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REACTIONS OF 4-UNSUBSTITUTED 4,5-DIHYDRO-1H-INDENO[1,2-*b*]PYRIDINES

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Alkylation of 3-methoxycarbonyl-2-methyl-5-oxo-4,5-dihydro-1H-indeno[1,2-b]pyridine and 12-oxo-12,13-dihydro-7H-7azaindeno[1,2-b]phenanthrene using methyl iodide or allyl bromide in DMF solution in the presence of NaH occurs with high selectivity and gives the corresponding C-alkyl derivatives in high yield. The acid cleavage of the 4a-alkylated 3-methoxycarbonyl-2-methyl-5-oxo-4a,5-dihydroindeno[1,2-b]pyridines has been studied.

Keywords: 12,13- and 12,12a-dihydro-7-azaindenophenanthrenes, 4,5- and 4a,5-dihydroindeno-pyridines.

We have previously shown [1] that alkylation of 4-aryl-4,5-dihydro-1H-indeno[1,2-*b*]pyridines in the anionic form using dimethyl sulfate or methyl *p*-toluenesulfonate gives the N-methyl derivatives exclusively while the reaction with methyl iodide shows a dual nature and gives a mixture of the N- and C-methyl products. When allyl and propargyl bromides or ethyl bromoacetate are used as alkylating agents in an aprotic medium in the presence of NaH a high selectivity is shown towards C-alkylation [2]. These results agree well with principles of hard and soft acids and bases. Mild alkylating agents (including reagents containing readily polarizable multiple bonds) react principally at the C-4a atom, i.e. the softer center of the ambident anion.

In this work we consider the alkylation reactions and acid cleavage of derivatives unsubstituted at atom C-4 in 5-oxodihydroindeno[1,2-*b*]pyridine **1** and the analogous indeno[1,2-*b*]phenanthrenone **2**.

Alkylation of compounds **1** and **2** using methyl iodide in DMF solution in the presence of NaH occurred with highly selective C-alkylation and the methyl derivatives **3a** and **5a** were obtained in 69 and 96% yield respectively. The N-methyl derivatives **4a** and **6a** formed upon alkylation were separated in 6 and about 1% yield respectively from the reaction mixture.

We have previously used KOH [1] instead of NaH for formation of the dihydropyridine anion but Na^+ binds more strongly at the hard reaction center and this shields the nitrogen atom. However, the ratio of C- and N-methyl derivatives (~ 10:1) in the case of the 4-unsubstituted indenopyridine **1** is clearly greater than in the alkylation of 4-phenylindenopyridine for which the ratio of C- and N-methylation products is 2.2:1. Evidently the absence of a substituent at atom C-4 allows formation of the 4a-methyl derivative **3a**. The high selectivity towards C-alkylation was also confirmed in the synthesis of the C-allyl derivatives **3b** and **5b** (71 and 86% yield respectively). The yield of the corresponding N-allyl derivatives **4b** and **6b** is 13 and 4.3%.

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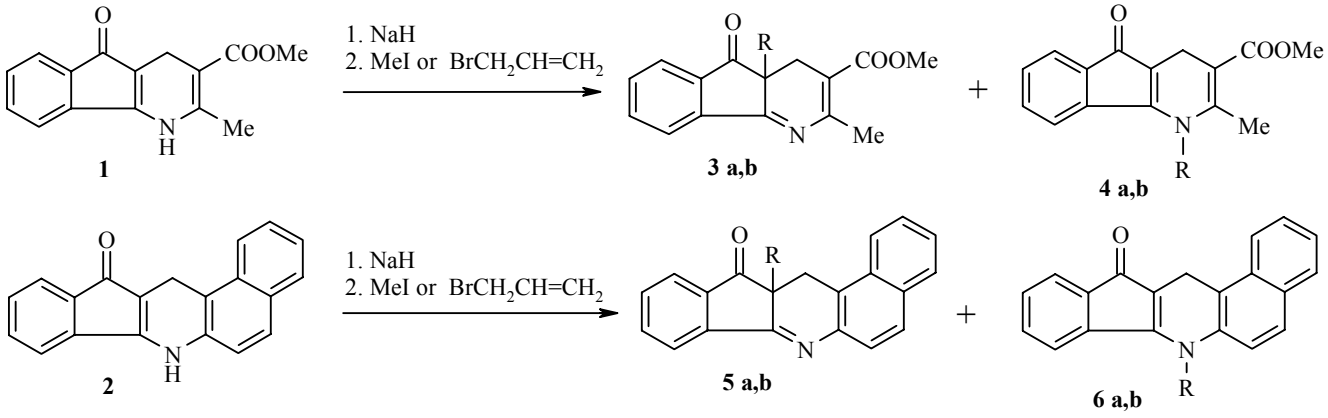
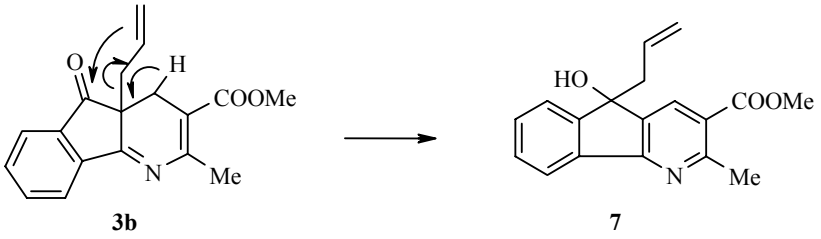
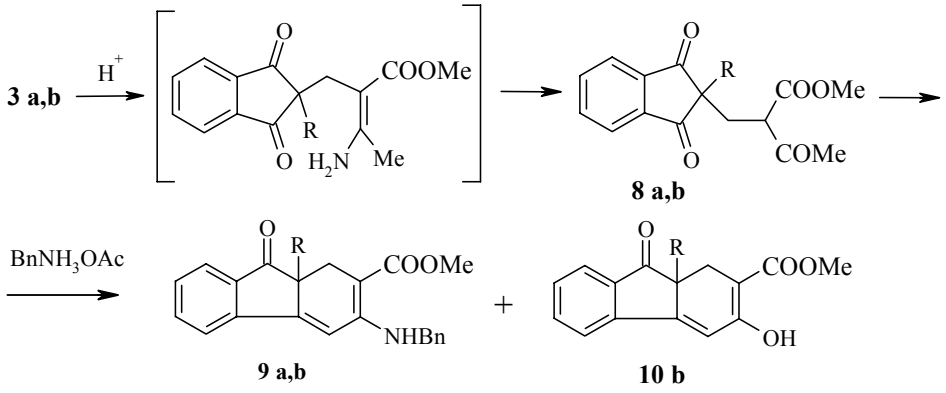


3–6 a R = Me, **b** R = $CH_2CH{=}CH_2$

It is interesting to note that allylation of the dihydroindenopyridine **1** gave an unexpected side product, i.e. the 5-allyl derivative of indenopyridine **7**. It can be assumed that compound **7** is the result of a rearrangement of the allyl derivative **3b** but the mechanism of the reaction is unknown.



Due to the rather slow reaction rate there also occurs a side oxidation reaction of the alkylated anion involving atmospheric oxygen, hence it has to be carried out in an inert atmosphere.



8–10 a R = Me, **b** R = $CH_2CH{=}CH_2$

According to [3, 4] the 4a-substituted 4-phenyldihydroindenopyridines undergo acid cleavage and as a result of an intramolecular condensation give fluorenone derivatives but this was not observed in the case of the 4-unsubstituted indenopyridines **3a,b**. The products of acid hydrolysis of the 4a-alkyl derivatives of the 4-unsubstituted dihydroindenopyridines **3a,b** are the α-acetyl-β-(1,3-dioxo-2,3-dihydro-1H-inden-2-yl)propionic acid derivatives **8a,b**. However, it was interesting to note that the reactions of these 2,2-dialkyl-substituted 1,3-indanediones with benzylamine acetate give fluorenone derivatives. The main cyclization products are the 3-benzylamino derivatives **9a** and **9b** with the 3-hydroxyfluorenone **10b** as a by-product.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury-200 (200 MHz) instrument using $CDCl_3$ (compounds **3a,b-6a,b, 7, 8a,b, 9a,b** and **10b**) or DMSO-d_6 (compounds **1** and **2**) with TMS as internal standard. Mass spectra were taken on an HP 6890 GCMS chromato-mass spectrometer with ionization energy 70 eV. Acros Kieselgel grade silica gel (0.035-0.070 mm) was used for preparative column chromatography.

3-Methoxycarbonyl-2-methyl-5-oxo-4,5-dihydro-1H-indeno[1,2-*b*]pyridine (1) was prepared by analogy with [5]. Yield 27%; mp 265-267ºC (AcOH). ^{1}H NMR spectrum, δ, ppm: 2.30 (3H, s, CH_3); 3.10 (2H, s, 4-CH_2); 3.63 (3H, s, OCH_3); 7.28-7.55 (4H, m, C_6H_4); 9.76 (1H, br. s, NH). Found, %: C 70.42; H 5.01; N 5.28. $C_{15}H_{13}NO_3$. Calculated, %: C 70.58; H 5.13; N 5.49.

12-Oxo-12,13-dihydro-7-aza-7H-indeno[1,2-*b*]phenanthrene (2). A mixture of 2-naphthylamine (6.00 g, 42 mmol) and paraformaldehyde (1.26 g, 42 mmol) in ethanol (75 ml) was heated to reflux and a solution of indane-1,3-dione (6.10 g, 42 mmol) in ethanol (75 ml) was added. The reaction mixture was cooled and the precipitate filtered off and recrystallized from acetic acid. Mp 258-264ºC. Yield 5.64 g (47%). ^{1}H NMR spectrum, δ, ppm: 3.92 (2H, s, 13-CH_2); 7.29-7.92 (10H, m, Ar); 9.40 (1H, br. s, NH). Found, %: C 84.30; H 4.50; N 4.73. $C_{20}H_{13}NO$. Calculated, %: C 84.78; H 4.62; N 4.94.

Reaction of Methyl 2-Methyl-5-oxo-4,5-dihydro-1H-indeno[1,2-*b*]pyridine-3-carboxylate with Methyl Iodide (General Method). Starting compound **1** (1.50 g, 5.88 mmol) was dissolved with stirring in DMF (80 ml) under an argon atmosphere and NaH (0.28 g, 1.2 eq., 7.06 mmol) as a 60% suspension in oil was added. When evolution of hydrogen had ceased methyl iodide (0.73 ml, 11.76 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. Solvent was evaporated and the residue was column chromatographed using hexane–acetone (4:1) as eluent. The following fractions were separated:

3-Methoxycarbonyl-2-methyl-5-oxoindeno[1,2-*b*]pyridine. Yield 0.10 g (6.8%); mp 185ºC. ^{1}H NMR spectrum, δ, ppm: 2.96 (3H, s, CH_3); 3.94 (3H, s OCH_3); 7.43-7.96 (4H, m, Ar); 8.4 (1H, s, 4-CH). Found, %: C 70.60; H 4.21; N 5.40. $C_{15}H_{11}NO_3$. Calculated, %: C 71.14; H 4.38; N 5.53.

3-Methoxycarbonyl-2,4a-dimethyl-5-oxo-4a,5-dihydro-4H-indeno[1,2-*b*]pyridine (3a). Yield 1.10 g (69%); mp 165-170ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (3H, s, 4a-CH_3); 2.25 (1H, dd, *J* = 17.7 and *J* = 2.7, 4-CH_2); 2.50 (3H, dd, *J* = 1.0 and *J* = 2.7, CH_3); 2.98 (1H, dd, *J* = 17.7 and *J* = 1.0, 4-CH_2); 3.80 (3H, s, OCH_3); 7.61-8.07 (4H, m, Ar). Found, %: C 71.89; H 5.08; N 5.22. $C_{16}H_{15}NO_3$. Calculated, %: C 71.36; H 5.61; N 5.20.

3-Methoxycarbonyl-1,2-dimethyl-5-oxo-4,5-dihydroindeno[1,2-*b*]pyridine (4a). Yield 0.10 g (6.3%), red oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.42 (3H, t, *J* = 1.1, CH_3); 3.20 (2H, br. s, CH_2); 3.54 (3H, s, N–CH_3); 3.69 (3H, s, OCH_3); 7.17-7.46 (4H, m, Ar).

Reaction of Methyl 2-Methyl-5-oxo-4,5-dihydro-1H-indeno[1,2-*b*]pyridine-3-carboxylate with Allyl Bromide. Similarly to the above from the indenopyridine **1** (2.0 g, 7.8 mmol), NaH (0.37 g, 9.3 mmol), and allyl bromide (1.35 ml, 15.6 mmol) in DMF (80 ml) to give compounds **3b**, **4b** and **7**.

4a-Allyl-3-methoxycarbonyl-2-methyl-5-oxo-4a,5-dihydro-4H-indeno[1,2-*b*]pyridine (3b). Yield 1.64 g (71%); mp 78-80ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.22 (1H, dd, *J* = 2.6 and *J* = 18.0, 4-CH_2); 2.32 (2H, d, *J* = 7.5, C$\underline{H_2}$–CH=); 2.57 (3H, dd, *J* = 1.1 and *J* = 2.6, CH_3); 3.10 (1H, dd *J* = 1.1 and *J* = 18.0, 4-CH_2); 3.79 (3H, s, OCH_3); 4.88-5.00 (2H, m, –CH=C$\underline{H_2}$); 5.49 (1H, m, –C$\underline{H}$=CH_2); 6.66-8.12 (4H, m, Ar). Found, %: C 73.16; H 5.80; N 4.59. $C_{18}H_{17}NO_3$. Calculated, %: C 73.20; H 5.80; N 4.74.

1-Allyl-3-methoxycarbonyl-2-methyl-5-oxo-4,5-dihydroindeno[1,2-*b*]pyridine (4b). Yield 0.13 g (13%), red oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.57 (3H, s, CH_3); 2.21 (1H, d, *J* = 14.6, 4-CH_2); 2.92 (1H, d, *J* = 14.6, 4-CH_2); 3.81 (3H, s, OCH_3); 3.92 (2H, m, C$\underline{H_2}$–CH=); 5.10-5.25 (2H, m, –CH=C$\underline{H_2}$); 5.96-6.20 (1H, m, –C$\underline{H}$=CH_2); 7.48-7.86 (4H, m, Ar).

5-Allyl-5-hydroxy-2-methoxycarbonylindeno[1,2-*b*]pyridine (7). Yield 0.36 g (15%); mp 160ºC. ^{1}H NMR spectrum, δ, ppm: 1.60 (1H, br. s, OH); 2.70-2.96 (2H, m, C$\underline{H_2}$–CH=); 2.82 (3H, s, CH_3); 3.93 (3H, s, OCH_3); 4.90-5.05 (2H, m, CH=C$\underline{H_2}$); 5.45-5.70 (1H, m, CH_2–C$\underline{H}$=); 7.36-7.88 (4H, m, Ar); 8.23 (1H, s, 4-CH). Found, %: C 72.76; H 5.69; N 4.61. $C_{18}H_{17}NO_3$. Calculated, %: C 73.20; H 5.80; N 4.74.

Reaction of 12-Oxo-12,13-dihydro-7H-7-azaindeno[1,2-*b*]phenanthrene with Methyl Iodide. From the phenanthrene **2** (2.0 g, 7.0 mmol), NaH (0.33 g, 8.4 mmol), and methyl iodide (0.87 ml, 14 mmol) in DMF (80 ml) by analogy with the reaction of indenopyridine **1** to give compounds **5a, 6a**.

12a-Methyl-12-oxo-12,12a-dihydro-13H-7-azaindeno[1,2-*b*]phenanthrene (5a). Yield 2.00 g (96%); mp 148-149ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, s, CH_3); 2.95 (1H, d, *J* = 16.6, 4-CH_2); 3.73 (1H, d, *J* = 16.6, 4-CH_2); 7.43-8.42 (10H, m, Ar). Found, %: C 84.89; H 5.00; N 4.69. $C_{21}H_{15}NO$. Calculated, %: C 84.82; H 5.08; N 4.71.

7-Methyl-12-oxo-12,13-dihydro-7-azaindeno[1,2-*b*]phenanthrene (6a). Yield 0.01 g (0.48%); mp 243-247ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.31 (3H, s, CH_3); 3.85 (1H, d, *J* = 10.1, 4-CH_2); 4.02 (1H, d, *J* = 10.1, 4-CH_2); 7.26-9.19 (10H, m, Ar).

Reaction of 12-Oxo-12,13-dihydro-7H-7-azaindeno[1,2-*b*]phenanthrene with Allyl Bromide. From the starting material **2** (1.38 g, 4.8 mmol), NaH (0.2 g, 5.0 mmol) and allyl bromide (0.83 ml, 9.6 mmol) in DMF (70 ml) similarly to the preparation and separation of compounds **5b, 6b**.

12a-Allyl-12-oxo-12,12a-dihydro-13H-indeno[1,2-*b*]phenanthrene (5b). Yield 1.33 g (86%); mp 112-114ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (2H, d, *J* = 7.3, C$\underline{H_2}$–CH=); 2.87 (1H, d, *J* = 16.8, 4-CH_2); 3.83 (1H, d, *J* = 16.8, 4-CH_2); 4.66-4.93 (2H, m, –CH=C$\underline{H_2}$); 5.40-5.65 (1H, m, CH_2–C$\underline{H}$=); 7.42-8.30 (10H, m, Ar). Found, %: C 85.46; H 5.27; N 4.32. $C_{23}H_{17}NO$. Calculated, %: C 85.42; H 5.30; N 4.33.

7-Allyl-12-oxo-12,13-dihydro-7-azaindeno[1,2-*b*]phenanthrene (6b). Yield 0.06 g (4.3%), red oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.10 (2H, s, 4-CH_2); 4.79-4.85 (2H, m, C$\underline{H_2}$–CH=); 5.37-5.53 (2H, m, CH=C$\underline{H_2}$); 6.11-6.31 (1H, m, CH_2–C$\underline{H}$=); 7.23-8.00 (10H, m, Ar).

Methyl α-Acetyl-β-(2-methyl-1,3-dioxo-2,3-dihydro-1H-inden-2-yl)propionate (8a). A suspension of indenopyridine **3a** (0.36 g, 1.3 mmol) in 80% ethanol (75 ml) and 0.1 M HCl (0.6 ml, 15 eq.) was refluxed for 5 h. The reaction mixture was diluted with water (40 ml), extracted with chloroform (3×40 ml), and dried over sodium sulphate. Solvent was evaporated off under reduced pressure and the residue was fractionated on a silica gel column using hexane–acetone (4:1) as eluent. Yield 0.33 g (90%); mp 96-98ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, s, CH_3); 2.20 (3H, s, $COCH_3$); 2.35 (1H, d, *J* = 6.4; CH_2); 2.40 (1H, d, *J* = 6.4, CH_2); 3.63 (3H, s, $COOCH_3$); 3.69 (1H, t, *J* = 6.4, CH); 7.83-8.00 (4H, m, Ar).

Methyl α-Acetyl-β-(2-allyl-1,3-dioxo-2,3-dihydro-1H-inden-2-yl)propionate (8b). The starting material **3b** (1.31 g, 4.4 mmol) was dissolved in glacial acetic acid (40 ml), conc. H_2SO_4 (4 ml) was added, and the product was stirred at room temperature for 2 days. It was then diluted with water (50 ml), neutralized with sodium carbonate (pH 8), and extracted with ethyl acetate (3×100 ml). The extract was dried over sodium sulphate, solvent was evaporated at reduced pressure, and the residue was fractionated on a silica gel chromatographic column using hexane–acetone (4:1) as eluent. Yield of product **8b** 1.06 g (77%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.14 (3H, s, $COCH_3$); 2.31 (1H, dd, *J* = 6.8 and *J* = 14.8, CH_2); 2.38 (1H, dd, *J* = 6.1 and *J* = 14.8, CH_2); 2.48 (1H, ddd, *J* = 2.9, 7.4 and *J* = 13.4, C$\underline{H_2}$–CH=); 2.51 (1H, ddd, *J* = 1.2, 7.4, and *J* = 13.4, C$\underline{H_2}$–CH=); 3.58 (3H, s, OCH_3); 3.61 (1H, dd, *J* = 6.8 and *J* = 6.1, CH); 4.87 (1H, dt, *J* = 1.2 and *J* = 10.0, CH=C$\underline{H_2}$); 4.99 (1H, ddd, *J* = 1.2, *J* = 3.0, and *J* =16.9, CH=C$\underline{H_2}$); 5.40 (1H, ddt, *J* = 7.4, *J* = 10.0, and *J* =16.9, CH_2–C$\underline{H}$=); 7.76-7.95 (4H, m, Ar).

3-(Benzylamino)-2-methoxycarbonyl-9a-methyl-9-oxo-9,9a-dihydro-1H-fluorene (9a). Benzylamine acetate (0.33 g, 2 mmol) was added to a solution of compound **8a** (0.05 g, 0.17 mmol) in glacial acetic acid (20 ml). The product was stirred for 6 h at 50ºC, diluted with water (40 ml), and extracted with dichloromethane (3×40 ml). The extract was dried over sodium sulphate, solvent was evaporated under reduced pressure, and the residue was fractionated on a silica gel chromatography column using hexane–acetone (4:1) as eluent. Yield of **9a** 0.04 g (66%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, s, CH_3); 2.26 (1H, d, *J* = 15.9, 1-CH_2); 3.02 (1H, d, *J* = 15.9, 1-CH_2); 3.73 (3H, s, OCH_3); 4.60 (2H, d, *J* = 6.2, NH–C$\underline{H_2}$–Ph); 6.62 (1H, s, 4-CH); 7.28-7.90 (9H, m, Ar); 9.27 (1H, br. t, *J* = 6.2, NH).

Reaction of Methyl α-Acetyl-β-(2-allyl-1,3-dioxo-2,3-dihydro-1H-inden-2-yl)propionate with Benzylamine Acetate. A solution of compound **8b** (0.62 g, 1.9 mmol) and benzylamine acetate (0.33 g, 2 mmol) was stirred at 50ºC in glacial acetic acid (20 ml) for 6 h. The reaction mixture was diluted with water (40 ml), extracted with dichloromethane (3×40 ml), and dried over sodium sulphate. Solvent was evaporated and the residue was fractionated as in the preceding example to give compounds **10b** and **9b** as low melting solids.

Methyl 9a-Allyl-3-hydroxy-9-oxo-9,9a-dihydro-1H-fluorene-2-carboxylate (10b). Yield 0.02 g (3.5%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (1H, d, *J* = 16.4, 1-CH_2); 2.31-2.40 (2H, m, C$\underline{H}_2$–CH=); 3.03 (1H, d, *J* = 16.4, 1-CH_2); 3.82 (3H, s, OCH_3); 4.84-4.98 (2H, m, CH=C$\underline{H}_2$); 5.39-5.63 (1H, d, –C$\underline{H}$=CH_2); 6.51 (1H, s, 4-CH); 7.33-7.90 (4H, m, Ar); 12.17 (1H, s, OH).

Methyl 3-Benzylamino-9a-allyl-9-oxo-9,9a-dihydro-1H-fluorene-2-carboxylate (9b). Yield 0.27 g (37%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (1H, d, *J* = 16.1, 1-CH_2); 2.35 (2H, d, *J* = 7.4, C$\underline{H}_2$–CH=); 3.12 (1H, d, *J* = 16.1, 1-CH_2); 3.72 (3H, s, OCH_3); 4.60 (2H, d, *J* = 6.4, N–CH_2); 4.74-4.87 (2H, m, CH=C$\underline{H}_2$); 5.30-5.54 (1H, m, C$\underline{H}$=CH_2); 6.65 (1H, s, 4-CH); 7.20-7.80 (9H, m, Ar); 9.28 (1H, br. t, *J* = 6.4, NH). ESI-MS, *m/z*: 386 $[M+H]^+$.

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