoylpropiolate was adventured with a mixed acid (fuming nitric acid and acetic anhydride)[12] at *ca.* −30°. Unfortunately, no desired products other than the resinous matter formed. Fortunately, however, ethyl 5-(2'-furyl)isoxazole-3-carboxylate (**3b**) was smoothly and efficiently nitrated to the desired ethyl 5-(5'-nitro-2'-furyl)isoxazole-3-carboxylate (**4b**), mp 136—137°, using of a mixed acid (fuming nitric acid and acetic anhydride)[12] in good yield at *ca.* −30°, and also one isomer of **4b**, ethyl 3-(5'-nitro-2'-furyl)isoxazole-5-carboxylate (**8b**), mp 169—170°, was readily derived from the reaction of 5-nitro-2-furohydroximoylchloride (**9b**)[13] with ethyl propiolate[8] in the presence of triethylamine in benzene (Chart 2). In this connection, when the nitration of ethyl 3(5)-(2'-furyl)pyrazole-5(3)-carboxylate (**10b**) was subjected to the same condition to above **3b**, the desired ethyl 3(5)-(5'-nitro-2'-furyl)pyrazole-5(3)-carboxylate (**11b**), mp 148—150° was obtained in 69% yield.

To make firm the most probable position substituted by nitro group at the furan ring in the both compounds (**4b**, and **11b**), the NMR spectra (in $CDCl_3$) was observed. The NMR spectrum of ethyl 5-(2'-furyl)isoxazole-3-carboxylate (**3b**) was clearly different from that of the corresponding nitro compound (**4b**). Namely, **3b** exhibited at δ 7.58 (1H, two doublet, $J_{5'4'}$=2 cps, $J_{5'3'}$=0.6 cps, a proton of 5'-position of furan ring), δ 6.98 (lH, two doublet, $J_{4'3'}$=3.6 cps, $J_{4'5'}$=2 cps, a proton of 4'-position of furan ring), and δ 6.82 (1H, singlet, a proton of 4-position of isoxazole ring). After the nitration of **3b**, the NMR spectrum (in $CDCl_3$) of the corresponding nitro compound (**4b**) displayed distinctively at δ 7.18 (1H, singlet, a proton of 4-position of isoxazole ring), δ 7.45 and δ 7.18 (each 1H, doublet, $J_{4'3'}=J_{3'4'}=$

12) *a*) H. Gilman and G.F. Wright, *J. Am. Chem. Soc.*, **53**, 1923 (1931); *b*) H. Saikashi, R. Kimura, and H. Hoshida, *J. Pharm. Soc.*, **72**, 1132 (1953) [*C.A.*, **48**, 12072 (1953)].
13) N.E. Bover and H.R.S. Snydver, *J. Am. Chem. Soc.*, **72**, 3593 (1950).

3.6 cps, proton of 4'- and 3'-position of furan ring), but the signal of δ 7.58 (1H, two doublet, a proton of 5'-position of furan ring) disappeared. In the IR spectrum (KBr) of **4b**, the absorption bands due to ν-NO_2 (aromatic) was observed at 1560 cm^{-1} and 1350 cm^{-1}.

Similarly, the NMR spectrum (in $CDCl_3$) of the nitro compound (**11b**) from ethyl 3(5)-(2'-furyl)pyrazole-5(3)-carboxylate (**10b**) showed also a singlet at δ 11.89 (1H, a proton of 1-position of pyrazole ring) and a singlet at δ 6.98 (1H, a proton of 4-position of pyrazole ring), and instead, the signal of two doublet at δ 7.42 due to a proton of 5'-position of furan ring distinctively disappeared. Additionally, in the IR spectrum (KBr) of **12b**, the absorption bands attributable to ν-NO_2 (aromatic) was newly observed at 1560 cm^{-1} and 1340 cm^{-1}.

Judging from the above facts and also elemental analyses, it was confirmed that the desired mononitro substitution occurred at 5'-position of furan ring.

Experimental[14]

Methyl 5-(2'-Furyl)isoxazole-3-carboxylate(3a) and Ethyl 5-(2'-Furyl)isoxazole-3-carboxylate (3b)——Method A: A solution of hydroxylamine hydrochloride (1.25 g, 0.081 mole) in absolute ethanol (10 ml) was neutralized with ethanolic sodium ethoxide (Na, 0.4 g) 10 ml and separated by filtration from precipitated sodium chloride. A portion (16 ml) of resultant solution was added to keto acetylenic ester (**1b**) (2.5 g, 0.014 mole) in ethanol (10 ml), and the mixture was allowed to stand overnight at room temperature. Extraction with ether then gave the ester (**3b**). The product formed was recrystallized from a mixture of ethanol and water; colorless prisms, yield, 2 g (72.5%), mp 51—52°. *Anal.* Calcd. for $C_{10}H_9O_4N$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.82; H, 4.43; N, 6.76. UV λ_{max}^{EtOH} mμ(ε): 290 (13700). NMR ($CDCl_3$)δ: 7.58 (1H, two doublet, $J_{5'4'}$=2 cps, $J_{5'3'}$=0.6 cps, 5'-H), 6.98 (1H, two doublet, $J_{3'4'}$=3.8 cps, $J_{3'5'}$=0.6 cps, 5'-H), 6.98 (1H, two doublet, $J_{3'4'}$=3.8 cps, $J_{3'5'}$=0.6 cps, 3'-H), 6.55 (1H, two doublet, $J_{4'3'}$=3.8 cps, $J_{4'5'}$=2 cps, 4'-H), 6.82 (1H, singlet, 4-H), 4.48 (2H, quartet, J=7.2, 10.8 cps, -COOC**H**$_2$CH$_3$), 1.42 (1H, triplet, -COOCH$_2$C**H**$_3$). Similarly, **3a** was obtained from **1a** (2.5 g, 0.014 mole) with hydroxylamine hydrochloride (1.35 g, 0.018 mole), and was recrystallized from a mixture of methanol and water; colorless prisms, yield, 1.9 g (75%), mp 69—70°. *Anal.* Calcd. for $C_9H_7O_4N$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.82; H, 3.62; N, 7.25. UV λ_{max}^{EtOH} mμ (ε): 270 (14500).

Method B: A solution of ethyl furoylpyruvate (**5**) (1.9 g, 0.01 mole) and hydroxylamine hydrochloride (0.84 g, 0.012 mole) in ethanol (30 ml) was refluxed for 4 hr and then evaporated under reduced pressure. The rcsulting crystalline produet was recrystallized from ethanol; colorless prisms, yield, 2.3 g (61.5%), mp 52—53°. This compound undepressed on mixed melting point test with specimen prepared by method A, and also the IR spectra were superimposable.

Methyl 3-(2'-Furyl)isoxazole-5-carboxylate (7a)——To a benzene solution of 2-furohydroximoylchloride (**9a**) (2.9 g, 0.02 mole) and methyl propiolate (1.7 g, 0.02 mole) was dropwise added triethylamine (2 g) with stirring and cooling. The resulting mixture was stirred at 50—60° for 2hr, and then cooled and filtrered. The benzene filtrete was washed with water, separated and dried over Na_2SO_4 and the organic solvent was removed under diminished pressure. The crystalline mass obtained was recrystallized from a mixture of benzene and cyclohexane; colorless plates, yield, 1.5 g (38%), mp 90—91°. *Anal.* Calcd. for $C_9H_7O_4N$: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.12; H, 3.74; N, 7.25. IR ν_{max}^{KBr} cm^{-1}: 1740 (-COOMe). UV λ_{max}^{EtOH} mμ (ε): 238 (19000). NMR ($CDCl_3$)δ: 7.58, 6.98, and 6.53 (each 1H, two doublet, 5'-, 3'-, and 4'-H), 7.18 (1H, singlet, 4-H), 3.99 (3H, singlet, -COOC**H**$_3$).

Methyl 3-(5'-Nitro-2'-furyl)isoxazole-5-carboxylate (8a)——To a benzene solution of 5-nitro-2-furohydroximoylchloride (5 g, 0.026 mole) and methyl propiolate (2.5 g, 0.03 mole) was dropwise added triethylamine (2.5 g) with stirring and cooling. The reaction mixture was treated as described above, and the final crystalline mass was recrystallized from methanol; pale yellow needles, yield, 3.8 g (61.3%), mp 169—170°. *Anal.* Calcd. for $C_9H_6O_6N_2$: C, 45.39; H, 2.54; N, 11.76. Found: C, 45.51; H, 2.70; N, 11.72. UV λ_{max}^{EtOH} mμ (ε): 316 (23000). NMR ($CDCl_3$) δ: 7.45 and 7.23 (each 1H, doublet, $J_{3'4'}$=$J_{4'3'}$=3.8 cps, 3'- and 4'-H), 7.26 (1H, singlet, 4-H), 3.99 (3H, singlet, -COOC**H**$_3$).

Methyl 3(5)-(2'-Furyl)pyrazole-5(3)-carboxylate(10a) and Ethyl 3(5)-(2'-Furyl)pyrazole-5(3)-carboxylate (10b)——Method A: a solution of hydrazine hydrate (0.82 g, 0.017 mole) in absolute ethanol (30 ml) was alowly added to an absolute ethanol sulution of keto acetylenic ester (**1b**) (2.5 g, 0.017 mole) with ice-cooling, and the mixture was allowed to stand overnight at room temperature. After diluting the solution

14) *a*) All melting points were determined using the Yanagimoto melting point test apparatus, and has not been corrected; *b*) IR spectra were measured on a Koken DS-301 spectrophotometer, and UV spectra were measured on a Hitachi-Perkin Elmer UV-Vis spectrophotometer Model 139; *c*) NMR spectra measured on a Nihondenshi Model C-60H NMR Spectrometer (60 MHz, TMS as the internal reference).

with water and extracted with ether, the crystalline mass (**10b**) obtained was recrystallized from ethanol; pale yellow prisms, yield, 1.3 g (39.9%), mp 137—138°. *Anal.* Calcd. for $C_{10}H_{10}O_3N_2$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.44; H, 4.26; N, 14.10. UV λ_{max}^{EtOH} mμ (ε): 259 (12000). NMR ($CDCl_3$) δ: 7.42 (1H, (two doublet, $J_{5'4'}=2.1$ cps, $J_{5'3'}=0.9$ cps, 5'-H), 6.72 (1H, two doublet, $J_{3'4'}=3.6$ cps, $J_{3'5'}=0.9$ cps, 3'-H), 6.42 (1H, two doublet, $J_{4'3'}=3.6$ cps, $J_{4'5'}=2.1$ cps, 4'-H), 11.89 (1H, singlet, 1-H), 6.98 (1H, singlet, 3-H), 4.33 (2H, quartet, $J=13.5$ and 7.5 cps, -COOC**H**$_2$CH$_3$), 1.32 (3H, triplet, -COOCH$_2$C**H**$_3$).

Similarly, **10a** was obtained from **1a** (2.5 g, 0.014 mole) with hydrazine hydrate (0.82 g, 0.017 mole), and recrystallized from a mixture of methanol and water; pale needles, yield, 2.21 g (80.3%), mp 135—136°. *Anal.* Calcd. for $C_9H_8O_3N_2$: C, 56.25; H, 4.26; N, 14.58. Found: C, 56.44; H, 4.26; N, 14.10. UV λ_{max}^{EtOH} mμ (ε): 258 (13000).

Method B: To an ethanol solution of ethyl furoylpyruvate (**5**) (2.1 g, 0.01 mole) and acetic acid (0.5 g) was added hydrazine hydrate (0.58 g, 0.012 mole) slowly with cooling. The mixture was refluxed for 3 hr, and then distilled off under reduced pressure. After cooling, the product (**10b**) formed was recrystallized from ethanol; pale yellow prisms, yield, 1.6 g (81.6%), mp 138°. This compound undepressed on mixed melting point test with specimen prepared by method A, and the IR spectra were completely superimposable.

Ethyl 5-(5'-Nitro-2'-furyl)isoxazole-3-carboxylate(4b)——A solution of **3b** (5 g, 0.027 mole) in 9 ml of acetic anhydride was dropweis added at −30° to a mixture acid prepared from 6.85 g (0.11 mole) of fuming HNO_3 (s.p. 1.51) and 15 ml of acetic anhydride. The mixture was stirred for more several hours at −30°, and poured into ice–water, and the precipitated nitro compound (**4b**) was collected by suction and washed with water. The crude product thus obtained was recrystallized from ethanol to give 4.5 g (72%) of nitro compound (**4b**) melting at 136—137°. *Anal.* Calcd. for $C_{10}H_8O_6N_2$: C, 47.72; H, 3.20; N, 11.11. Found: C, 47.70; H, 3.19; N, 11.04. IR νKs cm^{-1}: 1560 and 1350 (-NO_2), 1740 (-COOEt). NMR ($CDCl_3$) δ: 7.45 and 7.17 (each 1H, doublet, $J_{3'4'}=J_{4'3'}=3.6$ cps, 3'- and 4'-H), 6.28 (1H, singlet, 4-H), 4.28 (2H, quartet, $J=10.8$ and 7.2 cps, -COOC**H**$_2$CH$_3$), 1.42 (3H, triplet, -COOCH$_2$C**H**$_3$).

Ethyl 3(5)-(5'-Nitro-2'-furyl)pyrazole-5(3)-carboxylate (11b)——IIb was made in the same above way from **10b** (5 g, 0.026 mole) in 10 ml of acetic anhydride and 6.4 g (0.1 mole) of fuming HNO_3 (s.p. 1.51) in 15 ml of acetic anhydride. The crude product thus obtained was recrystallized from ethanol to give 4.1 g (69%) of nitro compound (**12b**) melting at 148—150°. *Anal.* Calcd. for $C_{10}H_9O_5N_3$: C, 47.81: H, 3.67; N, 16.73. Found: C, 47.80; H, 3.61; N, 16.56. IR ν_{max}^{KBr} cm^{-1}: 1560 and 1340 (-NO_2), 1710 (-COOEt). NMR ($CDCl_3$) δ: 7.43 and 7.03 (each 1H, doublet, $J_{3'4'}=J_{4'3'}=3.6$ cps, 3'- and 4'-H), 7.27 and *ca.* 9.90 (each 1H, singlet, 1- and 4-H), 4.43 (2H, quartet, $J=10.8$ and 7.2 cps, -COOCH$_2$CH$_3$), 1.42 (3H, triplet, -COOCH$_2$C**H**$_3$).

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