# Furan derivatives. CI. Nitration of methyl 2-cyano-3-R-3-(2-furyl)acrylates and some properties of their nitro derivatives

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Nitration of methyl 2-cyano-3-R-3-(2-furyl)acrylates (R = $CH_3$, $C_2H_5$, *n*-$C_3H_7$, i-$C_3H_7$, *n*-$C_4H_9$, i-$C_4H_9$, phenyl, 2-thienyl) and conformational analysis by means of $^1$H-n.m.r. spectrometry of the formed 5-nitrofuryl derivatives is described. The effect of the substituents upon the biological properties of the substances under investigation is discussed on the basis of antimicrobial tests.

Описывается нитрование метилэфиров 2-циано-3-R-3-(2-фурил)акриловой кислоты (R = $CH_3$, $C_2H_5$, *н*-$C_3H_7$, изо-$C_3H_7$, *н*-$C_4H_9$, изо-$C_4H_9$, фенил, 2-тиэнил) и определение конфигурации полученных 5-нитрофурилпроизводных $^1$H-ЯМР спектроскопией. На основании результатов антимикробиальных испытаний обсуждается влияние заместителей на биологические свойства изучаемых соединений.

According to their behaviour during nitration with fuming nitric acid in acetic anhydride, furan derivatives can be basically arranged [1—4] into two groups: those forming with the reagent an addition intermediate which has to be decomposed with a base, and those producing the nitro derivative directly [5]. We have previously described [6] the nitration of alkyl and aryl 2-furyl ketones belonging to the former class of furan derivatives. The formed intermediates were decomposed by their treatment with urea, pyridine or an alkali phosphate. Here we describe the nitration of methyl 2-cyano-3-R-3-(2-furyl)acrylates [7], the determination of the structure of the formed products by means of i.r., u.v., and $^1$H-n.m.r. spectroscopy, and the effect of the substituents at the position 3 upon the biological activity of the produced 5-nitro derivatives.

The nitration of methyl 2-cyano-3-R-3-(2-furyl)acrylates with acetyl nitrate was conducted at −10°C and the reaction mixture was decomposed by pouring it onto ice. The corresponding 5-nitrofuran derivatives were formed without an addition of a base. The physical constants of methyl 2-cyano-3-R-3-[2-(5-nitrofuryl)]acrylates are given in Table 1. When R was an alkyl the obtained yields of 5-nitrofuran derivatives were quite high (72—91%); when R was phenyl nitration took place partly on one, partly on both rings and under these conditions only 13% of the mononitro derivative, with the nitro group at the position 5 of the furan ring, was formed. The major reaction product (87%) was the dinitro derivative where the other nitro group was introduced into the *p*-position of the benzene ring. The two products formed were isolated by preparative thin-layer chromatography and identified by spectral methods. The results showed, that when R was 2-thienyl the nitration occurred on both aromatic rings to give a single product, *i.e.* methyl 2-cyano-3-R-3-[2-(5-nitrothienyl)]-3-[2-(5-nitrofuryl)]acrylate. The formation of a dinitro compound in this reaction can be attributed to the enhanced reactivity of the second aromatic ring in $S_E$ reaction.

Physical constants, i.r. and u.v. spectral data of the synthesized substances are given in Table 1 and $^1$H-n.m.r. data in Table 2. The $^1$H-n.m.r. spectra showed, that the obtained products were mixtures of *E* and *Z* isomers. The signal-isomer assignments were done as described previously [7] and were based on the fact that *E* and *Z* isomers show different chemical shifts for protons of a methylene, methyl and methine group located in a $\beta$-position to the alkoxycarbonyl group. The deshielding effect of an alkoxycarbonyl group given for $\alpha,\beta$-unsaturated esters is 0.25 p.p.m. [8]. This value, for 2-cyano derivatives should be by 0.08 p.p.m. lower [7] as a result of the anisotropic effect of the cyano group. The difference (0.17 p.p.m.) given in Table 2 for *II* agrees well with the presumed value. Compounds *III*—*VII* show somewhat larger differences, 0.30 and 0.46 p.p.m. for a $\beta$-methylene and $\beta$-methine group, respectively, which is in agreement with the data in the literature [8].

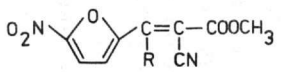
The $^1$H-n.m.r. spectra showed that the nitration has no effect upon the stereochemistry; thus, the *E,Z*-isomeric [7] starting materials give by nitration the same *E* and *Z* isomeric nitro derivatives, the latter being separable by fractional crystallization from methanol. The correct isomer-signal assignment was confirmed by the comparison of the individual signals with those produced by pure *E* isomers when irradiated in carbon tetrachloride with a mercury lamp.

It can be concluded that nitration of methyl 2-cyano-3-R-3-(2-furyl)acrylates with acetyl nitrate, when carried out without decomposing the nitration intermediate with a base, proceeds without alteration of the configuration and, most probably, is governed by an $S_E$ mechanism.

Table 3 shows biological activity of cyanoacrylic acid derivatives *I*—*IX*. The whole series of substances shows higher antibacterial than fungicidal and yeast-in-

*Table 1*

Physical properties of methyl 2-cyano-3-R-3-[2-(5-nitrofuryl)]acrylates




| No. | R | Formula | *M* | Calculated/found % C | % H | % N | Yield % | M.p. °C | $\lambda_{max}$, nm log $\varepsilon$ | $\nu$(CN) $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| *I*[a] | H | $C_9H_6N_2O_5$ | 222.15 | — | — | — | 63.2 | 212—214 | 350 | 2230 |
| | | | | — | — | — | | | 4.240 | |
| *II* | $CH_3$ | $C_{10}H_8N_2O_5$ | 236.18 | 50.84 | 3.41 | 11.87 | 72.3 | 107—109 | 350 | 2235 |
| | | | | 50.76 | 3.38 | 11.73 | | | 4.350 | |
| *III* | $C_2H_5$ | $C_{11}H_{10}N_2O_5$ | 250.21 | 52.81 | 4.03 | 11.20 | 82.5 | 94—95 | 348 | 2230 |
| | | | | 52.67 | 3.91 | 11.06 | | | 4.350 | |
| *IV* | *n*-$C_3H_7$ | $C_{12}H_{12}N_2O_5$ | 264.24 | 54.53 | 4.58 | 10.60 | 74.6 | 84—86 | 348 | 2230 |
| | | | | 54.65 | 4.61 | 10.55 | | | 4.362 | |
| *V* | i-$C_3H_7$ | $C_{12}H_{12}N_2O_5$ | 264.24 | 54.53 | 4.58 | 10.60 | 72.8 | 77—78 | 340 | 2230 |
| | | | | 54.30 | 4.50 | 10.37 | | | 4.260 | |
| *VI* | *n*-$C_4H_9$ | $C_{13}H_{14}N_2O_5$ | 278.26 | 56.08 | 5.07 | 10.07 | 81.5 | 80—81 | 346 | 2230 |
| | | | | 55.99 | 4.93 | 9.95 | 81.5 | | 4.334 | |
| *VII* | i-$C_4H_9$ | $C_{13}H_{14}N_2O_5$ | 278.26 | 56.08 | 5.07 | 10.07 | 90.5 | 78—80 | 346 | 2230 |
| | | | | 56.10 | 4.99 | 9.97 | | | 4.365 | |
| *VIIIA* | Phenyl | $C_{15}H_{10}N_2O_5$ | 298.25 | 60.40 | 3.38 | 9.39 | 98.1[b] | 178—179 | 350 | 2230 |
| | | | | 60.12 | 3.23 | 9.03 | | | 4.260 | |

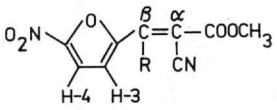
*Table 1* (Continued)

| No. | R | Formula | *M* | Calculated/found | | | Yield % | M.p. °C | $\lambda_{max}$, nm log $\varepsilon$ | $\nu$(CN) $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | % C | % H | % N | | | | |
| *VIIIB* | 4-$NO_2$-phenyl | $C_{15}H_9N_3O_7$ | 343.23 | 52.48 | 2.64 | 12.24 | *b* | 174—175 | 354 | 2230 |
| | | | | 52.23 | 2.39 | 12.02 | | | 4.284 | |
| *IX* | 5-$NO_2$-2-thienyl | $C_{13}H_7N_3O_7S$ | 349.27 | *c* | *c* | 12.03 | 79.7 | 186—187 | 350 | 2227 |
| | | | | | | 11.93 | | | 4.301 | |
| *X* | *d* | $C_9H_5N_3O_3$ | 203.15 | 53.21 | 2.48 | 20.68 | 77.1 | 145 | 350 | 2238 |
| | | | | 53.11 | 2.50 | 20.59 | | Decomposition | 4.477 | |

*a*) Ref. [9]; *b*) yield of *VIIIA* and *VIIIB* having a mixed m.p. 161—162°C; *c*) calculated: 9.10% S, found: 9.32% S; *d*) 2-cyano-3-methyl-[2-(5-nitro-furyl)]acrylonitrile.

*Table 2*

$^1$H-n.m.r. data for methyl 2-cyano-3-R-3-[2-(5-nitrofuryl)]acrylates




| No. | R | Isomer | β-$CH_2$ | γ-$CH_3$ | δ-$CH_3$ | H-3 | H-4 | $COOCH_3$ |
|---|---|---|---|---|---|---|---|---|
| *II* | $CH_3$ | *E* | 2.75[a] | — | — | 7.42 | 7.73 | 3.93 |
| | | *Z* | 2.58 | — | — | 7.27 | 7.37 | 3.91 |
| *III* | $C_2H_5$ | *E* | 3.22 | 1.25 | — | 7.42 | 7.71 | 3.91 |
| | | *Z* | 2.91 | 1.28 | — | 7.23 | 7.46 | 3.90 |
| *IV* | *n*-$C_3H_7$ | *E* | 3.18 | 1.57 | 1.27 | 7.42 | 7.70 | 3.90 |
| | | *Z* | 2.88 | 1.37 | 1.27 | 7.18 | 7.32 | 3.82 |
| *V* | i-$C_3H_7$ | *E* | 3.93[b] | 1.29 | — | 7.34 | 7.39 | 3.90 |
| | | *Z* | 3.47 | 1.29 | — | 6.74 | 7.38 | 3.82 |
| *VI* | *n*-$C_4H_9$ | *E* | 3.19 | 1.47 | 0.94 | 7.41 | 7.70 | 3.90 |
| | | *Z* | 2.89 | 1.31 | 0.94 | 7.18 | 7.35 | 3.84 |
| *VII* | i-$C_4H_9$ | *E* | 3.18 | 1.31 | 0.95 | 7.42 | 7.69 | 3.90 |
| | | *Z* | 2.80 | 1.29 | 1.00 | 7.15 | 7.37 | 3.89 |

*a*) Chemical shifts of β-methyl protons; *b*) chemical shifts of β-methine protons.

hibiting activity, the latter two being approximately the same for all substances under investigation. A higher concentration (200 μg/ml, and higher) had to be applied only in the case of *Pseudomonas aeruginosa,* known for its resistance towards antimicrobial substances. Compound *I* showed bleaching activity as well; even at the concentrations of 50 and 12.5 μg/ml a 100% aplastidy was indicated with *Euglena gracilis.* The bleaching activity disappeared when there was an alkyl or an aryl group at the position 3 of the studied series of substances. An exception was the isopropyl derivative showing 18% aplastidy at a concentration of 12.5 μg/ml. The substituted derivatives *II—IX* are more toxic than the unsubstituted derivative *I*, which possibly affects the induction of aplastidy. The compounds tested, when applied to *Mycobacterium fortuitum,* show bactericidal and bacteriostatic effects when used in high and low concentration, respectively. The protozoal strain — *Trichomonas foetus* is inhibited by concentrations of 50—200 μg/ml.

*Table 3*

Biological activity of the synthesized substances[a]

| No. | *Euglena gracilis* | | Minimum inhibition concentration against [c] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | lethal conc. | minimum bleaching conc.[b] | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* |
| *I* | 200 | 12.5 | 50 | 12.5 | 12.5 | 200 | 200 | 200 | 200/50 | 50 |
| *II* | 50 | — | 50 | 12.5 | 50 | >200 | 200 | 200 | 200/50 | 50 |
| *III* | 50 | — | 50 | 50 | 200 | >200 | 200 | 200 | 200/50 | 50 |
| *IV* | 50 | — | 50 | 12.5 | 12.5 | >200 | 200 | 200 | 200/50 | 200 |
| *V* | 50 | 12.5 | 50 | 50 | 50 | >200 | 200 | 200 | 200/50 | 200 |
| *VI* | 200 | — | 12.5 | 12.5 | 12.5 | 200 | 200 | 200 | 200/50 | 200 |
| *VII* | 200 | — | 12.5 | 12.5 | 12.5 | 200 | 200 | 200 | 200/50 | 200 |
| *VIIIB* | 800 | — | 50 | 12.5 | 12.5 | >200 | 200 | 200 | 200/50 | 200 |
| *IX* | 100 | — | 12.5 | 12.5 | 50 | >200 | 200 | 200 | 200/50 | 200 |

*a*) Values are given in μg/ml; the following concentrations were tested: 200, 50, 12.5, 3.125, 0.78 μg/ml.

*b*) Concentration causing the highest reachable alteration of heterotropic mutants is denoted minimum bleaching concentration.

*c*) Microorganisms tested: *1. Staphylococcus aureus; 2. Bacillus subtilis; 3. Escherichia coli; 4. Pseudomonas aeruginosa; 5. Candida pseudotropicalis; 6. Aspergillus fumigatus; 7. Mycobacterium fortuitum* (antibacterial/bacteriostatic conc.); *8. Trichomonas foetus.*

## Experimental

Methyl 2-cyano-3-R-3-(2-furyl)acrylates were prepared [7] by Knoevenagel condensation of alkyl and aryl 2-furyl ketones with methyl cyanoacetate, as modified by Cope.

The i.r. spectra of the solutions of methyl 2-cyano-3-R-3-[2-(5-nitrofuryl)]acrylates in chloroform were measured with a double-beam UR-20 spectrophotometer in a 1.04 mm cell. The concentration of the solution was 0.02 M. The u.v. spectra were obtained with a Specord UV VIS spectrophotometer (Zeiss, Jena). The measurements were run for the $3—5 \times 10^{-5}$ M solutions in dioxan and a 1 cm cell was used. The $^1$H-n.m.r. spectra for 15% solutions in choroform-d (internal standard tetramethylsilane) were obtained at 80 MHz using Tesla BS 487 C spectrometer.

### *Methyl 2-cyano-3-R-3-[2-(5-nitrofuryl)]acrylates I—IX*

A solution of the corresponding methyl ester (0.05 mole) in acetic anhydride (15 ml) was added during 30 min into the cooled (−10°C) nitration mixture consisting of acetic anhydride (41 g; 0.4 mole), sulfuric acid (4 drops), and fuming nitric acid (9.6 g; 0.15 mole). After stirring at −10°C for 1 h the mixture was poured onto crushed ice (200 g) and left for 10 h at room temperature. The obtained products were crystallized from methanol. The physical constants are summarized in Table 1.

### *Photoisomerization*

A stirred solution of methyl 2-cyano-3-methyl-3-[2-(5-nitrofuryl)]acrylate (*E* isomer) (1.18 g; 0.005 mole) in dry carbon tetrachloride (60 ml) was irradiated with a mercury 120 W lamp for 50 h (until discoloration could be observed). The solution was concentrated and the mixture of the formed isomers was identified by $^1$H-n.m.r. spectrometry.

### *Biological activity*

The synthesized compounds were tested by means of selected strains of bacteria (*Staphylococcus aureus, Bacillus subtilis* (gram-positive), *Escherichia coli, Pseudomonas aeruginosa* (gram-negative)), yeasts (*Candida pseudotropicalis*), fungi (*Aspergillus fumigatus*), applying the plate-diffusion method, modified to suit the different microorganisms. The bleaching activity was tested by means of *Euglena gracilis* [10], strain *Z*. The effect upon fast-growing strain *Mycobacterium fortuitum* and *Trichomonas foetus* was also studied.

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