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# SYNTHESIS OF 3,9,9,9a-TETRAMETHYL-1,2,3,9a-TETRAHYDRO-9H-IMIDAZO[1,2-*a*]-INDOL-2-ONES BY REACTION OF 2,3,3-TRIMETHYL-3H-INDOLE WITH 2-BROMOPROPIONAMIDES

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*Alkylation of 2,3,3-trimethyl-3H-indole with 2-bromopropionamide and the subsequent treatment of the formed 1-(1-carbamoylethyl)-2,3,3-trimethyl-3H-indolium bromide with a base afforded 3,9,9,9a-tetramethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-one. Condensation of the 1-(1-carbamoylethyl)-2,3,3-trimethyl-3H-indolium salt with 2-hydroxy-1-naphthaldehyde gave a mixture of diastereomeric 1-(1-carbamoylethyl)spiro[2H-indole-2,3'-[3H]naphtho[2,1-b]pyrans].*

**Keywords:** 2-bromopropionamide, imidazo[1,2-*a*]indole, spiro[2H-indole-2,3'-[3H]naphtho[2,1-*b*]-pyran], 2,3,3-trimethyl-3H-indole.

N-Alkylated derivatives of 2,3,3-trimethyl-3H-indole are useful starting materials for the synthesis of cyanine dyes and photochromic indolinobenzopyrans [1, 2]. The reaction of 2,3,3-trimethyl-3H-indole with such bifunctional reagents as α-haloacetamides and subsequent treatment of the formed 1-carbamoylmethyl-3H-indolium salts with a base leads to the formation of 1-carbamoylmethyl-3,3-dimethyl-2-methylene-2,3-dihydro-1H-indoles, which may then undergo cyclization to give 1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]indol-2-one derivatives [3]. It was found that the presence of such substituent as allyl or benzyl group at the amide nitrogen atom promotes nucleophilic addition of the mentioned nitrogen atom to the α-carbon of the indole nucleus, while phenyl substituent suppress imidazolidine ring closure [4]. 1-Carbamoylmethyl-3,3-dimethyl-2-methylene-2,3-dihydro-1H-indoles and their cyclic forms have found application in the preparation of photochromic indoline spiropyrans [5] and thermochromic styrylimidazo[1,2-*a*]indoles [6, 7]. It was found recently, that 1-(N-substituted carbamoylmethyl)indoline spiropyrans under influence of a strong base rearrange to pyrrolo[1,2-*a*]indole derivatives *via* short-living methylides [8, 9].

In the present work, we studied annelation of a five-membered lactam ring to the indole nucleus by the reaction of 2,3,3-trimethyl-3H-indole with 2-bromopropionamides.

Alkylation of indole **1a** with 2-bromopropionamide was carried out at 135°C in xylene. Treatment of the formed salt **2a** with a strong base gave 3,9,9,9a-tetramethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]indol-2-one **3a**.

The structure of compound **3a** was confirmed by means of NMR spectroscopy. Compound **3a** has two chiral centers at C-3 and C-9a. However, the $^1$H NMR spectrum shows only one set of proton signals, thus pointing to the formation of **3a** as a single diastereomer in a racemic form. In the $^1$H NMR spectrum three

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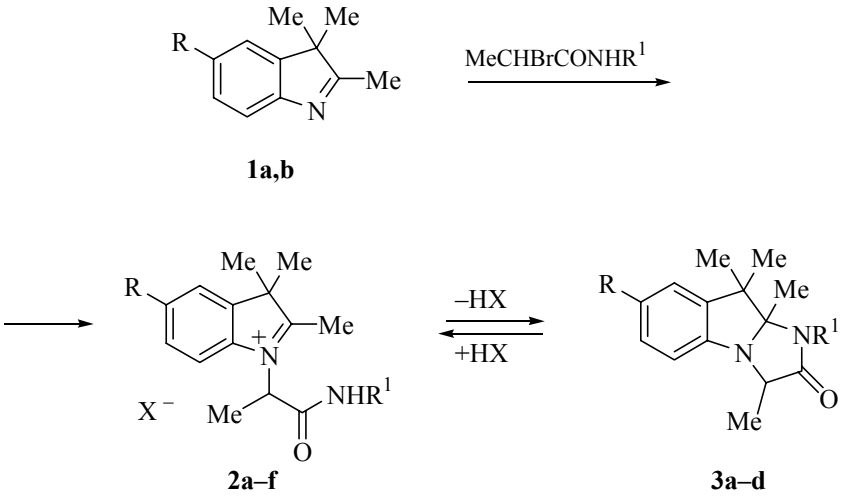
singlets of 10,10,10a-$CH_3$ groups are present in the 1.16-1.49 ppm region and a doublet of $CH_3$-3 group appears at 1.55 ppm ($J$ = 15.5 Hz). The $^{13}C$ NMR spectrum of **3a** contains the characteristic signals of annelated imidazolidinone ring skeleton carbons at 63.91 (C-3), 89.19 (C-9a), and 177.31 ppm (C=O). The absorption band at 1720 $cm^{-1}$ that is due to the carbonyl group and the band at the 3190 $cm^{-1}$ that corresponds to stretching vibrations of the N–H bond are observed in the IR spectrum of **3a**.




**1 a** R = H, **b** R = Me; **2 a** R = $R^1$ = H, **b** R = H, $R^1$ = Bn, **c** R = Me, $R^1$ = Bn, **d** R = H, $R^1$ = Ph, **e** R = $R^1$ = H, **f** R = Me, $R^1$ = Bn; **a-d** X = Br, **e**, **f** X = $ClO_4$; **3a** R = $R^1$ = H; **b** R = H, $R^1$ = Bn; **c** R = Me, $R^1$ = Bn; **d** R = H, $R^1$ = Ph

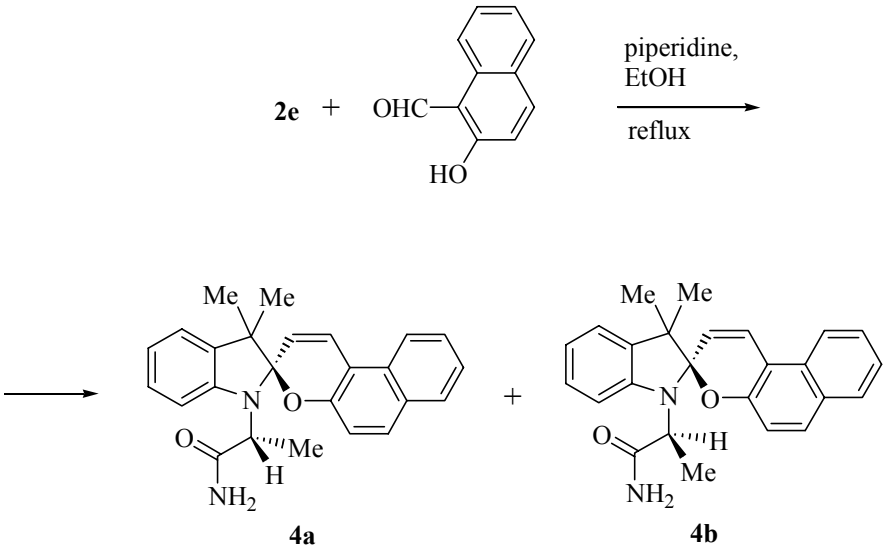
1-Benzyl-3,9,9,9a-tetramethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]indol-2-ones **3b**,**c** were obtained as single diastereomers from 3H-indoles **1a**,**b** and N-benzyl-2-bromopropionamide. The characteristic signal in the $^1H$ NMR spectra of the compounds **3b**,**c** is an AB-quadruplet of diastereotopic benzyl protons in the area of 4.06-5.10 ppm.

Reaction of 3H-indole **1a** with N-phenyl-2-bromopropionamide and the subsequent treatment of the reaction mixture with a base afforded 3,9,9,9a-tetramethyl-1-phenyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]-indol-2-one **3d** as the only isolable product. It has been shown earlier that a similar reaction of **1a** with N-phenyl-1-chloroacetamide gave 2-methylene-1-(N-phenylcarbamoyl)methyl-2,3-dihydro-1H-indole, which did not undergo further cyclization to imidazo[1,2-*a*]indole [4]. Therefore, it could be assumed that the presence of the methyl group instead of the hydrogen atom at the carbon atom located between indole ring nitrogen and carbonyl group of the salt **2d** facilitates ring closure. A similar effect of easy ring closure induced by *gem*-dialkyl groups, known as the Thorpe–Ingold effect, is explained by a significant entropy change when an open branched chain molecule transforms to a small or medium size cycle [10].

The structure of compound **3d** is confirmed by the presence of the signal of $sp^3$-hybridized α-carbon (C-9a) of the indole ring system at 91.51 ppm.

Opening of the imidazolidine ring occurred, and formation of 3H-indolium perchlorates **2e**,**f** took part, when compounds **3a**,**c** were treated with perchloric acid. The structure of perchlorate **2f** is proved by the presence in the $^1H$ NMR spectrum of the benzyl $CH_2$ group doublet at 4.25 ppm ($J$ = 6.8 Hz), and absorption bands in the IR spectrum at 3330 (N–H), 1685 (C=O) and 1550 $cm^{-1}$ (amide II) characteristic of the secondary amides.

Synthesis of diastereomeric indoline spiropyrans in a racemic form with chiral centers at C-2 and C-3 of the indole moiety was described in [11]. Coupling of (3*R*)-1,3-dimethyl-2-methylene-3-propylindoline with 5-nitro-salicylaldehyde afforded optically active diastereomeric (2*R*,3*R*)- and (2*S*,3*R*)-indoline spiropyrans, which demonstrated switchable optical activity [12].




Condensation of perchlorate **2e** with 2-hydroxy-1-naphthaldehyde in ethanol containing a catalytic amount of piperidine afforded a mixture of two diastereomeric 1-(1-carbamoyl)ethylindoline naphtho[2,1-*b*]-pyrans **4a**,**b** as racemates. Compounds **4a**,**b** possess chiral centers at C-2 of the indole ring system and C-1 of the N-(1-carbamoyl)ethyl side chain. $^{1}$H and $^{13}$C NMR spectra indicated a 3:2 ratio of the diastereomers in the mixture.

The $^{1}$H NMR spectrum of the mixture of **4a**,**b** contains overlapped doublets of H-2' at 5.74 ($J$ = 10.5 Hz) and 5.76 ppm ($J$ = 10.5 Hz) for the major and minor isomers, respectively. The signals of spiro atom C-2,3' at 104.35 (minor isomer) and 105.54 ppm (major isomer) in the $^{13}$C NMR spectrum of the mixture **4a**,**b** were identified by the DEPT method.

## EXPERIMENTAL

All melting points were determined with a Kleinfeld melting point apparatus and are uncorrected. $^{1}$H NMR spectra were recorded with JEOL FX-100 (100 MHz, compounds **3b**,**c**, **2e**,**f**) and Bruker ASW 300 instruments (300 MHz, $CDCl_3$, compounds **3a**,**d**, **4a**,**b**). $^{13}$C NMR spectra were obtained on a Bruker ASW 300 instrument (75 MHz, $CDCl_3$). Chemical shifts (ppm) are given relative to tetramethylsilane (TMS). IR spectra were recorded on a Perkin–Elmer Spectrum BXII spectrometer (KBr pellets). Mass spectra were recorded on a Waters ZQ 2000 spectrometer (ion spray). For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used.

**3,9,9,9a-Tetramethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]indol-2-one (3a).** A mixture of 2,3,3-trimethyl-3H-indole **1a** (1.99 g, 12.5 mmol) and 2-bromopropionamide (2.10 g, 13.8 mmol) was heated at 135°C for 12 h in an atmosphere of nitrogen. The reaction mixture was dissolved in 15 ml of acetone and poured into 150 ml of 5% hydrochloric acid. The solution was extracted with ether (2 × 20 ml); then the acidic layer was alkalified with 10% potassium hydroxide and extracted with ether (3 × 20 ml). The extract was washed with 1% hydrochloric acid (2 × 20 ml) and water (20 ml), and dried over calcium chloride. The solvent was evaporated under reduced pressure and the residue crystallized from ethanol to give 0.92 g (32%), of compound **3a**; mp 180-181°C. $^{1}$H NMR spectrum, δ, ppm ($J$, Hz): 1.16 (3H, s, $CH_3$-9); 1.21 (3H, s, $CH_3$-9); 1.49 (3H, s, $CH_3$-9a); 1.55 (3H, d, $J$ = 7.5, $CH_3$-3); 3.72 (1H, q, $J$ = 7.5, H-3); 6.65-7.10 (4H, m, ArH); 8.11 (1H, br. s, NH). $^{13}$C NMR spectrum, δ, ppm: 19.77 ($CH_3$); 24.98 ($CH_3$); 25.80 ($CH_3$); 26.51 ($CH_3$); 47.50 (C-9); 63.91 (C-3); 89.19 (C-9a); 112.77 (CH); 122.11 (CH); 122.51 (CH); 127.96 (CH); 139.18 (C); 151.01 (C); 177.31

(C=O). Mass spectrum (ES+), *m*/*z* (rel. intensity): 253 (M+Na, 100), 231 (M+1, 26); mass spectrum (ES-), *m*/*z* (rel. intensity): 229 (M-1, 100). Found, %: C 73.31; H 7.70; N 12.09. $C_{14}H_{18}N_2O$. Calculated, %: C 73.01; H 7.88; N 12.16.

**1-Benzyl-3,9,9,9a-tetramethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]indol-2-one (3b).** A mixture of 3H-indole **1a** (3.18 g, 20 mmol) and 2-bromo-N-benzylpropionamide (7.26 g, 30 mmol) was heated at 135°C for 6 h. The reaction mixture was dissolved in 20 ml of acetone, poured into 200 ml of 5% hydrochloric acid, and extracted with ether (2 × 30 ml). The acidic layer was basified with 10% potassium hydroxide and extracted with ether (2 × 20 ml). The extract was washed with 1% hydrochloric acid (2 × 20 ml) and water (20 ml), dried over calcium chloride, and evaporated under reduced pressure. The residue was purified by flash chromatography on aluminum oxide (eluent acetone–hexane, 3:5) to give 3.01 g (47%) of compound **3b** as a pale yellow oil. $^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.93 (3H, s, $CH_3$-9); 1.18 (3H, s, $CH_3$-9); 1.41 (3H, s, $CH_3$-9a); 1.60 (3H, d, *J* = 6.6, $CH_3$-3); 3.79 (1H, q, *J* = 6.6, CH); 4.06-5.08 (2H, AB-q, *J* = 15.4, $CH_2$); 6.74-7.40 (9H, m, ArH). Found, %: N 8.61. $C_{21}H_{24}N_2O$. Calculated, %: N 8.74.

**1-Benzyl-3,7,9,9,9a-pentamethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]indol-2-one (3c)** was obtained similarly to compound **3b** from (3.46 g, 20 mmol) of 3H-indole **1b** (3.46 g, 20 mmol) and 2-bromo-N-benzylpropionamide (7.26 g, 30 mmol). Yield of **3c** was 3.61 g (54%); mp 71-72°C (ether). $^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.94 (3H, s, $CH_3$-9); 1.18 (3H, s, $CH_3$-9); 1.39 (3H, s, $CH_3$-9a); 1.60 (3H, d, *J* = 6.6, $CH_3$-3); 2.24 (3H, s, $CH_3$-7); 3.75 (1H, q, *J* = 6.6, CH), 4.06-5.10 (2H, AB-q, *J* = 15.4, $CH_2$); 6.66-7.47 (8H, m, ArH). Found, %: N 8.50. $C_{22}H_{26}N_2O$. Calculated, %: N 8.38.

**3,9,9,9a-Tetramethyl-1-phenyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]indol-2-one (3d).** The reaction of 3H-indole **1a** (1.99 g, 12.5 mmol) and 4.28 g (18.75 mmol) of 2-bromo-N-phenylpropionamide was carried out according to the procedure described for compound **3a** and yielded 0.95 g (25%) of the title compound; mp 132-134°C (ethanol). IR spectrum: 1703 $cm^{-1}$ (C=O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, s, $CH_3$-9); 1.24 (3H, s, $CH_3$-9); 1.41 (3H, s, $CH_3$-9a); 1.60 (3H, d, *J* = 6.9, $CH_3$-3); 3.97 (1H, q, *J* = 6.9, H-3); 6.84-7.40 (9H, m, ArH). $^{13}$C NMR spectrum, δ, ppm: 21.32 ($CH_3$); 21.81 ($CH_3$); 26.45 ($CH_3$); 30.33 ($CH_3$); 50.26 (C-9); 61.06 (C-3); 91.51 (C-9a); 114.47 (CH); 122.25 (CH); 122.84 (CH); 127.71 (CH); 128.18 (3CH); 129.11 (2CH); 136.75 (C); 142.53 (C); 147.87 (C); 174.28 (C=O). Found, %: C 78.02; H 7.40; N 9.16. $C_{20}H_{22}N_2O$. Calculated, %: C 78.40; H 7.23; N 9.14.

**1-(1-Carbamoylethyl)-2,3,3-trimethyl-3H-indolium Perchlorate (2e).** To a solution of compound **3a** (0.46 g, 2 mmol) in 3 ml of ethanol, 60% perchloric acid was added to pH 2 and the solution was stored at 0°C for 14 h. The precipitated crystals were isolated by filtration and recrystallized from ethanol to yield 0.40 g (60%) of perchlorate **2e**; mp 139-140°C. IR spectrum, ν, $cm^{-1}$: 3420 (N–H), 3220 (N–H), 1720 (C=O), 1115 ($ClO_4^-$). $^1$H NMR spectrum (TFA + acetone-$d_6$), δ, ppm (*J*, Hz): 1.53 (6H, s, $CH_3$-3,3); 1.98 (3H, d, *J* = 7.2, $CH\underline{CH_3}$); 2.87 (3H, s, $CH_3$-2); 5.90 (1H, q, *J* = 7.2, $\underline{CH}CH_3$); 7.42-8.05 (6H, m, ArH, $CONH_2$). Found, %: C 50.55; H 6.08; N 7.98. $C_{14}H_{19}ClN_2O_5$. Calculated, %: C 50.84; H 5.78; N 8.47.

**1-[1-(N-Benzylcarbamoyl)ethyl]-2,3,3,5-tetramethyl-3H-indolium Perchlorate (2f)** was obtained similarly to **2e** from **3c** (2.01 g, 6 mmol) and 60% perchloric acid in 1.10 g (42%) yield; mp 138-139°C (ethanol). IR spectrum, ν, $cm^{-1}$: 3330 (N–H), 1685 (C=O), 1550 (amide II), 1110 ($ClO_4^-$). $^1$H NMR spectrum (TFA), δ, ppm (*J*, Hz): 1.21 (3H, s, $CH_3$-3); 1.25 (3H, s, $CH_3$-3); 1.70 (3H, d, *J* = 7.4, $CH\underline{CH_3}$); 2.11 (3H, s, $CH_3$-5); 2.50 (3H, s, $CH_3$-2); 4.25 (2H, d, *J* = 6.8, $NH\underline{CH_2}$); 5.51 (1H, q, *J* = 7.4, $\underline{CH}CH_3$); 6.91-7.18 (8H, m, ArH). Found, %: Cl 8.40. $C_{22}H_{27}ClN_2O_5$. Calculated, %: Cl 8.15.

**1-[(*R**)-1-(Carbamoyl)ethyl](2*R**)-3,3-dimethyl-1,3-dihydrospiro[2H-indole-2,3'-[3H]naphtho-[2,1-*b*]pyran] (4a) and Its (2*R**)-1-[(*S**)-1-(Carbamoyl)ethyl]isomer (4b).** To a solution of perchlorate **2e** (0.33 g, 1.0 mmol) and 2-hydroxy-1-naphthaldehyde (0.19 g, 1.1 mmol) in ethanol (4 ml) was added 2 drops of piperidine and the mixture was refluxed for 5 h. Then the reaction mixture was poured into 5% sodium acetate (30 ml) and extracted with ether (2 × 15 ml). The organic extract was washed with water (15 ml) and dried over $MgSO_4$; the solvent was evaporated and the residue crystallized from ethanol to afford 0.23 g (60%) of a

mixture of diastereomers **4a**,**b**. $^1$H NMR spectrum of the mixture of **4a**,**b**, δ, ppm (*J*, Hz): 1.17 (3H, s, $CH_3$, major isomer); 1.22 (3H, s, $CH_3$, minor isomer); 1.33 (3H, s, $CH_3$, major isomer); 1.37 (3H, s, $CH_3$, minor isomer); 1.45 (3H, d, *J* = 7.2, CH$\underline{CH}_3$, minor isomer); 1.55 (3H, d, *J* = 7.2, CH$\underline{CH}_3$, major isomer); 4.22 (1H, q, *J* = 7.2, $\underline{CH}CH_3$, minor isomer); 4.44 (1H, q, *J* = 7.2, $\underline{CH}CH_3$, major isomer); 5.35 (1H, br. s, NH, major isomer); 5.55 (1H, br. s, NH, minor isomer); 5.74 (1H, d, *J* = 10.5, H-2', major isomer); 5.76 (1H, d, *J* = 10.5, H-2', minor isomer); 6.41 (1H, br. s, NH, minor isomer); 6.52-8.03 (22H, m, ArH, major and minor isomers; NH, major isomer). $^{13}$C NMR spectrum, δ, ppm: 11.91, 14.89, 19.94, 20.18, 26.32, 26.80, 51.85, 52.28, 52.43, 52.77, 104.35, 105.54, 107.76, 109.98, 110.09, 110.70, 116.42, 116.47, 117.23, 117.72, 119.36, 120.30, 120.56, 120.74, 122.07, 122.20, 123.62, 123.89, 125.93, 126.53, 127.01, 127.19, 127.29, 127.51, 128.67, 127.70, 128.92, 129.18, 129.77, 129.80, 130.68, 130.85, 135.81, 137.33, 142.92, 143.09, 151.31, 151.59, 173.95, 175.25. Found, %: C 78.27; H 6.08; N 7.35. $C_{25}H_{24}N_2O_2$. Calculated, %: C 78.10; H 6.29; N 7.29.

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