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SYNTHESIS OF PYRROLO[*a*]- AND PYRROLO[*c*]PHENANTHRIDINE DERIVATIVES AND INDOLINYL AND INDOLYL-SUBSTITUTED 6-PHENANTHRIDINES

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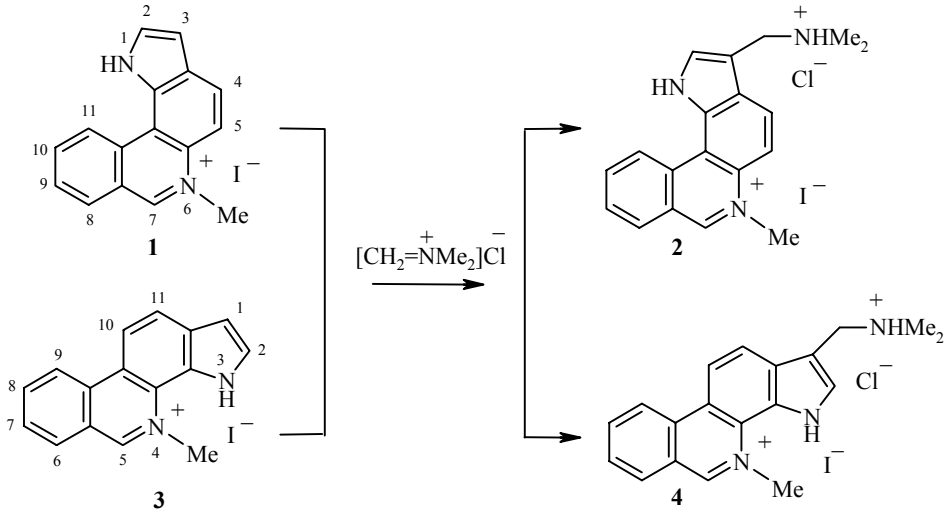
The corresponding Mannich bases have been synthesized by the aminomethylation of 6-methyl-1H-pyrrolo[2,3-a]- and 4-methyl-3H-pyrrolo[3,2-c]phenanthridinium iodides. The interaction of 6-chloro-phenanthridine with indoline and with 5-amino-N-acetylindoline gave the corresponding derivatives of phenanthridine. 6-(1-Indolyl)phenanthridine has been obtained by the dehydrogenation of 6-(1-indolinyl)phenanthridine with manganese dioxide.

Keywords: 6-(1-acetyl-5-indolinyl)phenanthridine, 6-(1-indolyl)phenanthridine, 6-methyl-1H-pyrrolo[2,3-*a*]- and 4-methyl-3H-pyrrolo[3,2-*c*]phenanthridinium Mannich bases.

Pyrrolophenanthridine derivatives obtained by us display high antitumor and antileukemic activity [1]. It therefore seemed of interest to broaden the limits of the investigation and to synthesize new derivatives of pyrrolophenanthridine with the aim of studying their biological activity.



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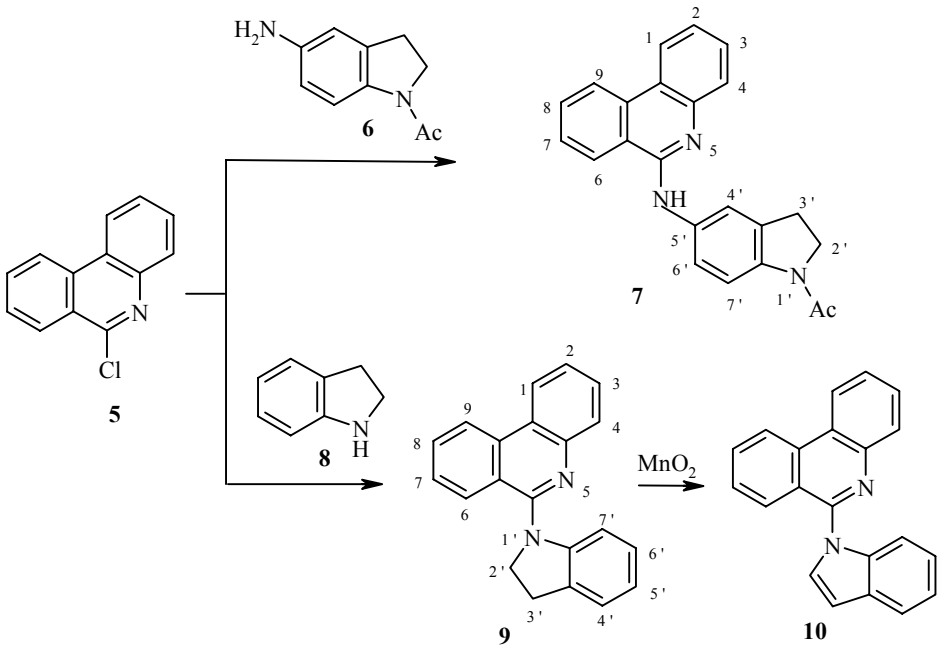
2-N,N-Dimethylaminomethyl-6-methyl-1H-pyrrolo[2,3-*a*]-6-phenanthridinium chloride-iodide (**2**) was obtained in high yield by the aminomethylation of 6-methyl-1H-pyrrolo[2,3-*a*]phenanthridinium iodide (**1**) [1] with crystalline Mannich reagent [2] in a mixture (5:2) of dry DMF and absolute ethanol. 1-N,N-Dimethylaminomethyl-4-methyl-3H-pyrrolo[3,2-*c*]-4-phenanthridinium chloride-iodide (**4**) was synthesized analogously from 4-methyl-3H-pyrrolo[3,2-*c*]phenanthridinium iodide (**3**) [1].

In addition the preparation of indoline and indole derivatives of phenanthridine may be of considerable interest for studying their biological activity, since the corresponding heteroaromatic systems in the acridine series (structural isomer of phenanthridine) display, as we have shown, high antitumor and antileukemic activity [3,4].

6-(1-Acetyl-5-indolinyl)aminophenanthridine (**7**) has been obtained by the alkylation of 1-acetyl-5-aminoindoline (**6**) [5] with 6-chlorophenanthridine (**5**) [6] in anhydrous pyridine at 80-90°C in a stream of argon. The interaction of 6-chlorophenanthridine **5** with indoline **8** under analogous conditions leads to the formation of 6-(1-indolinyl)phenanthridine (**9**). The synthesis of 6-(1-indolyl)-phenanthridine (**10**) was effected by dehydrogenation of the indoline fragment of compound **9** by the action of MnO_2 in *m*-xylene.



Weak absorption bands were present in the IR spectra of mixed salts **2** and **4** at 2730-2740 cm^{-1} corresponding to the stretching vibrations of a $^{+}$N–H bond. There was a characteristic absorption band at 3310 cm^{-1} in the IR spectrum of the indolylaminophenanthridine **7**, indicating the presence of a secondary amino group in the molecule, and also an absorption band at 1650 cm^{-1} belonging to the tertiary amide group (N–C=O) present in the molecule.

Signals for the β-protons of the pyrrole fragment were absent from the ^{1}H NMR spectra of the salts of Mannich bases **2** and **4**, but the signals of the α-protons were displayed as doublets at 8.26 and 8.2 ppm with J_{12} = 2.2 and J_{12} = 2.9 Hz for compounds **2** and **4** respectively. In addition signals were present in the ^{1}H NMR spectra of these compounds for the protons of the methylene groups at 4.67 ppm, and singlet signals at 2.77 ppm for the methyl group protons of the dimethylamino substituents. Signals for the protons of the methyl groups at the quaternized nitrogen atom of the pyridine fragment were displayed as singlets at 4.79 and 5.07 ppm for compounds **3** and **4**.

Signals were observed in the ^{1}H NMR spectra of compound **7** for the α- and β-protons of the indoline fragment as triplets with 4.13 and 3.23 ppm respectively with $J_{\alpha\beta}$ = 3.36 Hz. The aromatic protons of the indoline and phenanthridine fragments appeared at 7.2-8.97 ppm.

Triplet signals were observed in the ^{1}H NMR spectrum of compound **9** for the α- and β-protons of the indoline fragment at 4.34 and 3.22 ppm respectively ($J_{\alpha\beta}$ = 8.4 Hz). The signals of the protons of the indoline nucleus (ABCD system) were displayed as a multiplet at 6.49-7.28 ppm, and the multiplet signals of the phenanthridine fragment protons were at 7.68-8.82 ppm. Aromatization of the indoline fragment of compound **9** leads to the doublet signals of the α- and β-protons of the pyrrole nucleus being displayed in the spectrum of indolylphenanthridine **10** at 7.82 and 6.85 ppm respectively ($J_{\alpha\beta}$ = 3.36 Hz). The multiplet signals of the aromatic protons of the indole and phenanthridine fragments of the molecule were observed at 7.20-8.97 ppm.

There were peaks in the mass spectra of compounds **3**, **4**, **7**, **9**, and **10** for the molecular ions M^+ at 453, 453, 353, 296, and 294, and the character of the subsequent fragmentation did not conflict with the structures assigned to them.

EXPERIMENTAL

The IR spectra of the compounds obtained were taken on a Perkin Elmer 599 spectrometer in nujol. The ^{1}H NMR spectra were recorded on a Varian UNITY plus 400 spectrometer. Chemical shifts were measured relative to TMS as internal standard. The mass spectra were recorded on a Varian Mat 112 chromato-mass spectrometer. A check on the progress of reactions and the purity of compounds was carried out by TLC on Silufol UV 254 plates. Preparative chromatography of compounds was carried out on silica gel type L 40/100.

3-N,N-Dimethylaminomethyl-6-methyl-1H-pyrrolo[2,3-*a*]-6-phenanthridinium Chloride/iodide (2). N,N-Dimethylmethylenammonium chloride (crystalline Mannich reagent) (0.3 g, 0.005 mol) was added in two portions to a solution of 6-methyl-1H-pyrrolo[2,3-*a*]phenanthridinium iodide (**1**) (0.5 g, 0.0014 mol) obtained by heating to 80°C in a mixture of anhydrous DMF (10 ml) and absolute ethanol (4 ml). The mixture obtained was stirred at 80-90°C for 1 h and then cooled to room temperature. The precipitated yellow solid was filtered off, washed with absolute ethanol, and dried. The yield of Mannich base **2** 0.49 g (80%); mp 250°C (decomp.). IR spectrum, ν, cm^{-1}: 3490, 3210 (N–H), 2740 ($^+$N–CH$_3$), 2700 ($^+$N–H). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm, *J* (Hz): 13.13 (1H, br. s, NH); 11.3 (1H, br. s, $^+$NH); 10.35 (1H, s, 7-H); 9.42 (1H, d, 11-H); 8.75 (1H, d, 5-H); 8.65 (1H, d, 8-H); 8.45 (1H, d, 4-H); 8.45 (1H, t, 10-H); 8.26 (1H, d, J_{12} = 2.2, 2-H); 8.12 (1H, t, 9-H); 4.79 (3H, s, CH_3N^+); 4.68 (2H, d, $-CH_2N^+$); 2.77 [6H, s, $(CH_3)_2N^+$]. Found, %: C 50.1; H 4.7; N 9.2. $C_{19}H_{21}ClIN_3$. Calculated, %: C 50.3; H 4.6; N 9.3. Mass spectrum, *m/z* (I_{rel}, %): 453 (100). M^+ 453.

1-N,N-Dimethylaminomethyl-4-methyl-3H-pyrrolo[3,2-*c*]-4-phenanthridinium Chloride/iodide (4). Mannich base **4** was obtained analogously to compound **2** from 4-methyl-3H-pyrrolo[3,2-*c*]-phenanthridinium iodide (**3**). Yield 0.51 g (81%); mp 250°C (decomp.). IR spectrum, ν, cm^{-1}: 3480, 3210 (N-H), 2730 ($^+$N–CH$_3$), 2500 ($^+$N–H). ^{1}H NMR spectrum (DMSO-D$_6$), δ, ppm, *J* (Hz): 11.3 (1H, br. s, $^+$NH); 10.74 (1H, br. s, NH); 10.25 (1H, s, 5-H); 9.42 (1H, d, 11-H); 9.22 (1H, d, 9-H); 8.92 (1H, d, 10-H); 8.59 (1H, d, 6-H); 8.36 (1H, t, 8-H); 8.20 (1H, d, J_{12} = 2.9, 2-H); 8.06 (1H, t, 7-H); 4.79 (3H, s, CH_3N^+); 4.68 (2H, d, $-CH_2N^+$); 2.77 [6H, s, $(CH_3)_2N^+$]. Found, %: C 49.9; H 4.8; N 9.3. $C_{19}H_{21}ClIN_3$. Calculated, %: C 50.3; H 4.6; N 9.3. Mass spectrum, *m/z* (I_{rel}, %): 453 (100). M^+ 453.

6-(1-Acetyl-5-indolinyl)aminophenanthridine (7). A solution of 6-chloro-phenanthridine (**5**) (2.13 g, 0.01 mol) and N-acetyl-5-aminoindoline (1.76 g, 0.01 mol) in anhydrous pyridine (25 ml) was purged with argon for 15 min. The mixture was then heated to 85°C in a stream of argon and maintained at this temperature for 1 h. The mixture was cooled to room temperature, and poured into cold water (200 ml). The precipitated solid was filtered off, dried, and recrystallized from DMF. Yield was 2.75 g (78%) of mp >250°C (decomp.). IR spectrum, ν, cm^{-1}: 3110 (N–H), 1650 (CH_3C=O). ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: 9.17 (1H, s, NH); 8.69 (1H, d, 10-H); 8.65 (1H, d, 7-H); 8.64 (1H, d, 1-H); 8.49 (1H, d, 4-H); 8.04 (1H, s, 4'-H); 8.02 (1H, s, 7'-H); 7.71 (1H, d, 6'-H); 7.70 (1H, t, 3-H); 7.54 (1H, t, 8-H); 7.36 (1H, t, 2-H); 7.36 (1H, t, 9-H); 4.13 (2H, t, 2'-H); 3.23 (2H, t, 3'-H); 2.16 (3H, t, CH_3C=O). Found, %: C 78.3; H 5.3; N 11.9. $C_{23}H_{19}N_3O$. Calculated, %: C 78.2; H 5.4; N 11.9. Mass spectrum, *m/z* (I_{rel}, %): 353 (100). M^+ 353.

6-(1-Indolinyl)phenanthridine (9). Compound **9** was obtained analogously to compound **7** from 6-chlorophenanthridine (**5**) and indoline. After recrystallization from a mixture (5:1) of benzene–hexane 6-(1-indolinyl)phenanthridine (**9**) (2.1 g, 73%) was obtained having mp 122-124°C (decomp.). ^{1}H NMR spectrum (acetone-d_6), δ, ppm, *J* (Hz): 8.82 (1H, d, *J* = 8.4, 1-H); 8.67 (1H, d, 10-H); 8.24 (1H, d, 4-H); 7.94 (1H, t, 9-H); 7.94 (1H, t, 2-H); 7.70 (1H, t, 3-H); 7.68 (1H, d, 7-H); 7.58 (1H, t, 9-H); 7.28 (1H, d, 4'-H); 6.93 (1H, t, 6'-H); 6.81 (1H, t, 5'-H); 6.49 (1H, s, 7'-H); 4.94 (2H, t, 2'-H); 3.22 (2H, t, 3'-H). Found, %: C 85.1; H 5.3; N 9.5. $C_{21}H_{16}N_2$. Calculated, %: C 85.1; H 5.4; N 9.5. Mass spectrum, *m/z* (I_{rel}, %): 296 (100). M^+ 296.

6-(1-Indolyl)phenanthridine (10). Manganese dioxide (2.5 g) was added to 6-(1-indolinyl)phenanthridine (**9**) (2.96 g, 0.01 mol) dissolved in *m*-xylene (30 ml) and the mixture boiled with a water separator for 2.5-3 h. The solvent was distilled off in vacuum and the solid residue chromatographed (silica gel, benzene). Yield was 1.48 g (50%) of mp 140-143°C (from benzene–hexane, 5:1). ^{1}H NMR spectrum (acetone-d_6), δ, ppm, *J* (Hz): 8.84 (1H, d, 10-H); 8.10 (1H, d, 4-H); 8.07 (1H, d, J_{12} = 3.36, 1-H); 8.04 (1H, t, 2-H); 7.85 (1H, t, 3-H); 7.98 (1H, d, 7-H); 7.85 (2H, m, 8-H, 9-H); 7.82 (1H, d, 2'-H); 7.75 (1H, d, 7'-H); 7.44 (1H, d, 4'-H); 7.2 (2H, m, 5'-H, 6'-H); 6.85 (1H, d, 3'-H). Found, %: C 85.4; H 4.9; N 9.5. $C_{21}H_{14}N_2$. Calculated, %: C 85.7; H 4.8; N 9.5. Mass spectrum, *m/z* (I_{rel}, %): 294 (100). M^+ 294.

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