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# Reactions of α-Nitrocinnamic Acids Esters with Indole and Its Derivatives

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**Abstract**—Reactions of α-nitrocinnamic acids esters with indole and its derivatives lead to the formation of the products of alkylation at the $C^3$-reaction center of the heterocycle. The hydrogenation of the adduct of 1-methylindole and α-nitro-β-phenylacrylate on the Raney nickel catalyst afforded indolylaminopropanoate, that was used for the synthesis of ethyl 2-acetylamino-3-(1-methylindol-3-yl)-3-phenylpropanoate, a precursor of the methylated in the indole ring phenyl-substituted tryptophan.

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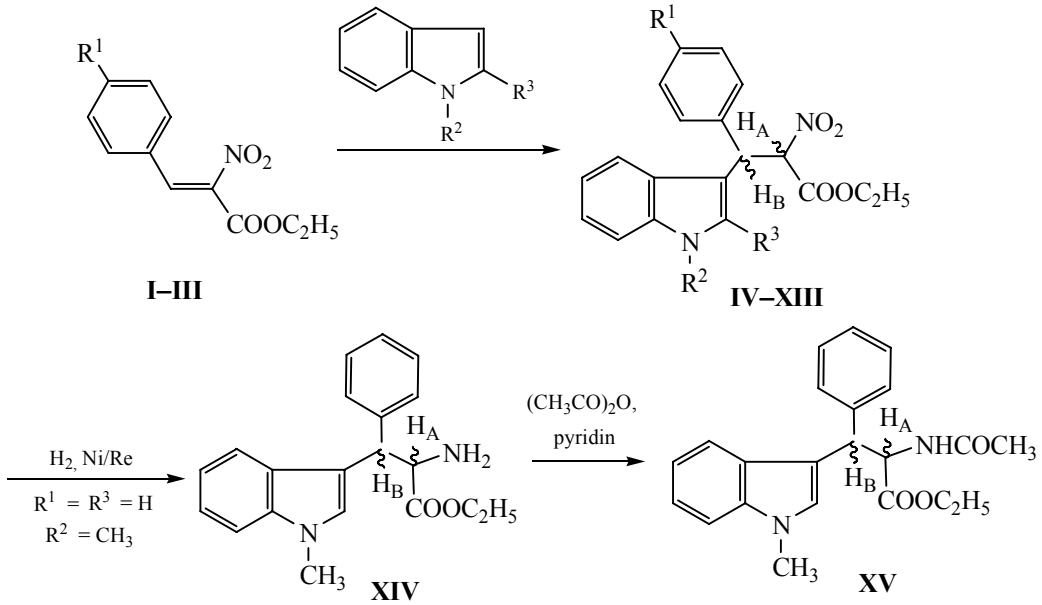
The preparatively accessible α-nitrocinnamic esters are promising starting reagents for the construction of potential biologically active structures with the desired carbon skeleton. It suffices to say that the esters of α-nitrocinnamic acids can be converted into α-amino acids by the hydrogenation and subsequent hydrolysis [1]. The study of the reactions aimed at the introduction of such pharmacophore moiety as indole into the β-aryl-α-nitroacrylate molecule is of undoubted interest [2]. It is known that indole derivatives are both key structures in the composition of many substances of natural origin and synthetic drugs. In particular, compounds related to them are the essential α-amino acid tryptophan, a mediator of nerve impulses serotonin, the biogenic amine tryptamine, and the widely used in medical practice antiinflammatory




$R^1$ = H (**I**), $CH_3O$ (**II**), Cl (**III**). $R^1$ = H: $R^2$ = $R^3$ = H (**IV**), $R^2$ = $CH_3$, $R^3$ = H (**V**), $R^2$ = $C_2H_5$, $R^3$ = H (**VI**), $R^2$ = H, $R^3$ = $CH_3$ (**VII**); $R^1$ = $CH_3O$: $R^2$ = $R^3$ = H (**VIII**), $R^2$ = $CH_3$, $R^3$ = H (**IX**), $R^2$ = $C_2H_5$, $R^3$ = H (**X**), $R^2$ = H, $R^3$ = $CH_3$ (**XI**); $R^1$ = Cl: $R^2$ = $R^3$ = H (**XII**), $R^2$ = $CH_3$, $R^3$ = H (**XIII**).

**Table 1.** Yields, melting points, and spectral data for indolylnitropropanoates **IV–XIII**[a]

| Comp. no. | mp, °C (**a**:**b**) | Yield, % | IR spectrum ($CHCl_3$), ν, $cm^{-1}$ | | | $^1H$ NMR spectra ($CDCl_3$), δ, ppm, *J*, Hz | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $NO_2$ | C=O | NH | $H_A$ ($H_B$) | $OCH_2CH_3$ ($OCH_3$) | $NCH_3$ (N–$CH_2CH_3$) [C–$CH_3$] | NH | Ar, Het |
| **IV**[b] | 142–144 | 55 | 1565, 1375 | 1740 | 3410 | 5.92 d (5.37 d) $J(H_AH_B)$ 11.77 | 0.95 t, 3.98 q | – | 8.13 s | 6.99–7.73 m |
| **Va** | 124–126 (1:1) | 91 | 1570, 1375 | 1755 | – | 5.92 d (5.36 d) $J(H_AH_B)$ 10.30 | 0.91 t, 3.99 q | 3.74 s | – | 6.97–7.61 m |
| **Vb** | | | | | | 5.87 d (5.36 d) $J(H_AH_B)$ 11.77 | 0.99 t, 4.03 q | 3.76 s | – | |
| **VIa** | 108–110 (1:1) | 66 | 1565, 1375 | 1765 | – | 5.92 5.37 d $J(H_AH_B)$ 11.03 | 0.99 t, 4.08 q | (1.45 t, 4.12 q) | – | 7.03–7.61 m |
| **VIb** | | | | | | 5.90 ( 5.37 d) $J(H_AH_B)$ 11.77 | 0.85 t, 3.97 q | (1.42 t, 4.09 q) | – | |
| **VII**[b] | 137–139 | 20 | 1565, 1375 | 1750 | 3470 | 6.31 d (5.28 d) $J(H_AH_B)$ 11.18 | 1.06 t, 4.12 q | [2.47 s] | 7.85 s | 7.07–7.68 m |
| **VIIIa** | 164–166 (2:1) | 54 | 1565, 1375 | 1745 | 3330 | 5.85 d (5.33 d) $J(H_AH_B)$ 11.03 | 1.05 t, 4.07 q (3.74 s) | – | 8.10 s | 6.73–7.65 m |
| **VIIIb** | | | | | | 5.87 d (5.31 d) $J(H_AH_B)$ 11.77 | 0.93 t, 3.99 q (3.75 s) | – | 8.10 s | |
| **IX** | 138–140 | 43 | 1565, 1375 | 1750 | – | 5.84 d (5.32 d) $J(H_AH_B)$ 11.03 | 1.04 t, 4.02 q (3.75 s) | 3.74 s | – | 6.73–7.60 m |
| **Xa** | 99–101 (6:1) | 20 | 1565, 1375 | 1750 | – | 5.84 d (5.31 d) $J(H_AH_B)$ 11.03 | 1.01 t, 4.02 q (3.73 s) | (1.44 t, 4.11 q) | – | 6.78–7.45 m |
| **Xb** | | | | | | 5.85 d (5.29 d) $J(H_AH_B)$ 11.77 | 1.03 t, 4.05 q (3.73 s) | (1.35 t, 4.14 q) | – | |
| **XIa** | 136–138 (8:1) | 54 | 1560, 1375 | 1750 | 3470 | 6.27 d (5.23 d) $J(H_AH_B)$ 11.90 | 1.12 t, 4.13 q (3.73 s) | [2.43 s] | 7.87 s | 6.78–7.87 m |
| **XIb** | | | | | | 6.24 d (5.29 d) $J(H_AH_B)$ 12.21 | 1.12 t, 4.12 q (3.73 s) | [2.42 s] | 7.87 s | |
| **XIIa** | 128–130 (1:8) | 32 | 1565, 1375 | 1750 | 3475 | 5.84 d (5.33 d) $J(H_AH_B)$ 10.78 | 1.05 t, 4.00 q | – | 8.14 s | 7.05–7.52 m |
| **XIIb** | | | | | | 5.86 d (5.33 d) $J(H_AH_B)$ 11.31 | 0.93 t, 3.98 q | – | 8.14 s | |
| **XIIIa** | 110–112 (5:1) | 54 | 1565, 1375 | 1750 | – | 5.83 d (5.33 d) $J(H_AH_B)$ 11.29 | 1.04 t, 4.05 q | 3.75 s | – | 7.06–7.55 m |
| **XIIIb** | | | | | | 5.85 d (5.32 d) $J(H_AH_B)$ 11.60 | 0.92 t, 4.03 q | 3.74 s | – | |

[a] Diastereomers with lower spin–spin coupling constant between methyne protons $H_A$ and $H_B$ are designated as "a," and with greater, as "b." [b] The IR spectra of compounds **IV** and **VII** were recorded in mineral oil.

and analgesic agent indomethacin, the antiarrhythmic and antihypertensive drug bopindalol, the antihypertensive diuretic Arifon, the hypolipidemic drug atorvastatin, and others. [3].

The study of the reaction of α-nitroacrylates **I–III** with indole and its alkyl-substituted derivatives showed that these reactions occur most efficiently at the fusion of equimolar amounts of the initial compounds in the solvent-free conditions, without additional catalytic agents, to form $C^3$-adducts with yields up to 91%.

The structure of compounds **IV–XIII** is confirmed by the spectral data (Table 1). Thus, the IR spectra contain the intense absorption bands of stretching

**Table 2.** The $^1$H NMR spectral data of indolylnitropropanoates (**XIV, XV**)[a]

| Comp. no. | $^1$H NMR spectra ($CDCl_3$), δ, ppm, *J*, Hz | | | | | |
|---|---|---|---|---|---|---|
| | $H_A$ ($H_B$) | $OCH_2$ | $CH_3$ (N–$CH_3$) | $COCH_3$ | NH ($NH_2$) | Ar, Ind |
| **XIVa** | 4.67 d (4.20 d), $J(H_AH_B)$ 6.00 | 4.04 q | 1.06 t (3.75 s) | – | (1.57 s) | 6.98–7.47 m |
| **XIVb** | 4.63 d (4.18 d), $J(H_AH_B)$ 6.80 | 4.00 q | 0.97 t (3.77 s) | – | (1.57 s) | |
| **XVa** | 5.44 d.d (4.88 d), $J(H_AH_B)$ 5.00, $J(H_ANH)$ 8.80 | 4.06 q | 1.09 t (3.78 s) | 1.95 s | 5.99 d, $J(NHH_A)$ 8.8 | 6.90–7.38 m |
| **XVb** | 5.30 d.d (4.68 d), $J(H_AH_B)$ 8.33, $J(H_ANH)$ 9.00 | 3.91 q | 0.93 t (3.78 s) | 1.89 s | 5.74 d, $J(NHH_A)$ 9.0 | |

[a] Diastereomers with a lower spin–spin coupling constant between methyne protons $H_A$ and $H_B$ are designated as "a," and with greater, as "b."

vibrations of non-conjugated nitro- (1560–1570, 1375 $cm^{-1}$) and carbonyl (1740–1765 $cm^{-1}$) groups. In the spectra of compounds **IV**, **VII**, **VIII**, **XI**, **XII** there are absorption bands belonging to the vibrations of NH-groups of indole rings (3330–3475 $cm^{-1}$).

In the $^1$H NMR spectra of indolylnitropropanoates **IV–XIII** the signals of protons of all the structural fragments are present. The $^1$H NMR spectra of compounds **V**, **VI**, **VIII**, **X–XIII** contain a double set of the proton signals, indicating the existence in the chloroform-*d* solution of a mixture of diastereomers. The adducts **IV**, **VII**, **IX** were isolated as individual diastereomers. Thus, in the $^1$H NMR spectrum of **IV** there are two clear doublets of the methine protons $H_A$ and $H_B$ at 5.92 and 5.37 ppm respectively with a spin-spin coupling constant $^3J(H_AH_B)$ 11.77 Hz. Methyl and methylene protons in $OCH_2CH_3$-fragment appear as a triplet and a quadruplet at 0.95 and 3.98 ppm, respectively. The protons of phenyl and indole rings are recorded as multiplets in the region of 6.99–7.73 ppm. The NH proton of indole ring resonates at 8.13 ppm.

It should be noted that recently the reaction was studied of β-aryl-α-nitroacrylate derivatives with indole and its derivatives in the presence of chiral metal complex catalysts in methylene chloride (toluene) at 0°C over 60–130 h [4]. The spectral characteristics of compound **VIII** and the adduct (*anti*-form) synthesized from indole and ethyl 2-nitro-3-(4-methoxyphenyl)propenoate described in [4] are very close.

The synthesized indolylnitropropanoates **IV–XIII** may be recommended as the initial reagents in the synthesis of aryl-substituted tryptophans. The principal possibility of their transformation into the modified analogs of tryptophan we showed by the example of reduction of the adduct of 1-methylindole and ethyl α-nitrocinnamate **V**.

The hydrogenation of compound **V** on a skeletal nickel catalyst at room temperature led to the indolylaminopropanoate **XIV** isolated as an oily substance in ~94% yield. The acylation of the latter with acetic anhydride in pyridine yields ethyl 2-acetylamino-3-(1-methylindol-3-yl)-3-phenylpropanoate **XV** (45%), the precursor of phenyl-substituted tryptophan methylated by the nitrogen of the indole ring.

The structure of the synthesized amino ester **XIV** and *N*-acetylamino ester **XV** was confirmed by the spectroscopic methods. Thus, the IR spectrum (KBr) of compound **XV** contains no absorption bands of the stretching vibrations of nitro groups, and there are intense absorption bands of stretching vibrations of carbonyl groups of ester and amide fragments at 1735 and 1675 $cm^{-1}$, respectively. The absorption band at 3430 $cm^{-1}$ can be assigned to the stretching vibrations of amide NH-group.

The $^1$H NMR spectra of amino ester **XIV** and *N*-acetylamino ester **XV** contain the signals of all the structural fragments of the molecules (Table 2). The double set of the proton signals indicates the existence in a solution in chloroform-*d* of diastereomeric mixtures (~1:1). In the $^1$H NMR spectrum of **XV** the protons NH, $H_A$ and $H_B$ of the three-spin ABC system are registered at 5.99, 5.44 and 4.88 ppm (diastereomer **a)** and at 5.74, 5.30 and 4.68 ppm (diastereomer **b**), respectively. Methyl and methylene protons in $OCH_2CH_3$-fragment appear as a triplet and quadruplet at 9.1, 4.06 ppm (diastereomer **a**) and at 0.93, 3.91 ppm (diastereomer **b**), respectively. The methyl group protons in the indole ring resonate at 3.78 ppm. Indole and phenyl ring protons are recorded as multiplets at 6.9–7.38 ppm.

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Bruker WM-400 (400 MHz) and Jeol JNM-ECX400A (400 MHz) spectrometers in chloroform-*d*. Chemical shifts (δ) were measured in ppm using residual $CHCl_3$ as an internal reference.

The IR spectra were taken on a Shimadzu IR Prestige-21 and InfraLum FT-02 spectrometers from the samples in chloroform (*c* 0.1–0.001 mol $l^{-1}$) or mineral oil. The elemental analysis was performed on a Eurovector EA3028 analyzer.

The mass spectra were registered on a MKh 1321 mass spectrometer with a direct injection of the sample into the ion source. Measuring conditions: ionizing voltage 70V, ionizing source temperature 180°C).

**Ethyl 3-(indol-3-yl)-2-nitro-3-phenylpropanoate (IV).** A mixture of 0.221 g (1 mmol) of ethyl 2-nitro-3-phenylpropenoate **I** and 0.12 g (1 mmol) of indole was heated up to melt under stirring and allowed to stand for 3 days at room temperature in the dark. The reaction mixture was treated with ethanol and filtered. Yield 0.187 g (55%), white crystals (individual diastereomer)**,** mp 142–144°C (ethanol). Found N, %: 8.23. $C_{19}H_{18}N_2O_4$. Calculated N, %: 8.28.

Compounds **V–XIII** were similarly prepared from the corresponding α-nitrocinnamic acids esters and indole or its derivatives.

**Ethyl 3-(1-methylindol-3-yl)-2-nitro-3-phenylpropanoate (V).** Yield 91%, diastereomers mixture (**a**:**b** ~1:1), mp 124–126°C (ethanol). Found N, %: N 7.92. $C_{20}H_{20}N_2O_4$. Calculated N, %: 7.95.

**Ethyl 2-nitro-3-phenyl-3-(1-ethylindol-3-yl)propanoate (VI).** Yield 66%, diastereomers mixture (**a**:**b** = 1:1), mp 108–110°C (ethanol). Found N, %: C 68.65, H 5.89, N 7.65. $C_{21}H_{22}N_2O_4$. Calculated, %: C 68.84, H 6.05, N 7.65. Mass spectrum, *m*/*z*: 366 [$M^+$], $M_{calc}$ 366.

**Ethyl 2-nitro-3-phenyl-3-(2-methylindol-3-yl)propanoate (VII).** Yield 20%, diastereomers mixture (**a**:**b** = 1:1), mp 137–139°C (ethanol). Mass spectrum, *m*/*z*: 352 [$M^+$], $M_{calc}$ 352.

**Ethyl 3-(indol-3-yl)-3-(4-methoxyphenyl)-2-nitropropanoate (VIII).** Yield 54%, diastereomers mixture (**a**:**b** = 2:1), mp 164–166°C (ethanol). Found N, %: 7.86. $C_{20}H_{20}N_2O_5$. Calculated N, %: 7.61.

**Ethyl 3-(1-methylindol-3-yl)-3-(4-methoxyphenyl)-2-nitropropanoate (IX).** Yield 43%, individual diastereomer, mp 138–140°C (ethanol). Found N, %: 7.37. $C_{21}H_{22}N_2O_5$. Calculated N, %: 7.33.

**Ethyl 3-(4-methoxyphenyl)-2-nitro-3-(1-ethylindol-3-yl)propanoate (X).** Yield 20%, diastereomers mixture (**a**:**b** = 6:1), mp 99–101°C (ethanol). Found N, %: N 6.64. $C_{22}H_{24}N_2O_5$. Calculated N, %: N 7.07.

**Ethyl 3-(2-methylindol-3-yl)-3-(4-methoxyphenyl)-2-nitropropanoate (XI).** Yield 54%, diastereomers mixture (**a**:**b** ~8:1), mp 136–138°C (ethanol). Found, %: C 66.34, H 5.90, N 7.17. $C_{21}H_{22}N_2O_5$. Calculated, %: C 65.96, H 5.80, N 7.33.

**Ethyl 3-(indol-3-yl)-2-nitro-3-(4-chlorophenyl)propanoate (XII).** Yield 32%, diastereomers mixture (**a**:**b** ~1:8), mp 128–130°C (ethanol). Found N, %: 7.09. $C_{19}H_{17}N_2O_4$. Calculated N, %: N 7.51.

**Ethyl 3-(1-methylindol-3-yl)-2-nitro-3-(4-chlorophenyl)propanoate (XIII).** Yield 54%, diastereomers mixture (**a**:**b** ~5:1), mp. 110–112°C (ethanol). Found, %: C 62.17, H 4.95, N 7.32. $C_{20}H_{19}ClN_2O_4$. Calculated N, %: C 62.10, H 4.95, N 7.24.

**Ethyl 2-amino-3-(1-methylindol-3-yl)-3-phenylpropanoate (XIV).** A solution of 1.1 g (0.3 mmol) of ethyl 3-(1-methylindol-3-yl)-2-nitro-3-phenylpropanoate **V** in 25 ml of methanol was charged into the flask for hydrogenation with a Raney nickel pre-saturated with hydrogen. The hydrogenation was carried out in methanol at shaking (atmospheric pressure) to complete absorption of the calculated amount of hydrogen (2 h). After the catalyst separating and solvent removal, the compound **XIV** was obtained (0.91 g, 94%) as a pale-green oil, which is a mixture of diastereomers **a**:**b** in a ratio of ~1:1 according to the $^1$H NMR spectroscopy. The obtained compound **XIV** was used without further purification in the acylation reaction.

**Ethyl 2-acetylamino-3-(1-methylindol-3-yl)-3-phenylpropanoate (XV).** To a solution of 0.9 g (0.25 mmol) of ethyl 2-amino-3-(1-methylindol-3-yl)-3-phenylpropanoate **XIV** in 4 ml of pyridine was added 4 ml of acetic anhydride. The mixture was kept for 3 days. Then it was poured into ice, the solid was filtered off. Yield 0.455 g (45%), diastereomers mixture (1:1), mp 96–98°C (ethanol). Found, %: C 72.60, H 6.53, N 7.51. $C_{22}H_{24}N_2O_3$. Calculated, %: C 72.50, H 6.64, N 7.69.

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