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Synthesis of a new bridged heterocyclic system: 5a,12a-propanoindolo[2,3-*c*][2]benzazepine

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Reaction of penta[*b*]indolylmagnesium iodide with 2-bromomethylbenzonitrile afforded 8b-(2-cyanobenzyl)-1,2,3,8b-tetrahydrocyclopenta[*b*]indole which was alkylated with iodomethane and gave the corresponding *N*-methyl-8b-(2-cyanobenzyl)penta[*b*]indolium iodide. Cyclization of the latter to new bridged heterocycles containing 5a,12-propanoindolo[2,3-*c*][2]benzazepine ring system has been studied.

Key words: heterocycles, penta[*b*]indoles, Grignard derivatives, 2-bromomethylbenzonitrile, 5a,12a-propanoindolo[2,3-*c*][2]benzazepine

INTRODUCTION

The tricyclic cycloalkano[*b*]indole ring system is a common structural element of a large variety of indole alkaloids [1]. More specifically, the cyclopenta[*b*]indole ring system occurs in a number of medicinally important tremorgenic mycotoxins (janthitrems, penitrems, paspaline, etc.) [2] and monoterpenoid alkaloids such as yeuhchukene [3]. Moreover, cyclopenta[*b*]indole derivatives were reported to exhibit a strong biological activity and inhibit RNA polymerase [4], modulate activity of liver-X-receptor [5] and are agonists of the human 5-HT2c receptor [6]. Some of indole alkaloids possess aza-cycloalkano[*b*]indole structures. For example, such alkaloids as eseroline (**1**) and physostigmine are based on a pyrrolo[2,3-*b*]indole unit, while the highly promising anticancer agent echitamine (**2**) [7] and its synthetic model compound echiboline (**3**) [8] incorporate the bridged 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole system. The synthetic alkaloid-like 1,2,3,4,5,5a,10,10a-octahydroazepino[2,3-*b*]indoles (**4**) were patented as potential sedatives [9].

In connection with our studies directed towards the synthesis of bridged indole derivatives [10] and in order to obtain a polycyclic bridged alkaloid-like system containing both penta[*b*]indole and azepine subunits, we planned the C-alkylation of cyclopenta[*b*]indole with 2-bromomethylbenzonitrile followed by intramolecular cyclization.

EXPERIMENTAL

General methods. Melting points were measured in open capillary tubes with a Kleinfeld melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer in KBr pallets. ^{1}H NMR spectra

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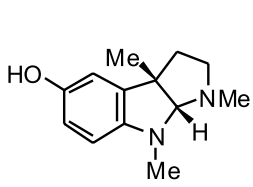
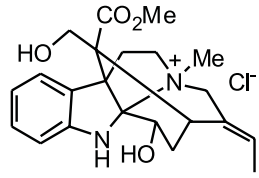


(-)-eseroline (**1**)



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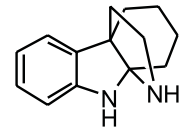
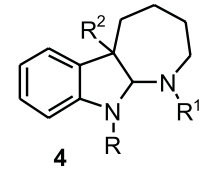


echiboline (**3**)



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R = R^1 = H, Et, Ac;
R^2 = H, OH, OAc

were obtained at 300 MHz, and ^{13}C NMR spectra were determined at 75 MHz with a Varian Unity Inova instrument. Chemical shifts are expressed in parts per million, relative to TMS. MS were measured using a Waters ZQ 2000 instrument (ion spray). For TLC analyses, Merck precoated TLC plates (silica gel 60 F254) were used. Separations by flash chromatography were performed on silica gel Merck, 9385, 230–400 mesh. The reagents were obtained from commercial suppliers and used without further purification.

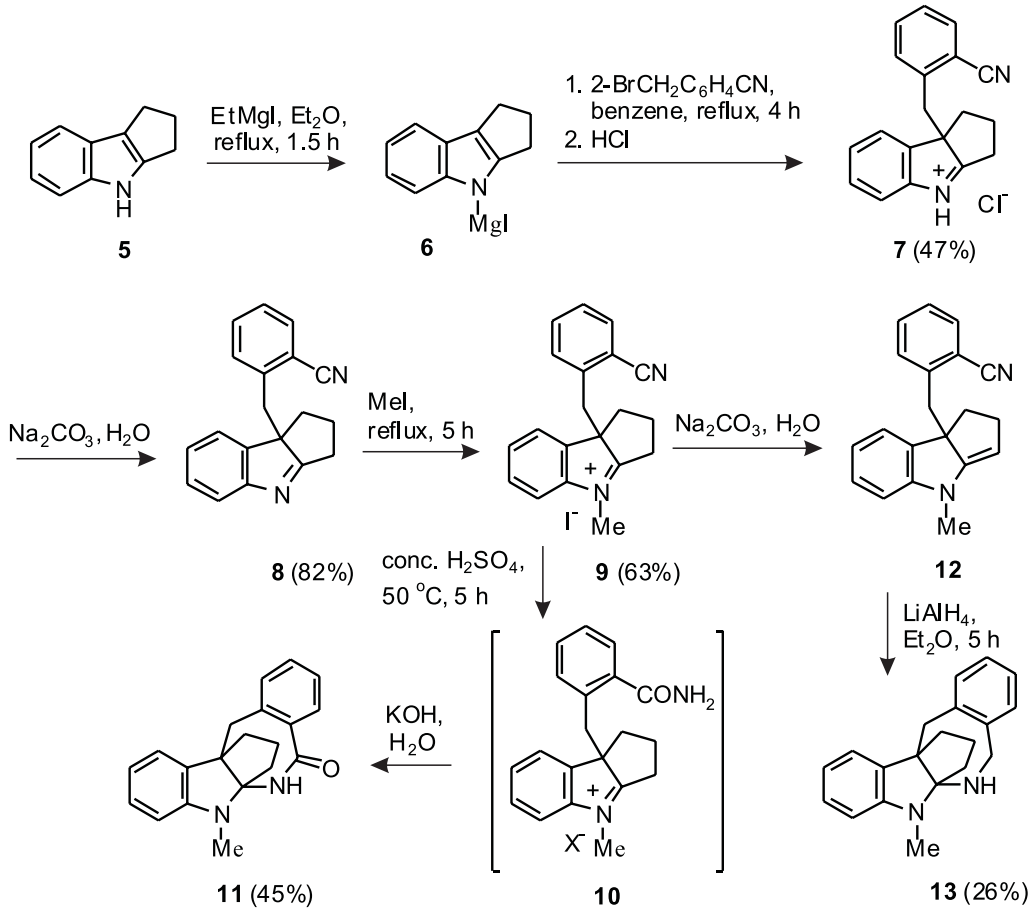
8b-(2-Cyanobenzyl)-1,2,3,8b-tetrahydrocyclopenta[*b*]indolium hydrochloride (7). To a solution of ethylmagnesium iodide, prepared from magnesium (0.33 g, 13.4 mmol) and iodoethane (2.05 g, 1.05 ml, 13.2 mmol) in dry Et_2O (16 ml) under argon atmosphere, a solution of 1,2,3,4-tetrahydrocyclopenta[*b*]indole **5** (1.1 g, 6.9 mmol) in dry Et_2O (6 ml) was added dropwise under reflux during 1 h. After stirring for an additional 30 min, Et_2O was distilled off and benzene (10 ml) was added. Then, to the resulting solution of cyclopenta[*b*]indolylmagnesium iodide **6**, a solution of 2-(bromomethyl)benzonitrile (1.61 g, 8.2 mmol) in benzene (10 ml) was added dropwise under reflux during 1 h. Stirring was continued at the same temperature for 3 h. Then the reaction mixture was cooled to room temperature, diluted with ether (10 ml) and poured onto a mixture of ice (20 g) and acetic acid (30%, 20 ml). The organic layer was separated and extracted with 3N HCl (3 × 50 ml), and the acidic extract was left at room temperature for 0.5 h. The precipitated crystalline material was washed with ether (5 ml) and filtered off to afford **7** (1.0 g, 47%) as white crystals with m.p. 137–138 °C (with decomposition). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07–2.58 (6H, m, $CH_2CH_2CH_2$), 3.12 (1H, d, ^2J = 13.7 Hz, ½ CH_2), 3.27 (1H, d, ^2J = 13.7 Hz, ½ CH_2), 6.31–7.74 (9H, m, Ar–H and N–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.2 (CH_2), 22.4 (CH_2), 36.1 (CH_2), 38.2 (CH_2), 59.3 (C), 104.4, 113.6, 117.5, 117.9, 125.1, 126.5, 127.5, 128.6, 131.7, 132.6, 132.7, 138.4, 141.6 (Ar–C, CN), 187.4 (N^+ = C). Mass spectrum (ES+), *m/z* (%): 274 ([M–Cl + H]$^+$, 100). Anal. calcd. for $C_{19}H_{16}N_2 \cdot HCl$: C, 73.90; H, 5.55; N, 9.07. Found: C, 73.76; H, 5.32; N, 9.13%.

8b-(2-Cyanobenzyl)-1,2,3,8b-tetrahydrocyclopenta[*b*]indole (8). Hydrochloride **7** (0.92 g, 3.0 mmol) was dissolved in water (10 ml), and the solution was basified (pH 9) with sodium carbonate. The oily substance was extracted with Et_2O (2 × 10 ml), the combined organic extract was washed with water (20 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford **8** (0.67 g, 82%) as white crystals with m. p. 185–186 °C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92–2.74 (6H, m, $CH_2CH_2CH_2$), 3.15 (1H, d, ^2J = 13.7 Hz, ½ CH_2), 3.25 (1H, d, ^2J = 13.7 Hz, ½ CH_2), 6.30–7.73 (8H, m, Ar–H). Anal. calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.69; H, 6.25; N, 10.10%.

8b-(2-Cyanobenzyl)-4-methyl-1,2,3,8b-tetrahydrocyclopenta[*b*]indolium iodide (9). A mixture of indole **8** (0.54 g, 2 mmol) and iodomethane (5 ml) was refluxed for 5 h. The reaction mixture was cooled down and Et_2O (10 ml) was added under stirring. The resulting precipitate was collected by filtration, washed with Et_2O and dried to afford the iodide **9** (0.52 g, 63%) with m. p. 170–171 °C (with decomposition, from ethanol). Mass spectrum (ES+), *m/z* (%): 287 ([M–I]$^+$, 60). Anal. calcd. for $C_{20}H_{19}IN_2$: C, 57.98; H, 4.62; N, 6.76. Found: C, 58.12; H, 4.53; N, 6.55%.

***cis*-5-Methyl-5a,6,12,12a-tetrahydro-5a,12a-propanoindolo[2,3-*c*][2]benzazepin-7(5*H*)-one (11).** A solution of compound **9** (0.34 g, 0.82 mmol) in concentrated sulfuric acid (7 ml) was heated at 50 °C for 5 h. The mixture was poured onto ice (50 g), neutralized with concentrated potassium hydroxide and extracted with Et_2O (3 × 20 ml). The combined organic extract was washed with water, followed by drying (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane / EtOAc, 1/1) to yield **11** (0.11 g, 45%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19–2.20 (6H, m, $CH_2CH_2CH_2$), 2.55 (3H, s, CH_3), 2.89 (1H, d, ^2J = 13.1 Hz, ½ CH_2), 3.41 (1H, d, ^2J = 13.1 Hz, ½ CH_2), 5.84–7.56 (9H, m, Ar–H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9 (CH_2), 27.6 (CH_3), 39.5 (CH_2), 40.9 (CH_2), 43.1 (CH_2), 63.1 (C–10a), 90.4 (C–5a), 103.9, 117.1, 122.6, 126.5, 127.8 (2×C), 129.9, 130.2, 131.7, 133.7, 136.1, 149.2 (Ar-C), 172.9 (C = O). Mass spectrum (ES+), *m/z* (%): 305 ([M + H]$^+$, 100). Anal. calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.63; H, 6.22; N, 9.22%.

***cis*-5-Methyl-5,5a,6,7,12,12a-hexahydro-5a,12a-propanoindolo[2,3-*c*][2]benzazepine (13).** A solution of the salt **9** (0.55 g, 1.34 mmol) in 15% ethanol (50 ml) was neutralized with sodium carbonate and extracted with Et_2O (3 × 10 ml). The combined organic extract was washed with water, followed by drying (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was dissolved in dry Et_2O (10 ml), $LiAlH_4$ (94 mg, 2.48 mmol) was added, and the mixture was refluxed under argon for 5 h. The reaction mixture



was allowed to cool to room temperature, and water (1 ml) was dropped carefully into the reaction flask. A finely suspended solid was a filtered off using a fritted glass filter, and the solid material was washed with ether (20 ml). The collected filtrate was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (hexane / EtOAc, 7/1) to yield **13** (0.1 g, 26%) as a viscous oil, R_f = 0.73 (hexane / EtOAc, 7/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13–1.99 (7H, m, $CH_2CH_2CH_2$, NH), 2.73 (3H, s, CH_3), 3.14 (1H, d, ^2J = 14.9 Hz, ½ CH_2), 3.52 (1H, d, ^2J = 14.9 Hz, ½ CH_2), 3.75 (1H, d, ^2J = 16.3 Hz, CH_2), 4.1 (1H, d, ^2J = 16.3 Hz, ½ CH_2), 6.25–7.02 (8H, m, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8 (CH_2), 27.6 (CH_3), 36.6 (CH_2), 40.1 (CH_2), 42.0 (CH_2), 46.5 (C–10a), 93.3 (C–5a), 104.4, 116.4, 122.4, 125.9, 126.1, 126.7, 127.4, 131.2, 135.2, 136.8, 140.5, 150.1 (Ar–C). Anal. calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.50; H, 7.24; N, 9.66%.

RESULTS AND DISCUSSION

It is known that alkylation of indoles at C-3 of the pyrrole ring can be achieved using the corresponding intermediate Grignard derivatives [11]. Treatment of cyclopenta[*b*]indolylmagnesium iodide with methyl iodide afforded 8b-methyl-1,2,3,8b-tetrahydrocyclopenta[*b*]indole [12]. A similar method was applied for the preparation of indole alkaloids. For example, reaction of indolylmagnesium iodide with 2-chloroacetonitrile afforded 3-cyanomethyl-3*H*-indole which was easily transformed into the pyrrolo[2,3-*b*]indole ring system [13].

Synthesis of the starting cyclopenta[*b*]indole **5** was performed by the Fisher reaction from phenylhydrazone and cyclopentanone [14]. Preparation of 1,2,3,4-tetrahydrocyclopenta[*b*]indolylmagnesium iodide **6** was carried out by treatment of the cyclopenta[*b*]indole with methylmagnesium iodide in diethyl ether. In the second step of synthesis, the reaction of the intermediate magnesium derivative **6**, prepared *in situ*, with 2-bromomethylbenzonitrile has been performed in benzene. Work-up of the reaction mixture with hydrochloric acid afforded 8b-(2-cyanobenzyl)-1,2,3,8b-tetrahydrocyclopenta[*b*]indole hydrochloride (**7**) in a 47% yield. The IR spectrum of hydrochloride **7** showed a sharp band at 2 220 cm^{-1}, assigned to the cyano group [15]. The ^{1}H NMR spectrum of **7** revealed the AB-quadruplet (J_{AB} = 13.7 Hz) at 3.20 ppm for diastereotopic methylene protons of the benzyl group, while the ^{13}C NMR spectrum contained the characteristic signal of the indolium N^+ = C moiety at 187.4 ppm.

Treatment of hydrochloride **7** with a base afforded 8a-(2-cyanobenzyl)penta[*b*]indole **8**. Alkylation of the latter with iodomethane gave *N*-methylpenta[*b*]indolium iodide **9** which was recrystallized from ethanol. The IR spectrum of iodide **9**

contained a characteristic absorption band at 2223 cm^{-1} (CN), and its mass spectrum (ion spray, ES+) revealed a peak with *m/z* (%) 287 ($[M–I]^+$, 60). However, the corresponding NMR spectra have been not registered because of the low solubility of compound **9** in organic solvents.

Hydrolysis of nitrile **9** with concentrated sulfuric acid at 50 °C afforded 5a, 12a-propanoindolo[2,3-*c*][2]benzazepin-7-(5*H*)-one **11** in a 45% yield after a basic aqueous work-up. It can be assumed that in the first step of this cyclization reaction the intermediate 8a-(2-carbamoylbenzyl)-3*H*-indolium salt **10** was formed. For the molecule **11**, a relative *cis*-structure was assigned, while the *trans*-fusion of pyrrolidine and azepine rings seems to be unfavourable for steric reasons [16].

The IR spectrum of compound **11** showed intensive bands at 3 361 and 1 660 cm^{-1}, assigned to the N-H and C = O groups of the lactam moiety, respectively. The ^{1}H NMR spectrum of compound **11** exhibited an AB-quadruplet (^2J = 13.1 Hz) of the diastereotopic benzylic methylene protons. In the ^{13}C NMR spectrum of **11**, the signal of the sp^3-hybridized C-5a atom appeared at 90.4 ppm, while the signal for the carbon atom of the carbonyl group was situated at 172.9 ppm [17].

Treatment of iodide **9** with sodium carbonate afforded the corresponding enamine **12** which was used without furher purification in the next step of synthesis. Thus, reduction of enamine **12** with $LiAlH_4$ in diethyl ether under reflux resulted in cyclization of the intermediate amine across the enamine moiety to afford 5a,12-propanoindolo[2,3-*c*][2]benzazepine **13**. The IR spectrum of **13** showed a band at 3365 cm^{-1}, assigned to the N-H group. In the ^{13}C NMR spectrum of **13**, the characteristic resonance signal of the diaminal carbon C-5a appeared at 93.3 ppm.

CONCLUSIONS

To summarize, we developed a synthetic strategy for a practical, efficient preparation of alkaloid-like indole derivatives containing a new bridged 5a,12a-propanoindolo[2,3-*c*][2] benzazepine ring system.

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NAUJOS TILTELINĖS HETEROCIKLINĖS SISTEMOS SINTEZĖ: 5a,12a-PROPANOINDOLO[2,3-*c*][2]BENZAZEPINAS

S a n t r a u k a

1,2,3,4-tetrahidrociklopentano[*b*]indolilmagnio jodidui reaguojant su 2-brommetilbenzonitrilu susidaro 8b-(2-cianobenzil)-1,2,3,8b-tetrahidrociklopenta[*b*]indolas. Alkilinant šį junginį jodmetanu buvo gautas atitinkamas *N*-metil-8b-(2-cianobenzil)penta[*b*]indolio jodidas. Šį junginį paveikus koncentruota sieros rūgštimi susidarė *N*-metil-8b-(2-karbamoilbenzil)penta[*b*]indolio druska, kuri dėl bazių poveikio ciklizavosi į 5a,12a-propanoindolo[2,3-*c*]benzazepin-7(5*H*)-oną. Apdorojus minėtą *N*-metil-8b-(2-cianobenzil)penta[*b*]indolio jodidą bazėmis, susidarė atitinkamas enaminas, kuris redukuojant ličioaliuminio hidridu ciklizavosi į 5a,12a-propanoindolo[2,3-*c*]benzazepiną.