# Preparation and spectral properties of the derivatives of 3-*N*-arylamino-2-cyanopropenoic acid

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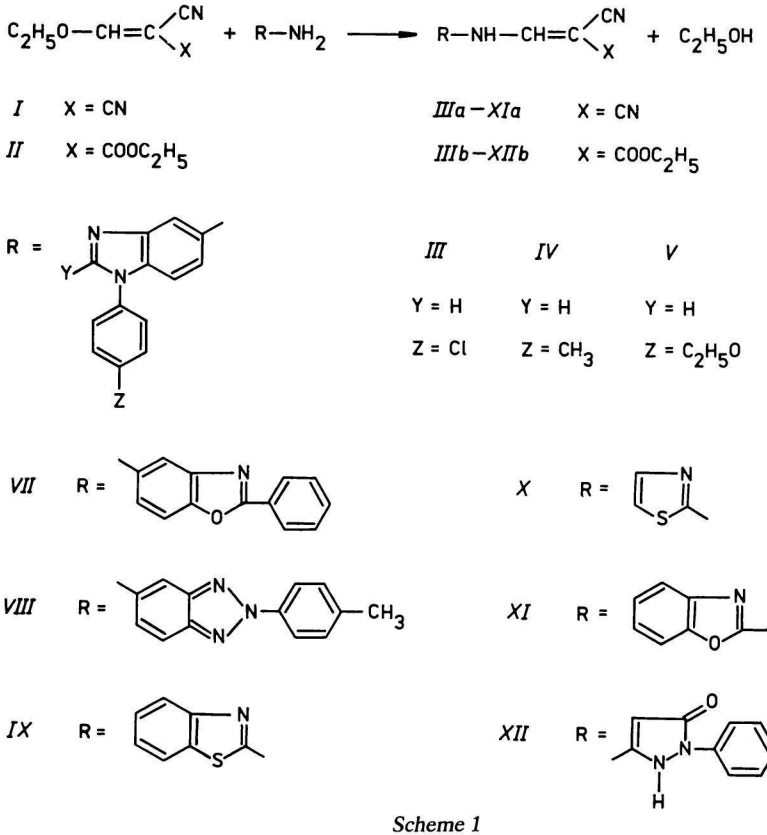
Synthesis of ethyl esters and nitriles of 3-aryl amino-2-cyanopropenoic acid has been described. Different reactivities of the amines used required four modifications of the reaction conditions for the preparation of the substitution products. The structures of the newly synthesized derivatives are discussed on the basis of infrared, ultraviolet, and $^1$H NMR spectra.

Описаны синтезы этиловых эфиров и нитрилов 3-ариламино--2-цианоакриловой кислоты. Из-за различных реакционных способностей использованных аминов требовались четыре модификации реакционных условий для получения продуктов замещения. Структуры новых синтезированных производных обсуждаются на основе их ИК-, УФ- и $^1$H ЯМР-спектров.

Nitrile (*I*) and ester (*II*) of 3-ethoxy-2-cyano-2-propenoic acid, respectively, readily undergoes nucleophilic substitution on the double bond, where the nucleophilic agent substitutes the leaving ethoxy group [1]. According to the so far published papers, the nucleophile substituting the ethoxy group is the amino group of variously substituted aromatic and heteroaromatic amines [2—4]. In dependence on the reaction conditions, substitution may be accompanied by subsequent cycloaddition reaction resulting in derivatives of the fused 4-hydroxypyridine or 4-iminopyridine [5—8]. The interest in the substitution products of the compounds *I* and *II* was initiated also by their expected biological activity [9—11].

In the present work we deal with preparation of the substitution products of the compounds *I* and *II* with some heterocyclic amines. With the chosen primary amines different nucleophility was expected due to the effect of the heterocyclic system to which the amino group had been attached (Scheme 1).




*Scheme 1*

Four methods have been examined in the preparation of the substitution derivatives (Table 1). With the more reactive amines, where the amino group was not attached to the heterocyclic ring, the reaction proceeded at mild conditions (reflux in benzene). The reactivity of these compounds was in accord with the idea about the deactivation effect of the fused heterocycle to the substituents on the aromatic ring. 2-Benzoxazolyl in the *p*-position of aniline had approximately the same effect on the amino group as the nitro group.

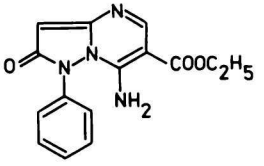
In the benzimidazole series the reactivity of *I* and *II* towards the same substrate was observed to be different. In some cases the dinitrile derivative afforded the substitution product at room temperature already, which was not so with the compound *II*. The compounds *IX* and *X* did not enter the reaction under the conditions mentioned above (Method *A*) and were reisolated from the reaction mixture. However, their solubility in benzene was not decreased when compared to the former derivatives. In ethanol (Method *B*) they gave the substitution products in good yields in the same reaction time. In those cases when the starting amino derivative was little soluble, addition of a small amount of hexamethylphosphor-

triamide sped up the reaction considerably (Method *C*).

The substitution reaction proceeding in melt at 140—160 °C was complete within 1/2—2 h. The progress of the reaction was indicated by the alcohol condensing on the walls of the reaction vessel and later also by solidification of the reaction mixture as the melting point of the substitution product is by approximately 100 °C higher than those of the starting components.

When the starting amine has in the *o*-position an atom with a lone electron pair (most frequently nitrogen as a part of the heterocyclic ring), cyclization of the originally formed substitution product may occur during the reaction proceeding in melt. In this way reacted 1-phenyl-3-amino-5-pyrazolone (*XII*) with the compound *II* in melt at 160 °C affording the compound *XIII* within 1 h. The substitution reaction did not take place when a secondary amine (*N*-phenyl-5-amino-1,2,3-thiadiazole) was used as the nucleophile.

*XIII*




The infrared spectra of the studied substitution products *III*—*XII* exhibited some characteristic absorption bands (Table 2). The stretching vibrations of the carbonyl group appeared at $\tilde{\nu} = 1675$—$1685$ cm$^{-1}$ with all derivatives *IIIb*—*XIIb*. In cases when the substituted ethylene was attached to the heterocyclic ring directly through the —NH— group (compounds *IX* and *X*) a shift to higher wavenumbers was observed. All derivatives showed the characteristic $\nu(C \equiv N)$ vibration. With the compounds *IIIb*—*XIIb*, except the derivatives *IXb* and *Xb*, this band appeared at $\tilde{\nu} = 2215$ cm$^{-1}$. The dinitrile analogues had this band at $\tilde{\nu} = 2225$ cm$^{-1}$. The stretching vibration of the cyano group was absent in the spectrum of the compound *XIII* indicating the cyclization of this compound.

The ultraviolet spectra of all derivatives prepared revealed three characteristic absorption bands (Table 3). Introduction of the polarized ethylene bond into the molecule of the heterocyclic amine brought about a bathochromic shift of the band occurring at the highest wavenumber as well as an increase in its intensity. The ratio of intensities of the absorption bands was reversed when compared to the unsubstituted amine. The spectrum of the substitution product differed considerably from that of the cyclic compound (derivatives *XIIb* and *XIII*). The band appearing at the highest wavenumber in the spectrum of 1-phenyl-2-oxo--pyrazolo[1,5-*a*]-6-ethoxycarbonyl-7-aminopyrimidine was hypsochromically shifted by 33 nm when compared to the acyclic compound.

The $^1H$ NMR spectral data of the studied derivatives are summarized in Table 4. The position of the signal belonging to hydrogen of the amino group varied ($\delta = 10$—$12$ ppm) in dependence on the attached heterocycle. It was a diffusion-like band and with some derivatives was not observed at all. By addition of $^2H_2O$ it vanished entirely from the spectrum. The olefinic proton on the deactivated double bond showed a signal at $\delta = 8.2$—$8.5$ ppm. Since a negligible splitting of this signal occurred due to the effect of the adjacent amino group ($J_{H,H} = 1$ Hz), the arrangement of these two protons may be considered as cisoid. Similar results were obtained by *Nishigaki et al.* [4] with pyridine analogues.

## Experimental

Melting points of the synthesized compounds are not corrected. Thin-layer chromatography was performed on aluminium(III) oxide Reanal (activity II according to Brockmann), the compounds were visualized with iodine vapours using UV lamp.

The synthesis of the heteroarylamines used has been described in [12—14]. The compounds *I* and *II* were prepared according to *Bollemont* [15]. Physicochemical data, methods of preparation, and yields of the studied derivatives are summarized in Table 1.

Infrared spectra (Table 2) of the prepared compounds were measured with a double-beam UR-20 (Zeiss, Jena) spectrophotometer by the KBr technique. Ultraviolet spectra (Table 3) were recorded on a Specord UV (Zeiss, Jena) apparatus in dioxan ($c = 3 \times 10^{-5}$ mol dm$^{-3}$; 1 cm cell thickness) at room temperature. $^1H$ NMR spectra (Table 4) were measured in DMSO-$d_6$ with a Tesla BS 847 C spectrometer at 80 MHz and 37 °C. Some derivatives were measured at 80 °C because of their low solubility.

### *Derivatives of 3-N-heteroarylamino-2-cyano-2-propenoic acid*

#### *Method A*

Equimolar amounts of the respective amine and the compounds *I* and *II*, respectively, were dissolved in dry benzene (1 g amine per 30 cm$^3$ benzene) and heated to boiling for the time necessary to complete the reaction (Table 1). Duration of the reaction was settled on the basis of expected reactivity of the substrate and by checking the presence of the starting compounds by means of thin-layer chromatography during the reaction. After cooling of the reaction mixture the precipitate was sucked, washed with petroleum ether, dried, and crystallized. If the product did not precipitate from the reaction mixture even after cooling, it was precipitated with petroleum ether.

*Method B*

The equimolar mixture of the amino derivative and the compounds *I* and *II*, respectively, was dissolved in absolute ethanol (1 g amine per 20 $cm^3$ ethanol) and heated under reflux for 15—20 h. After cooling the reaction mixture was evaporated and the precipitate was sucked, washed with dry ether, and crystallized from absolute ethanol.

*Method C*

The equimolar mixture of the starting compounds was dissolved in a small amount of hexamethylphosphortriamide (0.5 g compound per 5 $cm^3$ solvent) and heated to 100—150 °C for 4 h. Then the cooled mixture was poured into distilled water. The precipitate, formed after decomposition of hexamethylphosphortriamide with water, was sucked. When the product was an emulsion, the organic compound was extracted with ether. The extract was dried with anhydrous magnesium(II) sulfate, evaporated, and crystallized from absolute ethanol.

*Method D*

Equimolar amounts of the respective amine and the compound *II* were stirred thoroughly and melted on an oil bath approximately at the melting point of the amine used. The progress of the reaction was indicated with ethanol vapours condensed on the walls of the reaction flask. After a certain time (1/2—2 h) the reaction mixture solidified. The cooled melt was powdered and crystallized from a suitable solvent.

*Table 1*

Physicochemical properties of the prepared compounds

| Compound | Formula $M_r$ | $w_i$(calc.)/% $w_i$(found)/% | | | Yield[a] | M.p. | *t* | Method |
|---|---|---|---|---|---|---|---|---|
| | | C | H | N | % | °C | h | |
| *IIIa* | $C_{19}H_{15}N_4O_2Cl$ | 62.21 | 4.09 | 15.27 | 80 | 242—243 | 4 | *A* |
| | 366.8 | 62.19 | 3.95 | 15.19 | | | | |
| *IIIb* | $C_{17}H_{10}N_5Cl$ | 63.84 | 3.17 | 21.89 | 87 | 327—330 | 2 | *A* |
| | 319.8 | 63.91 | 3.14 | 21.75 | | | | |
| *IVa* | $C_{20}H_{18}N_4O_2$ | 69.35 | 5.24 | 16.18 | 74 | 237—239 | 5 | *A* |
| | 346.4 | 69.24 | 5.19 | 16.40 | | | | |
| *IVb* | $C_{18}H_{13}N_5$ | 72.22 | 4.38 | 23.40 | 79 | 325—327 | 3 | *A* |
| | 299.3 | 72.19 | 4.33 | 23.29 | | | | |
| *Va* | $C_{21}H_{20}N_4O_3$ | 67.01 | 5.36 | 14.89 | 90 | 189—191 | 3 | *A* |
| | 376.4 | 66.94 | 5.29 | 14.81 | | | | |
| *Vb* | $C_{19}H_{15}N_5O$ | 69.28 | 4.59 | 21.27 | 97 | 301—303 | 1 | *A* |
| | 329.4 | 69.21 | 4.47 | 21.36 | | | | |
| *VIa* | $C_{20}H_{17}N_4O_2Br$ | 56.48 | 3.99 | 13.17 | 79 | 236—238 | 5 | *A* |
| | 425.3 | 56.41 | 3.91 | 13.24 | | | | |
| *VIb* | $C_{18}H_{12}N_5Br$ | 57.16 | 3.17 | 18.51 | 83 | 365—367 | 3 | *A* |
| | 378.2 | 57.09 | 3.24 | 18.39 | | | | |
| *VIIa* | $C_{19}H_{15}N_3O_3$ | 68.46 | 4.54 | 12.61 | 87 | 177—178 | 15 | *A* |
| | 333.3 | 68.39 | 4.58 | 12.64 | | | | |
| *VIIb* | $C_{17}H_{10}N_4O$ | 71.32 | 3.52 | 19.57 | 91 | 298—301 | 10 | *A* |
| | 286.3 | 71.29 | 3.61 | 19.46 | | | | |
| *VIIIa* | $C_{19}H_{17}N_5O_2$ | 65.69 | 4.93 | 20.16 | 75 | 198—200 | 15 | *A*, *C* |
| | 347.4 | 65.61 | 5.00 | 20.09 | | | | |
| *VIIIb* | $C_{17}H_{12}N_6$ | 67.99 | 4.03 | 27.99 | 69 | 318—321 | 10 | *A*, *C* |
| | 300.3 | 67.92 | 4.09 | 28.03 | | | | |

*Table 1* (Continued)

| Compound | Formula<br>$M_r$ | $w_i$(calc.)/%<br>$w_i$(found)/% | | | Yield[a] | M.p. | *t* | Method |
|---|---|---|---|---|---|---|---|---|
| | | C | H | N | % | °C | h | |
| *IXa* | $C_{13}H_{11}N_3O_2S$ | 57.14 | 4.06 | 15.38 | 46 | 180—181 | 15 | *B, D* |
| | 273.3 | 57.11 | 4.01 | 15.47 | | | | |
| *IXb* | $C_{11}H_6N_4S$ | 58.41 | 2.67 | 24.77 | 57 | 190—191 | 10 | *B, D* |
| | 226 2 | 58.37 | 2.59 | 24.80 | | | | |
| *Xa* | $C_9H_9N_3O_2S$ | 48.43 | 4.06 | 18.83 | 45 | 139—141 | 20 | *B, D* |
| | 223.2 | 48.39 | 4.01 | 18.97 | | | | |
| *Xb* | $C_7H_4N_4S$ | 47.73 | 2.29 | 31.81 | 62 | 179—181 | 20 | *B, D* |
| | 176.1 | 47.68 | 2.24 | 31.72 | | | | |
| *XIa* | $C_{19}H_{15}N_3O_3$ | 68.46 | 4.54 | 12.61 | 89 | 241—242 | 10 | *A* |
| | 333.3 | 68.39 | 4.61 | 12.70 | | | | |
| *XIb* | $C_{17}H_{10}N_4O$ | 71.32 | 3.52 | 19.57 | 92 | 330—332 | 10 | *A* |
| | 286.3 | 71.29 | 3.48 | 19.64 | | | | |
| *XII* | $C_{15}H_{14}N_4O_3$ | 60.39 | 4.73 | 18.78 | 38 | 140—141 | 25 | *B* |
| | 298.3 | 60.33 | 4.81 | 18.71 | | | | |
| *XIII* | $C_{15}H_{14}N_4O_3$ | 60.39 | 4.73 | 18.78 | 80 | 283—285 | 1 | *D* |
| | 298.3 | 60.41 | 4.81 | 18.71 | | | | |

*a*) The yields presented relate to the method listed first.

*Table 2*

Infrared spectra ($\tilde{\nu}$/cm$^{-1}$) of the prepared compounds

| Compound | Vibrations of the skeleton | ν(C=O) | ν(C≡N) | ν(C—H) | ν(N—H) |
|---|---|---|---|---|---|
| *IIIa* | 1425; 1505; 1595; 1645 | 1685 | 2215 | 2970—3100 | 3200; 3275 |
| *IIIb* | 1435; 1507; 1595; 1665 | — | 2225 | 2980—3105 | 3215; 3295 |
| *IVa* | 1425; 1485; 1520; 1635 | 1675 | 2215 | 2950—3100 | 3195; 3265 |
| *IVb* | 1440; 1520; 1595; 1665 | — | 2225 | 2960—3100 | 3225; 3295 |
| *Va* | 1445; 1490; 1520; 1635 | 1675 | 2215 | 2940—3100 | 3215; 3275 |
| *Vb* | 1440; 1520; 1625; 1665 | — | 2225 | 2940—3100 | 3215; 3295 |
| *VIa* | 1450; 1495; 1525; 1635 | 1677 | 2215 | 2950—3080 | 3195; 3255 |
| *VIb* | 1430; 1495; 1595; 1645 | — | 2215 | 2850—3070 | 3195; 3295 |
| *VIIa* | 1455; 1485; 1615: 1645 | 1675 | 2215 | 2940—3070 | 3175; 3275 |
| *VIIb* | 1465; 1560; 1620; 1660 | — | 2225 | 2960—3100 | 3215; 3295 |
| *VIIIa* | 1425; 1510; 1580; 1620 | 1680 | 2215 | 2900—3080 | 3205; 3280 |
| *VIIIb* | 1455; 1515; 1570; 1645 | — | 2225 | 2900—3065 | 3205; 3285 |
| *IXa* | 1440; 1530; 1595; 1635 | 1725 | 2225 | 2950—3095 | 3195; 3255 |
| *IXb* | 1515; 1625 | — | 2217 | — | 3245 |
| *Xa* | 1495; 1560; 1605 | 1705 | 2205 | 2900—2990 | 3115; 3300 |
| *Xb* | 1495; 1555; 1635 | — | 2225 | 3105 | 3275 |
| *XIa* | 1460; 1505; 1610; 1620 | 1675 | 2215 | 2900—3060 | 3205; 3280 |
| *XIb* | 1455; 1505; 1615; 1655 | — | 2225 | 2945—3030 | 3195; 3295 |
| *XII* | 1495; 1590; 1630 | 1695 | 2215 | 2870—3080 | 3225; 3280 |
| *XIII* | 1440; 1495; 1665 | 1695 | — | 2980—3070 | 3270; 3365 |

*Table 3*

Ultraviolet spectra of the prepared compounds

| Compound | $\lambda_{max\ I}$ / nm | log $\varepsilon_1$ / ($dm^3\ mol^{-1}\ dm^{-1}$) | $\lambda_{max\ II}$ / nm | log $\varepsilon_2$ / ($dm^3\ mol^{-1}\ cm^{-1}$) | $\lambda_{max\ III}$ / nm | log $\varepsilon_3$ / ($dm^3\ mol^{-1}\ cm^{-1}$) |
|---|---|---|---|---|---|---|
| *IIIa* | 215 | 3.5 | 262 | 3.3 | 335 | 3.5 |
| *IIIb* | 215 | 3.3 | 263 | 3.3 | 325 | 3.4 |
| *IVa* | 214 | 3.4 | 257 | 3.2 | 336 | 3.5 |
| *IVb* | 215 | 3.4 | 261 | 3.3 | 328 | 3.4 |
| *Va* | 214 | 3.4 | 253 | 3.2 | 335 | 3.4 |
| *Vb* | 214 | 3.0 | 257 | 3.2 | 326 | 3.4 |
| *VIa* | 218 | 3.4 | 259 | 3.2 | 335 | 3.5 |
| *VIb* | 215 | 3.3 | 260 | 3.2 | 328 | 3.4 |
| *VIIa* | 213 | 3.3 | 278 | 3.3 | 334 | 3.5 |
| *VIIb* | 215 | 3.2 | 284 | 3.4 | 329 | 3.5 |
| *VIIIa* | 215 | 3.2 | 300 | 3.3 | 363 | 3.6 |
| *VIIIb* | 216 | 3.2 | 300 | 3.3 | 356 | 3.5 |
| *IXa* | 216 | 3.3 | 240 | 2.8 | 333 | 3.5 |
| *IXb* | 223 | 3.3 | 252 | 2.9 | 380 | 3.2 |
| *Xa* | 223 | 2.8 | 274 | 2.7 | 390 | 3.0 |
| *Xb* | 228 | 3.0 | 274 | 2.9 | 380 | 3.1 |
| *XIa* | 215 | 3.0 | 229 | 3.0 | 353 | 3.5 |
| *XIb* | 218 | 3.0 | 248 | 3.1 | 327 | 3.2 |
| *XII* | 218 | 3.0 | 260 | 3.2 | 370 | 3.0 |
| *XIII* | 214 | 3.2 | 270 | 3.4 | 337 | 3.2 |

*Table 4.* $^1$H NMR spectra ($\delta$/ppm) of the prepared compounds

| Compound | H—C= | —NH— | $H_{arom}$ | —$CH_2$— | $H_3C$— |
|---|---|---|---|---|---|
| *IIIa* | 8.3 s | 10.7 s | 7.8—7.4 m | 4.2 q | 1.3 t |
| *IIIb* | 8.4 s | 9 | 7.8—7.4 m | — | — |
| *IVa* | 8.5 s | 10.9 d | 7.9—7.3 m | 4.2 q | 1.2 t |
| *IVb* | 8.4 s | 9 | 7.4 d, 7.8 d | — | — |
| *Va* | 8.4 s | 10.6 s | 7.8—7.0 m | 4.1 q | 1.3 t |
| *Vb* | 8.5 s | 11.1 s | 7.8—7.3 m | — | — |
| *VIa* | 8.3 s | 10.7 s | 7.8—7.1 m | 4.1 q | 1.3 t |
| *VIb* | 8.5 s | 11.1 s | 7.8—7.1 m | — | — |
| *VIIa* | 8.3 s | 10.9 d | 8.2—7.5 m | 4.2 q | 1.2 t |
| *VIIb* | 8.4 s | 9 | 8.2—7.5 m | — | — |
| *VIIIa* | 8.4 s | 10.9 s | 8.1—7.4 m | 4.2 q | 1.3 t |
| *VIIIb* | 8.6 s | 11.2 s | 8.2—7.4 m | — | — |
| *IXa* | 8.3 s | 12.4 s | 8.0—7.3 m | 4.3 q | 1.3 t |
| *IXb* | 8.4 s | 9 | 8.0—7.3 m | — | — |
| *Xa* | 8.2 s | *a* | 8.2 d, 7.6 d | 4.3 q | 1.3 t |
| *Xb* | 8.0 s | 9 | 8.2 d, 7.6 d | — | — |
| *XIa* | 8.4 s | 10.9 s | 8.2—7.3 m | 4.2 q | 1.3 t |
| *XIb* | 8.6 s | 11.3 s | 8.4—7.3 m | — | — |
| *XII* | 8.4 s | 9 | 8.1—7.1 m | 4.1 q | 1.2 t |
| *XIII* | 8.3 s | 9 | 7.9—7.1 m | 4.2 q | 1.3 t |

*a*) The N—H signal was not observed at 0—12 ppm.
s — singlet, d — doublet, t — triplet, q — quadruplet, m — multiplet.

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