Studies on the Synthesis of the Azocino[4,3-*b*]indole Framework and Related Compounds

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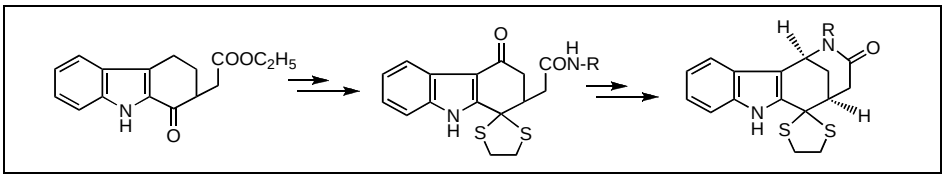

An efficient method for the synthesis of C-4 position alkylated azocino[4,3-*b*]indole **13** and **18** is described. Reduction of compounds **5, 6, 7** and **8** yielded the corresponding alcohols. Compounds **5, 6, 7** and **8** were synthesized through several steps starting from **1**. The resulting alcohols underwent acid catalyzed ring closure to give tetracyclic azocino[4,3-*b*]indole **9, 10, 11** and **12**. Finally, compounds **9** and **17** were alkylated at C-4 position to the corresponding products **13** and **18**. The structure of the compounds **13** and **18** has been confirmed by X-ray single crystal analysis.

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INTRODUCTION

The tetracyclic azocino[4,3-*b*]indole skeleton constitutes the structural basis of most strychnos alkaloids. Most of them belong to curan skeletal type Strychnos alkaloids. These substructures are represented by a large number of alkaloids bearing one-carbon substituent at C-16 and two-carbon substituent at C-20 position such as tubifoline (Figure 1). In this study, our approach is first forming azocino[4,3-*b*]indole framework by starting from suitable 4-oxo-1,2,3,4,9-tetrahydrocarbazole derivative and afterwards to introduce the required functionality at the azocino[4,3-*b*]indole 4-position, which has the same structure as at C-20 in Strychnos alkaloids. Several different synthetic strategies were developed for the synthesis of azocino[4,3-*b*]indole framework [1-25]. Our concept is based on the acid catalyzed ring closure of 4-hyroxy-1,2,3,4,9-tetrahydrocarbazole derivative, which were obtained from related 4-oxo-1,2,3,4,9-tetrahydrocarbazole derivatives **5**, **6**, **7** and **8**.

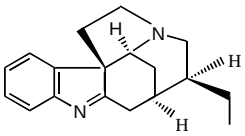
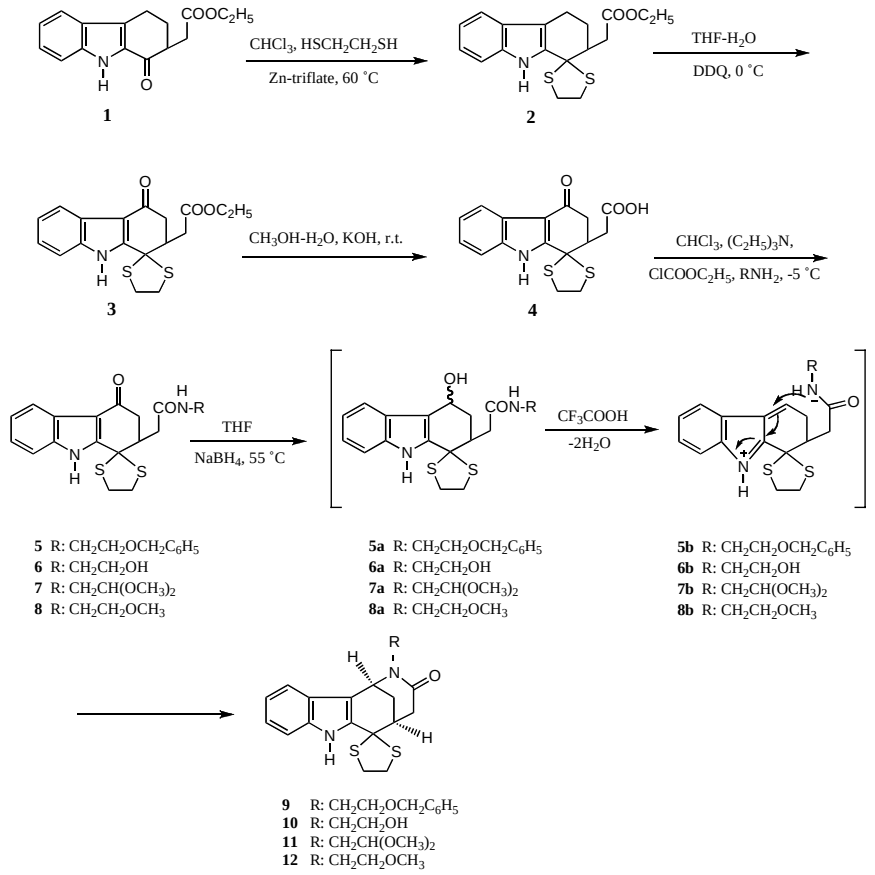


Figure 1

RESULTS AND DISCUSSION

The required compounds **5**, **6**, **7** and **8** were prepared from ethyl 2-(1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetate **1** (Scheme I) [26]. Synthesis of thioketal **2** was achieved under mild condition by refluxing of **1** for 20 h in chloroform using 1,2-ethanedithiol and zinc triflate as a catalyst [27]. Compound **2** was oxidized to the corresponding 4-oxo-tetrahydrocarbazole **3** by treatment with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone at 0 °C [28]. Hydrolysis of ketoester **3** by using 15% potassium hydroxide in methanol-water (3:1) yielded compound **4**. The acid **4** was converted into keto-amide **5**, **6**, **7** and **8** by treatment with ethyl chloroformate, triethylamine in chloroform [1], followed by the addition of the required amine. The reduction of the ketone **5**, **6**, **7** and **8** to the corresponding 4-hydroxy-tetrahydrocarbazole was carried out with an excess of sodium borohydride in tetrahydrofuran at 50 °C. The alcohols obtained in each reaction were used for the next reaction without isolation. The acid-catalyzed cyclization of the initially formed 4-hyroxy-tetrahydrocarbazole was accomplished by using trifluoroacetic acid to give the azocino[4,3-*b*]indole compounds **9**, **10**, **11** and **12** [22]. After successful synthesis of the tetracyclic indole, our next goal was to introduce alkyl groups to the position C-4 of azocino[4,3-*b*]indole. For this purpose, we selected model compound **9**. Treatment of **9** with sodium hydride and iodomethane in benzene at 80 ºC afforded the desired compound **13** (Scheme II). The structure of **13** determined by X-ray crystal analysis [29]. Next, according to our synthetic plan (Scheme III), we aimed to introduce a β-ethyl substituent at C-4 of the azocino[4,3-*b*]indole skeleton. Therefore, we protected the indole N-H of **3** with methoxymethyl-bromide using tetrabutylammonium hydrogen sulfate as phase-transfer catalyst [30]. Similarly, hydrolysis of the ester **14** to **15**, formation of **16** from **15** and subsequent

Scheme I



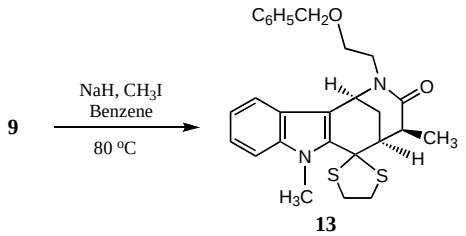
cyclisation to **17** were performed the same as for the preparation of compounds **4, 8** and **12**. Finally, conversion of **17** into **18** was carried out using sodium hydride and iodoethane in tetrahydrofuran at 60 °C [31].

Suprisingly, only isolable product was single epimer **18** although we expected to obtain a mixture of epimers. The structure of **18** was determined by X-ray single crystal analysis [32]. The reason for this result is probably the steric hindrance of the thiolane ring.

CONCLUSION

In summary, starting from **1**, we completed the construction of tetracyclic ring system having a α-ethyl substituent in C-4 position. The application of this strategy may allow the synthesis of a variety of curan types alkaloids.

Scheme II

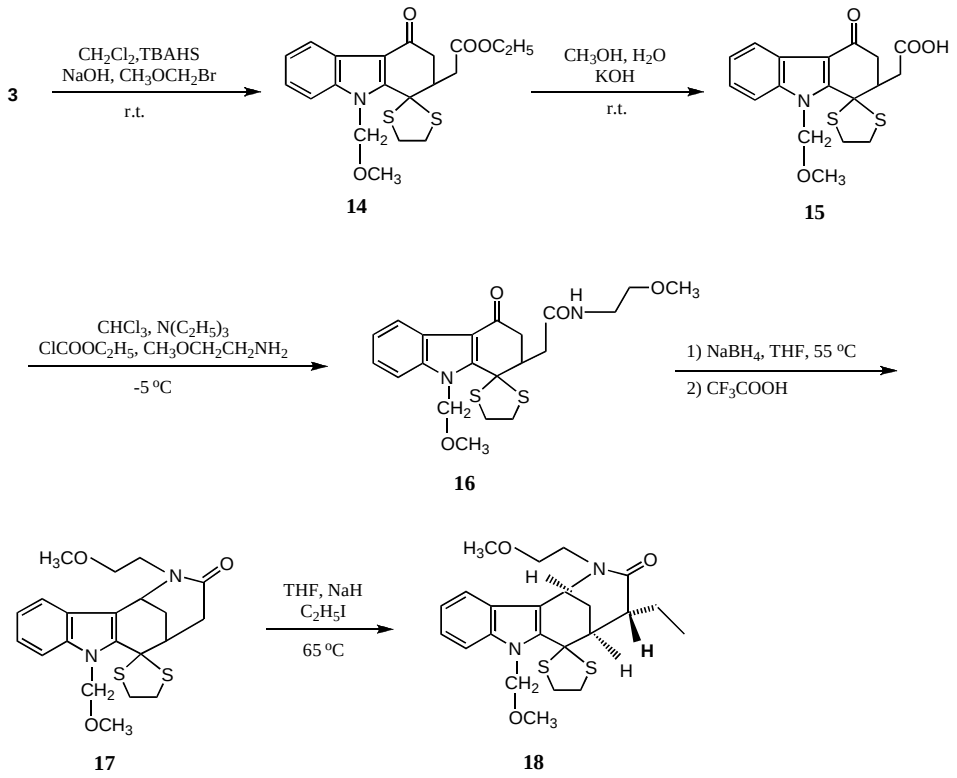


EXPERIMENTAL

^{1}H-NMR spectra were recorded on a BRUKER 400 spectrometer operating at 400 MHz. Spectra were registered in $CDCl_3$ and DMSO-d_6, using the solvent as internal standard at 400 MHz for ^{1}H and ^{13}C at 25 ºC. Chemical shifts are expressed in terms of parts per million (δ) and the coupling constants are given in Hz. IR spectra were recorded by using Mattson 1000 FT-IR spectrometer. Mass spectra were measured by means of Agilent 5973 model of GC-MS. Melting points were determined in a capillary tube on Electro thermal IA 9000 apparatus and were uncorrected. Reactions were monitored by thin layer chromatography (silica gel 60 F254). Purification of solvents were performed according to standard methods.

Ethyl{2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane]-2-yl}-2-acetate (2). To a solution of (5.0 g, 18.4 mmoles) ethyl 2-(1-oxo-2,3,4,9-tetrhydro-1*H*-carbazol-2-yl)-acetate in 100 mL chloroform were added (5.5 g, 15 mmoles) zinc triflate, (2.0 g, 15 mmoles) zinc chloride and (5 mL, 60 mmoles) ethane-1,2-dithiol. This mixture was refluxed for 20 h and then poured in 250 mL 10% hydrochloric acid. The organic layer was separated and washed several times with 50 mL 10% sodium hydroxide and dried over anhydrous magnesium sulfate. The solvent was

Scheme III



evaporated and the residue was purified by silica gel chromatography using dichloromethane to give, 6.1 g, 95% of **2**, mp 125 °C; ir (potassium bromide): ν 3406, 1711, 1371, 736 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.32 (t, 3H, *J*=7.13 Hz), 1.94-1.98 (m, 1H), 2.30-2.35 (m, 1H), 2.53 (dd,1H, *J*=9.42 and 15.52 Hz), 2.77-2.82 (m, 2H), 2.89-2.93 (m,1H), 3.04 (dd, 1H, *J*=4.31 and 15.53 Hz), 3.39-3.62 (m, 4H), 4.19-4.25 (m, 2H), 7.11 (t, 1H, *J*=7.95 Hz), 7.21 (t, 1H, *J*=8.19 Hz), 7.34 (d, 1H, *J*=0.68 Hz), 7.48 (d, 1H, *J*=7.92 Hz), 8.25 (s, 1H). *Anal*. Calcd for $C_{18}H_{21}NO_2S_2$: C 62.21; H 6.09; N 4.03. Found: C 62.23; H 6.07; N 4.05.

Ethyl{2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetate (3). Compound **2** (5.0 g, 14.3 mmoles) were dissolved in 50 mL of 90% tetrahydrofuran (10% water) and cooled 0 °C. Under nitrogen atmosphere a solution of (13.0 g, 57.5 mmoles) 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in 50 mL tetrahydrofuran was added dropwise and stirred for 8 h at room temperature. The mixture was poured into 500 mL cold 10% sodium hydroxide and extracted with ethyl acetate. The solvent was evaporated and the residue was crystallized from diethyl ether, 4.4 g, 84% of **3**, (mp 192 °C) was isolated; ir (potassium bromide): ν 3157, 2974, 1730, 1628, 1458, 760 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, *J*=7.14 Hz), 2.55-2.61 (m, 1H), 2.69-2-76 (m, 1H), 2.98-3.10 (m, 2H), 3.27-.3.32 (m, 1H), 3.47-3.71 (m, 4H), 4.15-4.20 (q, 2H), 7.26-7.33 (m, 2H), 7.40-7.42 (m, 1H), 8.20-8.24 (m, 1H), 9.04 (s, 1H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 14.52, 36.52, 41.23, 42.03, 44.01, 45.23, 60.75, 66.97, 67.02, 110.80, 112.78, 121.13, 122.67, 124.12, 124.36, 136.84, 153.55, 172.10, 190.55; ms: m/z 361 (100) $[M]^+$, 316 (13), 299 (25), 286 (39), 254 (42), 227 (32), 219 (47), 167 (37). *Anal*. Calcd for $C_{18}H_{19}NO_3S_2$: C 59.81; H 5.29; N 3.87. Found: C 59.83; H .5.33; N 3.85.

{2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetic acid (4). Ketoester **3** (5.0 g, 13.8 mmoles) was dissolved in 20 mL tetrahydrofuran and 50 mL 20% potassium hydroxide (methanol-water 1:1) was added into this solution. The mixture was stirred at room temperature for 4 h. Then the mixture was poured into cold solution of 250 mL 10% hydrochloric acid. The precipitate was collected by filtration, dried and recrystalized from diethyl ether to give 4.1 g, 89% of **4**, mp 275 °C ; ir (potassium bromide): ν 3362, 3287, 1714, 1697, 1464, 752 cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide): δ 2.40-2.56 (m, 2H), 2.51 (dd, 1H, *J*=3.6 and 16.8 Hz), 3.00-3.09 (m, 2H), 3.45-3.51 (m, 1H), 3.56-3.69 (m, 2H), 3.73-3.85 (m, 1H), 7.17-7.27 (m, 2H), 7.49 (di 1H, *J*=8.01 Hz), 7.95 (d, 1H, *J*=7.*65* Hz), 11.95 (s, 1H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 36.53, 41.23, 42.00, 44.05, 67.04, 110.79, 112.78, 121.13, 122.65,124.36 136.86, 153.74, 173.63, 190.75. *Anal*. Calcd for $C_{16}H_{15}NO_3S_2$: C 57.64; H 4.53; N 4.20. Found: C 57.65; H 4.55; N 4.18.

General procedure for the compounds 5, 6, 7 and 8. Compound **4** (5.0 g, 15 mmoles) was dissolved in 50 mL of absolute chloroform and (2.27 g, 22.5 mmoles) triethylamine was added, cooled and kept at -10 °C. Later on, into this mixture (2.44 g, 22.5 mmoles) of ethyl chloroformate was added dropwise while the temperature of the mixture was kept -5 °C for 3 h. Then 22.5 mmoles of corresponding amine was added and stirred for 3 h. This mixture was washed with 50 mL 10% sodium hydroxide and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated.

***N*-(2-Benzyloxyethyl){2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetamide (5).** Compound **5** was prepared according to the general procedure from **4** (5.0 g,

15 mmoles) and (3.40 g 22.5 mmoles) benzyloxyethylamine. The residue was purified by silica gel chromatography using chloroform-acetone (4:1) to give 6.1 g, 87% of **5**, mp 197 °C; ir (potassium bromide): ν 3323, 3175, 2920, 1630, 1454, 746 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.27-2.33 (q, 1H), 2.94-3.09 (m, 2H), 3.29-3.36 (m, 1H), 3.44-3.66 (m, 8H), 4.53 (dd, 2H, *J*=7.8 and 15.7 Hz), 5.90 (d, 1H, *J*=5.1 Hz), 7.26-7.41 (m, 8H), 8.21-8.23 (m, 1H), 8.96 (s, 1H); ^{13}C nmr (deuteriochloroform+ deuteriodimethylsulfoxide): δ 37.69, 39.20, 41.11, 41.71, 43.66, 45.55, 67.38, 69.02, 72.58, 111.01, 112.55, 121.19, 122.34, 123.75, 124.47, 127.68, 127.90, 128.02, 128.44, 128.69, 136.79, 138.65, 153.38, 171.07, 190.96; ms: m/z 466 (11) $[M]^+$, 407 (13), 346 (9), 255 (40), 228 (18), 167 (16), 91 (100). *Anal*. Calcd for $C_{25}H_{26}N_2O_3S_2$: C 64.35; H 5.62; N 6.00. Found: C 64.37; H 5.61; N 5.97.

***N*-(2-Hydroxyethyl){2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetamide (6).** Compound **6** was prepared according to the general procedure from **4** (5.0 g, 15 mmoles) and (1.37 g, 22.5 mmoles) ethanolamine. The residue was purified by silica gel chromatography using ethyl acetate to give 4.3 g, 76% of **6**, mp 156 °C; ir (potassium bromide): ν 3462, 3275, 3185, 2931, 1660, 1634, 1553, 1456, 750 cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide): δ 2.36-2.50 (m, 2H), 2.63-2.68 (q, 1H), 2.84-2.88 (q, 1H), 3.05-3.12 (m, 1H), 3.14-3.18 (m, 2H), 3.41-3.50 (m, 3H), 3.56-3.69 (m, 2H), 3.74-3.82 (m, 1H), 4.66 (bs, 1H), 7.11-7.38 (m, 2H), 7.49 (d, 1H, *J*=7.86 Hz), 7.96 (d, 1H, *J*=7.71 Hz), 8.01 (t, 1H, *J*=5.48 Hz), 11.93 (s, 1H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 42.39, 46.03, 46.67, 46.81, 48.50, 50.26, 65.10, 72.07, 115.64, 117.53, 125.89, 127.34, 128.79, 129.15, 141.58, 158.50, 175.74, 195.81. *Anal*. Calcd for $C_{18}H_{20}N_2O_3S_2$: C 57.42; H 5.35; N 7.44. Found: C 57.44; H 5.33; N 7.45.

***N*-(2-Dimethoxyethyl){2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetamide (7).** Compound **7** was prepared according to the general procedure from **4** (5.0 g, 15 mmoles) and (2.36 g, 22.5 mmoles) aminoacetaldehyde dimethyl acetal. The residue was crystallized from ethyl acetate to give 5.3 g, 84% of **7**, mp 158 °C; ir (potassium bromide): ν 3308, 3184, 2930, 1633, 1458, 746 cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide): δ 2.38-2.67 (m, 2H), 2.83-2.87 (dd, 1H), 3.03-3.13 (m, 1H), 3.14-3.24 (m, 2H), 3.28 (d, 6H, *J*=3.1 Hz), 3.45-3.50 (m, 1H), 3.58-3.68 (m, 2H), 3.76-3.81 (m, 1H), 4.37 (t, 1H, *J*=5.4 Hz), 7.16-7.26 (m, 2H), 7.49 (d, 1H, *J*=8.02 Hz), 7.94-8.13 (m, 1H), 11.94 (s, 1H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 37.53, 40.90, 41.28, 41.93, 43.64, 45.57, 53.65, 53.73, 67.27, 102.43, 110.88, 112.77, 121.12, 122.62, 124.06, 124.38, 136.83, 153.72, 171.17, 190.99. *Anal*. Calcd for $C_{20}H_{24}N_2O_4S_2$: C 57.12; H 5.75; N 6.66. Found: C 57.15; H 5.76; N 6.64.

***N*-(2-Methoxyethyl){2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetamide (8).** Compound **8** was prepared according to the general procedure from **4** (5.0 g, 15 mmoles) and (1.68 g, 22.5 mmoles) 2-methoxyethylamine. The residue was crystallized from ethyl acetate to give 5.4 g, 92% of **8**, mp 246 °C; ir (potassium bromide): ν 3370, 3186, 1668, 1618, 1539, 738 cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide): δ 2.33-2.46 (m, 2H), 2.63 (d, 1H, *J*=16.69 Hz), 2.83 (d, 1H, *J*= 14.41 Hz), 3.06 (t, 1H, *J*=9.4 Hz), 3.26 (s, 3H), 3.28-3.32 (m, 2H), 3.34-3.38 (m, 2H), 3.45-3.81 (m, 4H), 7.16-7.26 (m, 2H), 7.49 (d, 1H, *J*=8.06 Hz), 7.95 (d, 1H, *J*=7.66 Hz), 8.07 (s, 1H, NH-amide), 11.93 (s, 1H, NH-indole); ^{13}C nmr (deuteriodimethylsulfoxide): δ 37.59, 38.93, 41.27, 41.92, 43.70, 45.54, 67.30, 71.07, 110.88, 112.76, 121.12, 122.60, 124.39, 136.83, 153.73, 170.98, 191.01; ms: m/z 390 (50) $[M]^+$, 331 (68), 254 (100), 228 (49), 167 (40), 102 (47), 76 (62). *Anal*. Calcd for $C_{19}H_{22}N_2O_3S_2$: C 58.44; H 5.68; N 7.17. Found: C 58.45; H 5.66; N 7.15.

General procedure for the compounds 9, 10, 11 and 12. A mixture of 5 g corresponding amide and 5 g sodium borohydride in 50 mL tetrahydrofuran was heated to 60 °C. To this mixture 30 mL methanol was added dropwise (*ca*. 4 h). This mixture poured into cold solution of 250 mL 10% sodium hydroxide and extracted with ethyl acetate organic layer dried and evaporated. The residue was dissolved in dichloromethane, and 5 mL of trifluoroaceticacid was added. The mixture was allowed to stand in a refrigerator overnight, washed with 10% potassium carbonate solution and then dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by silica gel chromatography or by crystallization.

***N*-(2-Benzyloxyethyl)-6-(1,2-dithiolane-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-3-one (9).** Compound **9** was obtained according to the general procedure from **5** (3.0 g, 6.42 mmoles) and sodium borohydride (3.0 g, 79.3 mmoles). The residue was crystallized from ethyl acetate-diethyl ether to give 2.35 g, 81% of **9**, mp 129 °C; ir (potassium bromide): ν 3213, 3298, 1622, 1452, 742 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.29-2.34 (m, 1H), 2.55-2.87 (m, 4H), 3.22-3.72 (m, 7H), 4.15-4.33 (m, 1H), 4.51-4.33 (m, 1H), 4.51 (s, 2H), 4.86 (s, 1H), 7.00-7.30 (m, 8H), 7.52 (d, 1H, *J*=7.9 Hz), 8.39 (s, 1H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 31.15, 32.75, 36.60, 41.60, 43.03, 46.12, 48.52, 68.37, 70.01, 72.58, 112.14, 113.54, 119.13, 119.82, 122.59, 125.12, 127.91, 128.10, 128.77(2c), 134.53, 136.86, 137.01, 138.96, 168.85; ms: m/z 450 (25) $[M]^+$, 359 (18), 344 (22), 316 (38), 240 (82), 212 (100), 180 (59), 168 (51), 167 (53), 91 (79). *Anal*. Calcd for $C_{25}H_{26}N_2O_2S_2$: C 66.64; H 5.82; N 6.22. Found: C 66.63; H 5.86; N 6.19.

***N*-(2-Hyroxyethyl)-6-(1,2-dithiolane-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-3-one (10).** Compound **10** was prepared according to the general procedure from **6** (5.0 g, 13.28 mmoles) and (5.0 g, 132 mmoles) sodium borohydride. The residue was purified by silica gel chromatography using ethyl acetate to give as a brown oil (3.8 g, 79%) of **10**, which was crystallized from diethyl ether-n-hexane; mp, 120 °C; ir (potassium bromide): ν 3348, 3267, 1641, 1454, 738 cm^{-1}; ^1H nmr (deuteriochloroform+ deuteriodimethylsulfoxide): δ 1.60-1.69 (m, 1H), 2.02-2.09 (m, 1H), 2.19-2.35 (m, 1H), 2.42-2.73 (m, 1H), 2.74-2.82 (m, 1H), 3.11-3.17 (m, 2H), 3.28-3.38 (m, 1H), 3.40-3.56 (m,2H), 3.59-3.65 (m, 1H), 3.73-3.79 8m, 1H), 4.63 (t, 1H, *J*=5.5 Hz), 6.89-7.01 (m, 1H), 7.05-7.09 (m, 1H), 7.33 (t, 1H, *J*=8.4 Hz), 7.96 (t, 1H, *J*=5.46 Hz), 10.68 (s, 1H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 19.69, 28.54, 37.43, 41.49, 41.91, 42.03, 45.50, 60.44, 68.82, 109.87, 111.67, 118.82, 122.17, 126.52, 128.78, 137.03, 137.41, 171.91. *Anal*. Calcd for $C_{18}H_{20}N_2O_2S_2$: C 59.97; H 5.59; N 7.76. Found: C 60.01; H 5.60; N 7.77.

***N*-(2-Dimethoxyethyl)-6-(1,2-dithiolane-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-3-one (11).** Compound **11** was prepared according to the general procedure from **7** (5.0 g, 11.88 mmoles) and (5.0 g, 132 mmoles) sodium borohydride. The residue was crystallized from diethyl ether to give 4.2 g, 87% of **11**, mp 200 °C; ir (potassium bromide): ν 3184, 2929, 1634, 1553, 1457, 748 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30-2.36 (q, 1H), 2.63-2.69 (q, 1H), 2.97-3.04

(m, 2H), 3.22-3.65 8m, 13H), 4.40 (t, 1H, *J*=5.3 Hz), 5.78 (s, 1H), 7.27-7.30 (m, 2H), 7.39-7.41 (m, 1H), 8.19-8.21 (m, 1H), 9.10 (s, 1H). *Anal.* Calcd for $C_{20}H_{24}N_2O_3S_2$: C 59.37; H 5.97; N 6.92. Found: C 59.39; H 6.00; N 6.93.

***N*-(2-Methoxyethyl)-6-(1,2-dithiolane-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-3-one (12).** Compound **12** was prepared according to the general procedure from **8** (5.0 g, 12.81 mmoles) and (5.0 g, 132 mmoles) sodium borohydride. The residue was crystallized from ethyl acetate to give 4.3 g, 89% of **12**, mp 244 °C; ir (potassium bromide): ν 3269, 2936, 1616, 1452, 752 cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide): δ 2.33-2.36 (m, 1H), 2.44-2.61 (m, 3H), 2.79-2.85 (m, 2H), 3.13-3.20 (m, 1H), 3.26 (s, 3H), 3.48-3.63 (m, 4H), 3.73-3.79 (m,1H), 3.95-4.06 (m, 1H), 4.79 (t, 1H), 7.00-7.13 (m, 1H), 7.34 (d, 1H, *J*=8.06 Hz), 7.57 (d, 1H, *J*=7.84), 11.22 (s, 1H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 31.14, 32.75, 36.60, 41.60, 43.04, 45.88, 48.22, 58.69, 70.02, 70.39, 112.14, 113.57, 119.11, 119.81, 122.59, 125.13, 134.48, 137.01, 168.87; ms: m/z 374 (77) $[M]^+$, 316 (88), 240 (60), 212 (100), 180 (58), 167 (58). *Anal.* Calcd for $C_{19}H_{22}N_2O_2S_2$: C 60.93; H 5.92; N 7.47. Found: C 60.91; H 5.93; N 7.46.

***N*-(2-Benzyloxyethyl)-7-methyl-6-(1,2-dithiolane-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-3-one (13).** Compound **9** (1.0, g, 2.2 mmoles) and (0.5 g,10.4 mmoles, 50% suspension in paraffin oil) of sodium hydride and 2 mL iodomethane in 20 mL benzene were refluxed for 6 h. After cooling the mixture, 2 mL methanol, and then 20 mL water were added. The organic layer was separated and evaporated. The residue was purified by using column chromatography and crystallized from *n*-hexane to give 0.85 g, 80% of **13**, mp 146 °C; ir (potassium bromide): ν 2953, 1628, 1464, 742 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (d, 3H), 2.26-2.31 (m, 2H), 2.48 (d, 1H, *J*=12.90 Hz), 2.75-2.80 (m, 1H), 3.17-3.23 (m, 1H), 3.29-3.36 (m, 1H), 3.39-3.46 (m 1H), 3.48-3.52 (m, 2H), 3.61-3.72 (m, 2H), 3.90 (s, 3H), 4.11-4.16 (m, 1H), 4.51 (t, 2H, *J*= 12.68 Hz), 4.85 (s, 1H), 7.03 (t, 1H, *J*=7.37 Hz), 7.13-7.31 (m, 7H), 7.56 (d, 1H, *J*=7.87 Hz). *Anal.* Calcd for $C_{26}H_{32}N_2O_2S_2$: C 67.74; H 6.31; N 5.85. Found: C 67.75; H 6.28; N 5.83.

Ethyl{9-methoxymethylene-2,3,4-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetate (14). A mixture of (10.0 g, 27.6 mmoles) of 4-oxo-ester **3**, (0.5 g, 1.47 mmoles) tetrabutylammonium hydrogen sulfate and 30 mL 25% sodium hydroxide in 150 mL dichloromethane was cooled in ice bath. 8 mL methoxymethylbromide was added dropwise and stirred for 2 h. Later on, phases were separated by adding 50 mL water. Organic layer was dried over with anhydrous magnesium sulfate, and evaporated. The residue was crystallized from diethyl ether to give 104 g, 92% of **14**, mp 108 °C; ir (potassium bromide): ν 2971, 1715, 1621, 1495, 1418, 742 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, *J*= 7.14 Hz), 2.50-2.57 (q, 1H), 2.71-2.77 (q, 1H), 3.10-3.26 (m, 3H), 3.40 (s, 3H), 3.57-3.71 (m, 4H), 4.14-4.20 (q, 2H), 5.88 (d, 1H, *J*=10.34 Hz), 6.00 (d, 1H, *J*=10.34 Hz), 7.29-7.37 (m, 2H), 7.56-7.58 (q, 1H), 8.31-8.33 (q, 1H). *Anal.* Calcd for $C_{20}H_{23}NO_4S_2$: C 59.23; H 5.71; N 3.45. Found: C 59.23; H 5.73; N 3.46.

{9-Methoxymethylene-2,3,4-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetic acid (15). Ketoester **14** (3.0 g, 7.4 mmoles) was dissolved in 15 mL tetrahydrofuran and 30 mL 20% potassium hydroxide (methanol-water 1:1) was added and stirred for 4 h at room temperature. This solution was poured into 50 mL cold solution of 10% of hydrochloric acid and extracted with ethyl acetate. The organic layer was evaporated and the residue was crystallized from diethyl ether to give 2.6 g, 86% of **15**, mp 185 °C; ir (potassium bromide): ν 3450, 1718, 1626, 1496, 748 cm^{-1}; ^1H nmr (deuteriodimethylsulfoxide): δ 2.33-2.39 (q, 1H), 2.58-2.64 (q, 1H), 2.86 (d, 1H, *J*=15.49 Hz), 2.95-3.11 (m, 2H), 3.34 (s, 3H), 3.54-3.60 (m, 1H), 3.68-3.80 (m, 3H), 5.90 (dd, 2H, *J*=10.22 and 22.37 Hz), 7.25-7.36 (m, 2H), 7.66 (d, 1H, *J*=8.22 Hz), 8.09 (d, 1H, *J*=7.81 Hz), 12.44 (bs, 1H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 36.57, 41.86, 42.05, 42.78, 48.14, 56.07, 60.21, 67.63, 75.04, 112.44, 114.22, 121.36, 123.49, 123.62, 124.86, 138.46, 147.69, 173.55, 191.97. *Anal.* Calcd for $C_{18}H_{19}NO_4S_2$: C 57.27; H 5.07; N 3.71. Found: C 57.29; H 5.04; N 3.72.

***N*-(2-Methoxyethyl){9-methoxymethylene-2,3,4-tetrahydrospiro[1*H*-carbazole-1,2'[1,3]dithiolane-4-one]-2-yl}-2-acetamide (16).** Compound **16** was obtained according to the preparation of **5** from **15** (3.0 g, 7.94 mmoles) and methoxyethylamine (2.0 g, 26.6 mmoles). The residue was crystallized from diethyl ether to give 3.1 g, 89% of **16**, mp 119 °C; ir (potassium bromide): ν 3286, 1680, 1638, 1552, 748 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.27-2.33 (q, 1H), 2.65-2.71 (q, 1H), 3.05-3.20 (m, 1H), 3.24-3.29 (m, 2H), 3.37, (s, 3H), 3.41 (s, 3H), 3.44-3.49 (m, 4H), 3.56-3.69 (m, 4H), 5.87 (d,1H, *J*=10.20 Hz), 6.00 (d, 1H, *J*=10.20 Hz), 7.29-7.38 (m, 2H), 7.56-7.58 (q, 1H), 8.30-8.33 (q, 1H). *Anal.* Calcd for $C_{21}H_{26}N_2O_4S_2$: C 58.03; H 6.03; N 6.44. Found: C 58.04; H 6.07; N 6.41.

***N*-(2-Methoxyethyl)-6-(1,2-dithiolane-2-yl)-7-methoxymethylene-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]-indole-3-one (17).** Compound **17** was obtained according to the preparation of **9** from **16** (3.0 g, 6.9 mmoles) and (3.0 g, 79.3 mmoles) sodium borohydride. Subsequent purification by silica gel chromatography using chloroform-acetone (4:1) yielded 2.2 g, 76% of **17**, mp 139 °C (from diethyl ether); ir (potassium bromide): ν 2939, 1638, 1465, 1112, 757 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35-2.40 (m, 1H), 2.65-2.76 (m, 2H), 2.87-2.92 (m, 1H), 3.07 (d, 1H, *J*=19.34 Hz), 3.36.3.39 (m, 2H), 3.42 (s, 3H), 3.44 (s, 3H), 3.46-3.66 (m, 5H), 4.21-4.26 (m, 1H), 4.89 (t, 1H, *J*=2.33 Hz), 5.70 (d, 1H, *J*=10.20 Hz), 5.94 (d, 1H, *J*=10.20 Hz), 7.16-7.38 (m, 2H), 7.54 (d, 1H, *J*=8.30 Hz), 7.65 (d, 1H, *J*=7.87 Hz); ^{13}C nmr (deuteriochloroform): δ 31.99, 36.29, 39.65, 41.19, 44.45, 46.74, 49.34 55.78, 59.07, 70.51, 71.67, 75.27, 111.29, 116.90, 118.84, 120.90, 123.61, 125.11, 130.52, 138.53, 169.48. *Anal.* Calcd for $C_{21}H_{26}N_2O_3S_2$: C 60.25; H 6.26; N 6.69. Found: C 66.26; H 6.24; N 6.71.

***N*-(2-Methoxyethyl)-4-ethyl-6-(1,2-dithiolane-2-yl)-7-methoxymethylene-1,2,3,4,5,6-hexahydro-1,5-methanoazocino-[4,3-*b*]indole-3-one (18).** Amide **17** (1.0 g, 2.4 mmol) was dissolved in tetrahydrofuran. To this solution (0.2 g, 4.2 mmoles, 50% suspension in paraffin oil) sodium hydride, 2 mL iodoethane were added and refluxed for 16 h. The mixture was poured into 30 mL 10% sodium hydroxide solution, extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified by silica gel chromatography using chloroform-acetone (4:1) and crystallized from diethyl ether-*n*-hexane (0.98 g, 92%), mp 136 ºC; ir (potassium bromide): ν 2929, 1633, 1459 759 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.05 (t, 3H, *J*=7.4 Hz), 1.85-1.95 (m, 1H), 2.10-2.18 (m, 1H), 2.31-2.36 (m, 1H), 2.49 (d, 1H, *J*=0.93 Hz), 2.63 (d, 1H, *J*=13.17 Hz), 2.89-2.91 (m, 1H), 3.32-3.39 (m, 2H), 3.41 (s, 3H), 3.43 (s, 3H), 3.53-3.68 (m, 5H), 4.22-4.27 (m, 1H), 4.86 (t, 1H, *J*=2.43 Hz), 5.70 (d, 1H, *J*=10.25 Hz), 5.96 (d, 1H, *J*=10.24 Hz), 7.15-7.29 (m, 2H), 7.53 (d, 1H, *J*=8.26 Hz), 7.65 (d, 1H, *J*=7.86 Hz); ^{13}C nmr (deuteriochloroform): δ 10.67, 28.10, 31.26, 39.77, 41.02, 45.89,

46.97, 49.18, 49.58, 55.72, 59.06, 70.87, 71.81, 75.23, 111.25, 117.34, 118.84, 120.85, 123.54, 125.17, 130.68, 138.51, 172.02. *Anal*. Calcd for $C_{23}H_{30}N_2O_3S_2$: C 61.85; H 6.77; N 6.27. Found: C 61.86; H 6.75; N 6.29.

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