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Synthesis of *N*-Allyl- and *N*-Acyl-2-vinylindoline

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Abstract—Heating a mixture of (2*R**,3*R**)- and (2*R**,3*S**)-2-[(1*S**)-1-iodoethyl]-3,5-dimethyl-1-[(2-nitrophenyl)sulfonyl]indolines with *N*-isopropylpiperidine in xylene resulted in (2*S**,3*R**)-3,5-dimethyl-1-[(2-nitrophenyl)sulfonyl]-2-vinylindoline. The latter reacted with thiophenol to afford (2*S**,3*R**)-3,5-dimethyl-2-vinylindoline, whose reaction with allyl halides or acetyl bromide gave rise to *N*-allyl-, *N*-propenyl-, or *N*-acetyl derivatives. Nitration of 1-acetyl-3,5-dimethyl-2-vinylindoline yielded *ortho*-nitro derivative.

Keywords: 2-vinylindoline, elimination, acylation

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2-Vinylindole derivatives have drawn considerable attention [1–5] due to their wide use as intermediates in the synthesis of some alkaloids [6–8], carbazoles of various hydrogenation degree [9–17] or pyrrolo[1,2-*a*]-indoles [6, 7].

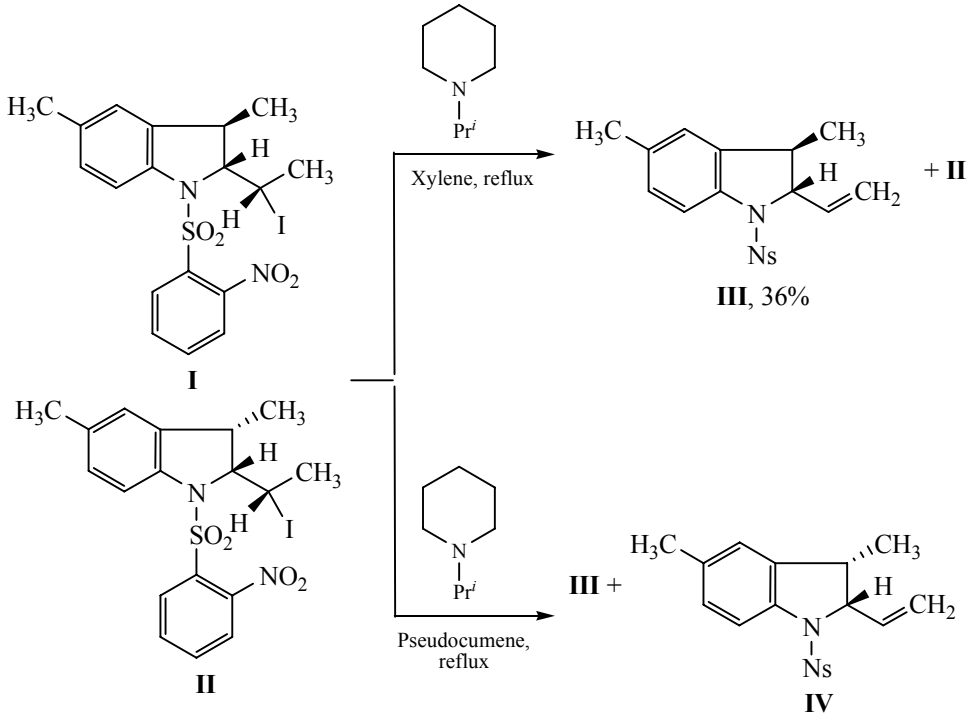
Vinylindolines and their dehydrogenated analogs can be obtained by various methods. For example, 2-vinylindoline derivatives have been synthesized by reacting conjugated dienes with a 2-haloanilines [13, 18] and by oxidative cyclization of 2-alkenylanilines under metal complex catalysis [19–21]. Vinylindoles have been prepared by Wittig methylenation of 2-indolylcarbaldehyde [7, 22] and Hofmann elimination of *N*-[2-(2-indolyl)ethyl-*N*,*N*,*N*-trimethylammonium quaternary salts in the presence of wet silver oxide [1].

This work presents the results of our studies on the synthesis of 2-vinylindolines starting from *ortho*-alkenylanilines. We have already made some attempts to obtain compounds of this series via dehydrohalogenation of 2-(1'-iodoethyl)-substituted indolines *N*-arylsulfonates by heating in an amine base [23]. Despite the fact that 2-vinylindoline *N*-tosylates can be isolated only by fractional recrystallization of the reaction products, further removal of tosyl group is a challenging task. Aiming to select more easily removable group, we continued research in this direction.

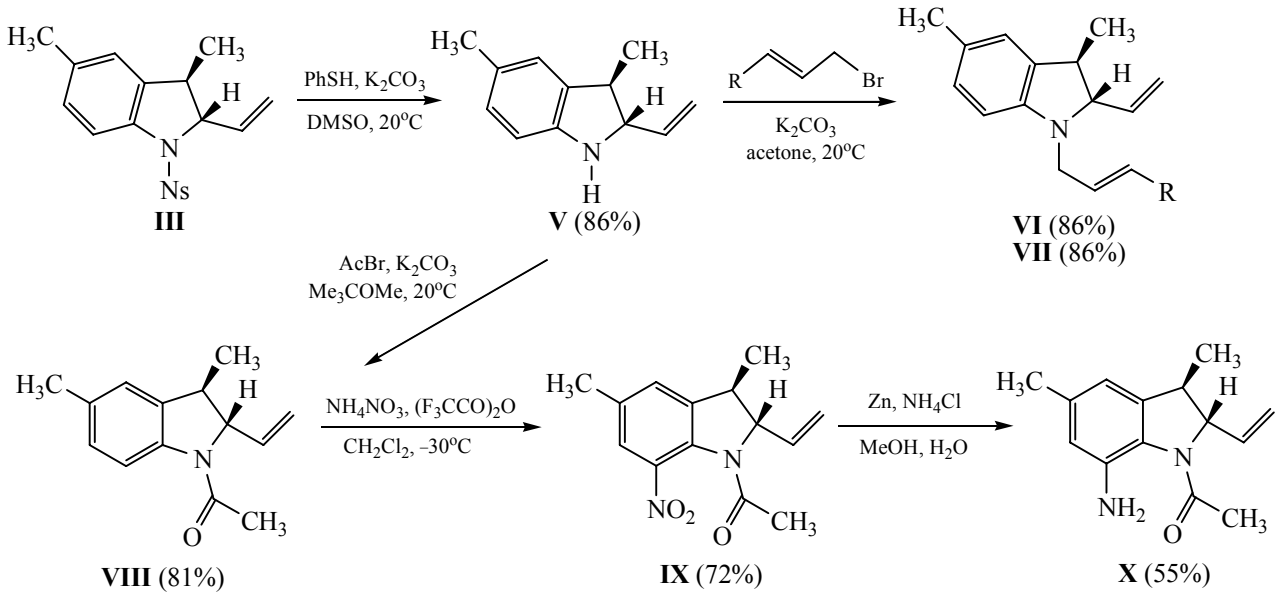
Previously it was shown that the heterocycles **I** and **II** resulting from iodocyclization cannot be separated by recrystallization; they were isolated as 4 : 1 mixture [23]. Therefore, we investigated of the mixture of these compounds. We found that the rate of dehydrohalogenation of isomers **I** and **II** depends on the temperature. Refluxing a mixture of heterocycles **I** and **II** in xylene leads to the reaction of only *trans*-indoline **I** resulting in *trans*-2-vinylindoline **III** with a yield of 36%. Prolonged boiling of the mixture of **I** and **II** in pseudocumene in the presence of 4 eq of *N*-isopropylpiperidine resulted in *trans*- and *cis*-vinylindolines **III**, **IV** in a ratio of ~ 4 : 1 (see Scheme 1). Probably, it is due to the steric factor. We assumed that different orientation of the methyl and iodoethyl fragments does not prevent such mutual arrangement of the molecules of **I** and amine relative to each other as is required for dehydroiodination; whereas *cis*-orientation of these substituents and spatial orientation of iodine atoms and methyl group create probably some difficulties for dehydroiodination process. Perhaps this obstacle is overcome when the temperature rises by another 15–20°C, which is impossible in the case of xylene.

Since compounds **I** and **II** cannot be separated by the column chromatography, we assumed that their refluxing in xylene in the presence of an amine to from vinyl derivative **III** and halogen derivative **II** allows us to facilitate this task. Therefore, the heating time was increased to 20 h. However we failed to isolate isomer **II** in pure form, since it was eluted together with the

Scheme 1.



Scheme 2.



R = H (**VI**), Me (**VII**).

isomer **I** when chromatographed. Vinylindoline **III** can be obtained in pure form by column chromatography and subsequent recrystallization from ethanol.

The removal of nitrophenylsulfonyl group was carried out by stirring compound **III** with thiophenol in DMSO in the presence of K_2CO_3. The reaction of indoline **V** [23] with allyl or crotyl bromide in the presence of K_2CO_3 afforded the corresponding *N*-alkenyl derivatives **VI** or **VII**. The acylation of indoline **V** with acetyl bromide gave rise to compound **VIII** [21]. The nitration of indoline **VIII** with trifluoroacetyl nitrate under mild conditions yielded nitro derivative **IX**. The reduction of the latter with

zinc in the presence of ammonium chloride in methanol resulted in amine **X**. Relative orientation of the methyl and vinyl groups in the five-membered ring was established by NOESY NMR experiments (see Scheme 2).

In summary, we found dependence of elimination of (2*R**,3*R**)- and (2*R**,3*S**)-2-[(1*S**)-1-iodoethyl]-3,5-dimethyl-1-[(2-nitrophenyl)sulfonyl]indulines on the spatial orientation of the substituents at the nitrogen-containing ring and the boiling point of the solvent. New 2-vinylindoline derivatives were obtained.

EXPERIMENTAL

IR spectra were recorded on an IRPrestige-21 Shimadzu Fourier-spectrophotometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker AM-300 spectrometer operating at 300.13 and 75.47 MHz, respectively. Mass spectrum of compound **X** was obtained on a Therm-Finnigan MAT 95 XP instrument using direct input mode under standard conditions. Elemental analysis was performed on a CHNS Elemental Analyzer EURO EA-3000. Column chromato-graphy was performed on silica gel Lankaster LS (40/100 μ). TLC analysis was carried out using Sorbfil PTLC-AF-B plates (Sorbpolimer, Krasnodar) detecting with iodine vapors.

(2*R,3*S**)-3,5-Dimethyl-1-[(2-nitrophenyl)sulfonyl]-2-vinylindoline (III).** A mixture of isomers **I** and **II** (2.58 g, 5.3 mmol) and 3.2 mL (21.2 mmol) of isopropylpiperidine in 11 mL of xylene was refluxed for 20 h. After cooling to room temperature, 50 mL of xylene and 50 mL of 5% aqueous HCl were added to the mixture. Then the organic phase was separated, washed with water, and dried over $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column (benzene–petroleum ether, 1 : 4). The first fractions yielded 0.104 g of a mixture of isomers **I** and **II** in a ratio of ~1 : 2 (4%). Recrystallization of the subsequent fractions from ethanol gave 0.559 g (36%) of compound **III** as colorless crystals. R_f 0.7 (C_6H_6), mp 136°C (EtOH). Data of ^{1}H NMR spectra were identical to those described in [21]. Found, %: C 60.24; H 5.01; N 7.79; S 8.86. $C_{18}H_{18}N_2O_4S$. Calculated, %: C 60.32; H 5.06; N 7.82; S 8.95.

(2*R,3*S**)-3,5-Dimethyl-2-vinylindoline (V).** To a suspension of 0.647 g (1.807 mmol) of compound **III** and 1.243 g (9.035 mmol, 5.00 eq) of K_2CO_3 in 2.5 mL of DMSO was added 0.542 mL (5.403 mmol, 3.00 equiv) of thiophenol. After stirring at room temperature for 4 h, 20 mL of petroleum ether and 7 mL of water were added to the reaction mixture. The organic layer was separated and dried over $MgSO_4$. Then the solvent was evaporated, and the residue was chromatographed on a silica gel column (benzene–petroleum ether, 1 : 4). The first fraction yielded 0.384 g of 1-nitro-2-(phenylsulfanyl)benzene. In the subsequent fractions 0.267 g (86%) of compound **V** was obtained as a light-brown liquid. Spectral characteristics were identical to the data in [23].

(2*R,3*S**)-1-[(2*E*)-But-2-en-1-yl]-3,5-dimethyl-2-vinylindoline (VII).** To a suspension of 0.220 g (1.3 mmol) of compound **V** and 0.439 g (3.18 mmol) of K_2CO_3 in 5 mL of acetone was added 0.181 g (1.34 mmol) of crotyl bromide. The reaction progress was monitored by TLC (eluent benzene). When **V** was consumed, the residue was filtered off and washed with petroleum ether. After the solvent removal, the filtrate was chromatographed on a short column filled with silica gel (eluent diethyl ether). Yield 0.177 g (61%), R_f 0.7 (C_6H_6). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 d (3H, CH_3, *J* 6.7 Hz), 1.70 d.d (3H, CH_3, *J* 0.7, 6.5 Hz), 2.28 s (3H, CH_3), 2.91 d. q (1H, H^3, *J* 6.7, 10.5 Hz), 3.42 d.d (1H, H^2, *J* 8.5, 10.5 Hz), 3.47 d.d (1H, $H^{1"A}$, *J* 7.6, J_{gem} 15.9 Hz), 3.78 d.d. q (1H, $H^{1"B}$, J_{gem} 15.5, *J* 3.0, 1.5 Hz), 5.25 d.d (1H, $H^{2'A}$, *J* 2.0, 8.0 Hz), 5.28 d.d (1H, $H^{2'B}$, *J* 2.0, 16.5 Hz), 5.44–5.49 m (1H, $H^{2"}$), 5.63 d. q (1H, $H^{3"}$, *J* 6.5, 15.2 Hz), 5.87 d.d.d (1H, $H^{1'}$, *J* 8.5, 10.5, 16.5 Hz), 6.41 d ($1H_{arom}$, *J* 7.9 Hz), 6.82 s (1H, H^4), 6.85 d ($1H_{arom}$, *J* 7.9 Hz). Found, %: C 84.41; H 9.25; N 5.98. $C_{16}H_{21}N$. Calculated, %: C 84.53; H 9.31; N 6.16.

(2*R,3*S**)-1-Acetyl-3,5-dimethyl-2-vinylindoline (VIII).** To a suspension of 0.17 g (1 mmol) of indoline **V** and 0.28 g (2 mmol) of K_2CO_3 in 5 mL of $CHCl_3$ was added at stirring dropwise 0.16 g (1.3 mmol) of acetyl bromide. The reaction progress was monitored by TLC (eluent benzene). After the reaction completion 5 mL of water was added to the mixture. After stirring for 30 min the mixture was extracted with 50 mL of $CHCl_3$. The organic layer was dried over $MgSO_4$. Then the solvent was removed, and the residue was chromatographed on silica gel (eluent benzene). Yield 0.19 g (88%). Physicochemical characteristics were identical to those described in [21].

(2*R,3*S**)-1-Acetyl-3,5-dimethyl-7-nitro-2-vinylindoline (IX).** To a solution of 0.226 g (1.24 mmol) of compound **VIII** in 1 mL of CH_2Cl_2 at –30°C was added triftoracetyl nitrate [prepared by stirring 0.48 g (6 mmol) of NH_4NO_3 and 4.3 g (20.4 mmol) of

trifluoroacetic anhydride in 1 mL of CH_2Cl_2]. After 1 h, the reaction mixture was poured into ice (20 g) and extracted with 50 mL of CH_2Cl_2. The organic layer was washed with water (10 mL) and dried over Na_2SO_4. After the solvent removal the residue was chromatographed on a silica gel column (eluent C_6H_6). Yield 0.234 g (72%), yellow viscous liquid, R_f 0.45 (C_6H_6–EtOAc, 8 : 1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.35 d (3H, CH_3, *J* 7.2 Hz), 2.20 s (3H, CH_3), 2.39 s (3H, CH_3), 3.02 q (1H, H^3, *J* 7.2 Hz), 4.51 d. t (1H, H^2, *J* 1.5, 2.7 Hz), 5.20 d (1H, $H^{2'A}$, *J* 10.1 Hz), 5.49 d (1H, $H^{2'B}$, *J* 17.1 Hz), 5.87 d.d.d (1H, $H^{1'}$, *J* 4.4, 10.1, 17.1 Hz), 7.17 s (1H_{arom}), 7.48 s (1H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.65, 21.26, 21.94 ($3CH_3$), 42.94 (C^3), 70.72 (C^2), 115.42 ($C^{2'}$), 122.71, 129.03, 135.11 ($C^{1'}$, C^4, C^6), 130.65, 134.97, 140.17, 140.43 (C^{3a}, C^5, C^7, C^{7a}), 167.96 (C=O). Found, %: C 65.41; H 6.14; N 10.69. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.60; H 6.20; N 10.76.

(2*R,3*S**)-7-Amino-1-acetyl-3,5-dimethyl-2-vinylindoline (X).** To a solution of 0.211 g (0.81 mmol) of compound **IX** in 5 mL of MeOH was added a solution of 0.045 g (0.83 mmol) of NH_4Cl in 1.5 mL of water. Then 0.26 g (4.05 mmol) of zinc dust was added in portions with vigorous stirring. The reaction progress was monitored by TLC (C_6H_6–EtOAc, 8:1). The precipitate was filtered off and washed with methyl *tert*-butyl ether (30 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated in a vacuum, and the residue was chromatographed on silica gel (eluent – C_6H_6). Yield 0.102 g (55%), R_f 0.4 (C_6H_6–EtOAc, 4 : 1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 d (3H, CH_3, *J* 7.0 Hz), 2.14 s (3H, CH_3), 2.16 s (3H, CH_3), 2.74 q (1H, H^3, *J* 7.0 Hz), 4.22 d.d (1H, H^2, *J* 0.9, 6.0 Hz), 4.60 br.s (2H, NH_2), 5.02 d. t (1H, $H^{2'A}$, *J* 10.1, 1.0 Hz), 5.10 d. t (1H, $H^{2'B}$, *J* 17.0, 1.0 Hz), 5.70 d.d.d (1H, $H^{1'}$, *J* 6.0, 10.1, 17.0 Hz), 6.27 s (1H_{arom}), 6.29 s (1H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.80, 21.12, 21.48 ($3CH_3$), 43.23 (C^3), 72.20 (C^2), 115.52 ($C^{2'}$), 118.19 (C^6), 125.65 (C^{7a}), 125.86 (C^4), 135.74 ($C^{1'}$), 129.63, 136.64, 138.74 (C^{3a}, C^5, C^7), 168.04 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 230.1 $[M]^+$ (100), 187.1 $[M - CH_3CO]^+$ (45). Found, %: C 72.92; H 7.84; N 12.08. $C_{14}H_{18}N_2O$. Calculated, %: C 73.01; H 7.88; N 12.16.

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