Synthesis and Ring Opening of Alkaloid-Type Compounds with a Novel Indolo[2,3-*c*][2]benzazepine Skeleton

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Abstract: Alkylation of the magnesium salts of 2,3-disubstituted indoles with 2-bromomethylbenzonitrile gave 3-(2-cyanobenzyl)-3*H*-indole derivatives. Reduction of the cyano group of *N*-methyl 3-(2-cyanobenzyl)-3*H*-indolium salts afforded previously unreported indolo[2,3-*c*][2]benzazepines, while acid hydrolysis gave the corresponding indolo[2,3-*c*][2]benzazepinones. The action of strong protonic acids on indolo[2,3-*c*][2]benzazepines causes opening of the benzazepine ring annelated to the indole system to form 3*H*-indolium salts.

Key words: alkaloids, indoles, indolo[2,3-*c*][2]benzazepines, ring closure, ring opening

The indole nucleus is a key structural feature in (bio)organic chemistry, as it constitutes the main structural element of tryptophane and its metabolites such as tryptamine, serotonine, and others. Fused heterocycles, bearing at the *b*-edge of the indole nucleus a saturated azaheterocycle, are found in a wide range of biologically active indole alkaloids. The chemistry of hexahydropyrrolo[2,3-*b*]indoles, as exemplified by the calabar alkaloid (–)-physostigmine (**1**, Figure 1) and the analogues phenserine and (–)-eseroline,[2] has received considerable interest in drug research and for synthetic applications.[3] Moreover, the hexahydropyrrolo[2,3-*b*]indole ring system is also present in akuammiline alkaloids, such as echitamine, which is a promising cytotoxic compound.[4] Echibolines, incorporating the 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole structure **2**,[5] and 2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indoles,[6] for example, compounds **3** and **4** with anti-inflammatory activity,[7] also comprise structurally related classes of alkaloids with synthetic and medicinal potential. Benzo-annulated derivatives of hexahydro-1*H*-pyrido[2,3-*b*]indoles, that is, 5a,6,10b,11-tetrahydro-5*H*-quinindolines, like structure **5**,[8] are of interest within the synthetic study of communesin A (**6a**) and cytotoxic communesin B (**6b**),[9] whereas the homologues of 2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indoles with a 1,2,3,4,5,5a,10,10a-octahydroazepino[2,3-*b*]indole (**7**) unit, have received some attention because of their sedative properties[10] and as photodiscoloration prevention agents.[11]

In the present paper, the straightforward synthesis and study of the ring–chain transformations of tetracyclic compounds with a hitherto unreported 5,5a,6,7,12,12a-hexahydroindolo[2,3-*c*][2]benzazepine (**8**) system is described. These syntheses, based on a 2-cyanobenzylation of indoles at C-3, followed by reductive or hydrolytic cyclization, can act as a model for the synthesis of alkaloid-

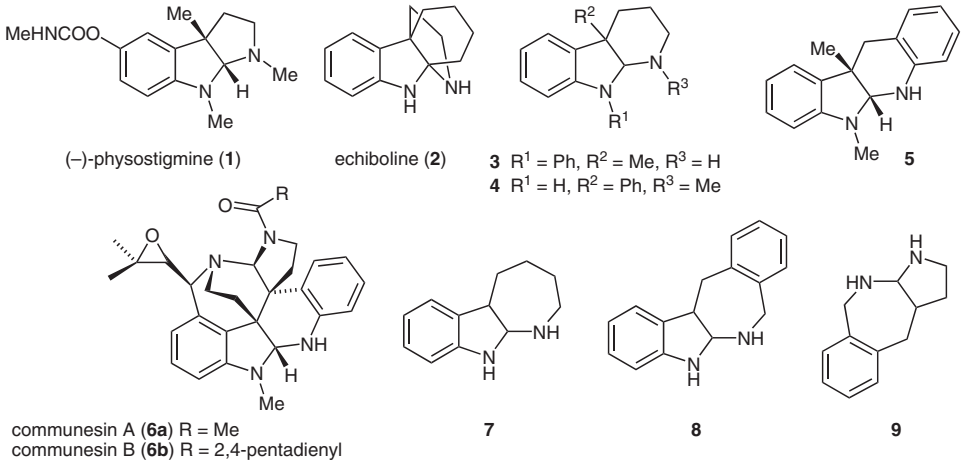

Figure 1

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like compounds since the 5,5a,6,7,12,12a-hexahydroindolo[2,3-*c*][2]benzazepine (**8**) structural element incorporates the aforementioned 1,2,3,4,5,5a,10,10a-octahydroazepino[2,3-*b*]indole (**7**) moiety as well as the 2,3,3a,4,9,10-hexahydro-1*H*-pyrrolo[2,3-*c*][2]benzazepine (**9**) scaffold which is also present in the structure of communesins **6**.[9c]

The starting compounds, 2,3-dimethyl-1*H*-indole **10a** and 2,3,4,9-tetrahydro-1*H*-carbazole **10b**, prepared by Fischer indole synthesis, were alkylated at C-3 by treatment with ethylmagnesium iodide and subsequent reaction with 2-bromomethylbenzonitrile in benzene under reflux to give the corresponding 2-cyanobenzylated indoles **11a**,**b** in 53% and 76% yield, respectively (Scheme 1).[12] When the alkylation of 2,3-dimethylindole **10a** was performed in a mixture of benzene and diethyl ether, the yield of compound **11a** decreased (36% yield) and 12a-methyl-12,12a-dihydrobenzo[4,5]cyclohepta[1,2-*b*]indol-7(5*H*)-imine (**12a**) was formed as a minor product (17% yield).[13]

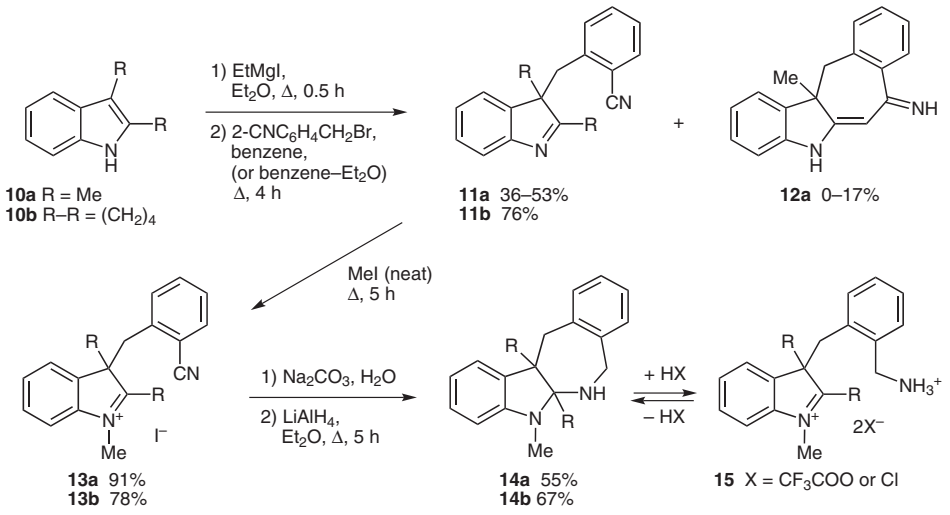
The 3*H*-indoles **11** were N-methylated in 78–91% yield upon reflux in iodomethane for 5 hours leading to 3*H*-indolium salts **13** which were crystallized from ethanol. These salts disclosed a typical N^+=C signal at δ = ca. 195.0 ppm in the ^{13}C NMR spectrum (DMSO-d_6).

The dehydroiodination of compounds **13** with sodium carbonate to afford the corresponding enamines, followed by reduction with $LiAlH_4$ in diethyl ether under reflux, resulted in cyclization of the intermediate amine across the enamine to afford indolo[2,3-*c*][2]benzazepines **14** (Scheme 1).[14] The structure of 5,5a,12a-trimethylindolo[2,3-*c*][2]benzazepine **14a** was established by full spectroscopic investigations and the strong NOE interactions between the 5a-CH_3 and 12a-CH_3 groups suggested a *cis* relative configuration. It is necessary to point out that compounds **14a**,**b** in solution of $CDCl_3$ show a dynamic behavior, which leads to more or less broadening of most signals in the NMR spectra. The action of strong protonic acids on the indolo[2,3-*c*][2]benzazepines **14** leads to opening of the azepine ring with the formation of 3*H*-indolium salts **15**, which in turn form the initial cyclic adducts **14** under neutral conditions. The transformation of compounds **14a**,**b** to the open form dications **15a**,**b** in deuterated trifluoroacetic acid is indicated by the appearance of the characteristic signal of the indolium N^+=C moiety in the ^{13}C NMR spectrum at δ = 197.9 and 199.3 ppm, respectively. The absorption maxima observed in the UV spectrum of compound **14a** in ethanol are specific for indoline derivatives [λ_{max} (log ε): 212 (2.99), 254 (2.86), 304 (2.51) nm]. The UV spectrum of compound **14a** in a 100:1 (v/v) mixture of ethanol with concd hydrochloric acid, when compared with the corresponding spectrum in pure ethanol, showed a hypsochromic displacement of the absorption bands [λ_{max} (log ε): 208 (3.05), 232 (2.84), 272 (2.73) nm], indicating that 3*H*-indolium salt **15** (R = Me, X = Cl) is formed.[15]

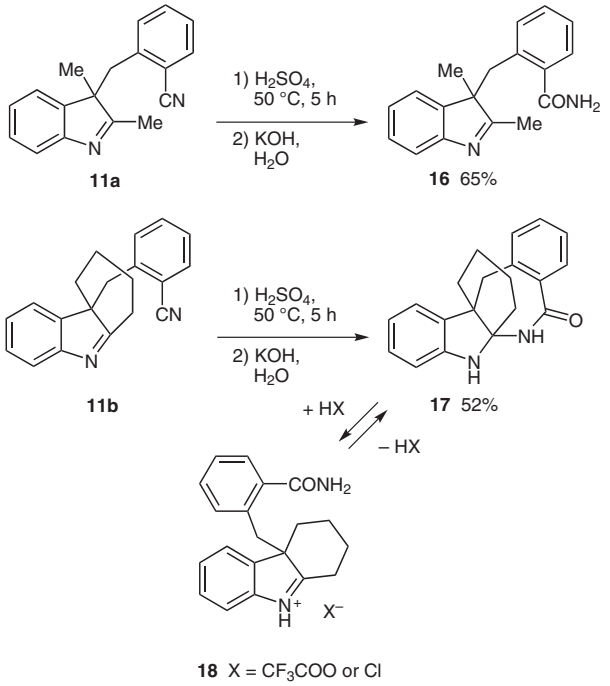
Hydrolysis of the cyano group of 3*H*-indole **11a** with concentrated sulfuric acid at 50 °C resulted in the formation of 2-(2,3-dimethyl-3*H*-indol-3-ylmethyl)benzamide (**16**) in 65% yield after basic aqueous work up (Scheme 2).

Applying the former hydrolytic conditions to compound **11b** afforded directly the indolo[2,3-*c*][2]benzazepinone **17**. The identification of the open amide **16** and the ring-closed lactam **17** was based on their full spectroscopic analysis with characteristic signals in the ^{13}C NMR spectra at δ = 187.3 (C=N) and 172.4 (C=O) ppm for the amide **16** ($CDCl_3$) and at δ = 79.5 (aminal C-5a) and 171.5 (C=O) ppm for the lactam **17** (DMSO-d_6). In a solution of deuterated trifluoroacetic acid, the lactam **17** transforms to the 3*H*-indolium cation form **18**, possessing a characteristic N^+=C signal at δ = 203.3 ppm in the ^{13}C NMR spectrum (TFA-*d*).

Acid hydrolysis of the substituted 3*H*-indolium iodides **13** followed by basic aqueous workup led to the formation of indolo[2,3-*c*][2]benzazepinones **19** (Scheme 3), the structure of which was fully proved by elemental and spectral analysis.[16] The NOE between the 5a-CH_3 and 12a-CH_3 groups is indicative for the *cis*-configuration of structure **19a**.

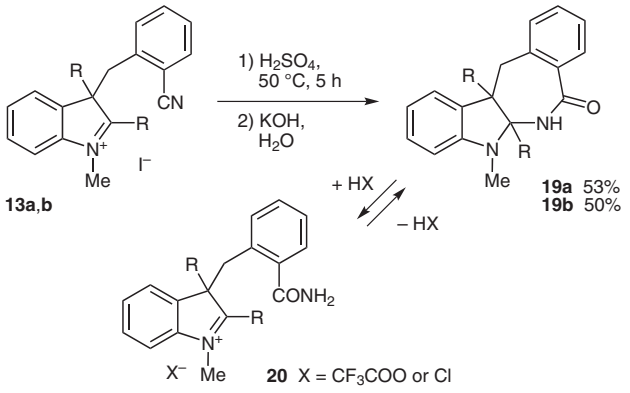


Scheme 1



Scheme 2

Spectroscopic analysis of lactams **19** in deuterated trifluoroacetic acid, showing characteristic N^+=C signals at δ = ca. 200.0 ppm, demonstrated again that treatment with protonic acids leads to cleavage of the C–N bond of the azepinone ring of compounds **19** with formation of the corresponding 3*H*-indolium salts **20**. Typical changes in the absorption bands of the UV spectra of compound **19a** in ethanol upon addition of concentrated hydrochloric acid also demonstrated the formation of the corresponding 3*H*-indolium chloride **20** (R = Me, X = Cl).



Scheme 3

In summary, it was found that alkylation of the magnesium salts of 2,3-disubstituted indoles with 2-bromomethylbenzonitrile and subsequent reduction or hydrolysis of the introduced cyano group resulted in a straightforward synthesis of a novel type of heterocyclic systems with an indolo[2,3-*c*][2]benzazepine and -benzazepinone skeleton, respectively. The structure and ring–chain transformations of the latter polycyclic alkaloid-type compounds were established by full spectroscopic and elemental analysis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Analytical and Spectroscopic Data for Compound 12a** Yellow solid, mp >250 °C (from DMSO, with decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.78 (3 H, s, CH_3), 3.04 (1 H, d, ^2J = 14.2 Hz, 12-H), 3.09 (1 H, d, *J* = 14.2 Hz, 12-H), 3.40 (1 H, s, C=NH), 5.91 (1 H, s, 6-H), 6.34 (1 H, br s, NH), 6.96 (1 H, m, 2-H), 7.13 (2 H, m, 3-H, 4-H), 7.29 (1 H, d, *J* = 7.3 Hz, 1-H), 7.38–7.40 (3 H, m, 9-H, 10-H, 11-H),

7.75 (1 H, m, 8-H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.3 (CH_3), 39.7 (C-12), 51.2 (C-12a), 96.6 (C-6), 117.2 (C-4), 120.9 (C-1), 122.6 (C-2), 127.1 (C-9), 127.6 (C-3), 127.7 (C-8), 129.7 (C-10), 131.8 (C-11), 133.8 (C-7a), 136.4 (C-11a), 144.5 (C-12b), 151.8 (C-7), 155.3 (C-4a), 185.3 (C-5a). IR (KBr): 3430 (NH), 3310 (NH), 1655 (N=C) cm^{-1}. MS (ES$^+$): *m/z* (%) = 262 (50) [M + 2H]$^+$, 261 (100) [M + H]$^+$. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 82.74; H, 5.99; N, 10.44.

(14) **Typical Procedure for the Preparation of an Indolo[2,3-*c*][2]benzazepine**

A solution of 3*H*-indolium salt **13a** (0.5 g, 1.24 mmol) in EtOH (15 mL) was poured in a solution of 5% Na_2CO_3 (50 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O, dried over 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 r.t. and H_2O (1 mL) was dropped carefully into reaction flask. A finely suspended solid was filtered off using a fritted glass filter, and the solid material washed with Et_2O (20 mL). The filtrate was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 7:1) to yield **14a** (0.19 g, 55%) as a viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (3 H, s, 5a-CH_3), 1.15 (3 H, s, 12a-CH_3), 1.68 (1 H, s, NH), 2.36 (1 H d, ^2J = 14.3 Hz, 12-H), 2.72 (3 H, s, NCH_3), 3.56 (1 H, d, ^2J = 15.1 Hz, 7-H), 3.68 (1 H, d, ^2J = 14.3 Hz, 12-H), 4.52 (1 H, d, ^2J = 15.1 Hz, 7-H), 6.47 (1 H, d, *J* = 7.6 Hz, 4-H), 6.71 (1 H, t, *J* = 7.3 Hz, 2-H), 7.00 (1 H, d, *J* = 7.1 Hz, 1-H), 7.05 (1 H, m, 8-H), 7.11 (1 H, t, *J* = 7.6 Hz, 3-H), 7.14–7.19 (3 H, m, 9-H, 10-H, 11-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.7 (12a-CH_3), 18.9 (5a-CH_3), 27.0 (NCH_3), 44.7 (C-12), 45.3 (C-7), 46.2 (C-12a), 87.9 (C-5a), 106.5 (C-4), 117.5 (C-2), 121.1 (C-1), 126.3 (C-8, C-9), 126.6 (C-10), 127.4 (C-3), 130.3 (C-11), 137.5 (C-12b), 138.4 (C-11a), 143.0 (C-7a), 149.1 (C-4a). ^{15}N NMR (50.7 MHz, $CDCl_3$, ref.: $MeNO_2$): δ = –333.3 (N-6), –305.4 (N-3). IR (KBr): 3365 (NH) cm^{-1}. MS (ES$^+$): *m/z* (%) = 280 (50) [M + 2H]$^+$, 279 (100) [M + H]$^+$. Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.48; H, 7.60; N, 10.34.

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(16) **Typical Procedure for the Preparation of an Indolo[2,3-*c*][2]benzazepin-7(5*H*)-one**

A solution of 3*H*-indolium salt **13a** (0.5 g, 1.24 mmol) in concentrated H_2SO_4 (12 mL) was heated at 50 °C for 5 h. The mixture was poured onto crushed ice, neutralized with 10% KOH solution and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 2:1) to yield **19a** (0.195 g, 53%), mp 226–227 °C (from EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (3 H, s, 5a-CH_3), 1.45 (3 H, s, 12a-CH_3), 2.30 (3 H, s, NCH_3), 2.44 (1 H, br s, 12-H), 3.29 (1 H, d, ^2J = 12.7 Hz, 12-H), 5.85 (1 H, br s, 4-H), 6.54 (1 H, br s, 11-H), 6.66 (1H, br t, *J* = 7.4 Hz, 2-H), 6.82 (1 H, br s, NH), 6.94 (1 H, br t, *J* = 7.6 Hz, 3-H), 7.03 (1 H, br s, 10-H), 7.07 (1 H, d, *J* = 7.2 Hz, 1-H), 7.16 (1 H, br t, *J* = 7.3 Hz, 9-H), 7.57 (1 H, br d, *J* = 7.5 Hz, 8-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5 (5a-CH_3), 21.5 (12a-CH_3), 26.1 (NCH_3), 47.6 (C-12), 55.1 (C-12a), 84.3 (C-5a), 104.5 (C-4), 117.1 (C-2), 121.9 (C-1), 126.5 (C-8, C-9), 128.1 (C-3), 128.9 (C-11), 130.1 (C-10), 131.8 (C-12b), 134.9 (C-7a), 136.3 (C-11a), 147.5 (C-4a), 172.8 (C=O). IR (KBr): 3180 (NH), 1650 (C=O) cm^{-1}. MS (ES$^+$): *m/z* (%) = 293 (100) [M + H]$^+$. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.31; H, 6.91; N, 9.65.