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Reaction of 2-chloroindole-3-carbaldehyde with epihalogenohydrins. Tandem oxirane-opening—1,3-oxazole-closure process

Konstantin F. Suzdalev [a,*], Sophia V. Den'kina [a], Gennadii S. Borodkin [a], Valerii V. Tkachev [b], Mikhail A. Kiskin [c], Mikhail E. Kletsky [d], Oleg N. Burov [d]

[a] Research Institute of Physical and Organic Chemistry of Southern Federal University, Stachki Street 194/2, 344090 Rostov-on-Don, Russian Federation
[b] Institute of Problems of Chemical Physics, Russian Academy of Sciences, N.N. Semyonov Street 1, 142432 Czernogolovka, Moscow region, Russian Federation
[c] N.S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninsky prosp. 31, 119991 Moscow, Russian Federation
[d] Chemical Department of Southern Federal University, Sorge Street 7, 344090 Rostov-on-Don, Russian Federation

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ABSTRACT

Reaction of 2-chloroindole-3-carbaldehyde with epibromohydrin gives the expected 1-(oxiran-2-ylmethyl) derivative. However the analogous reaction with epichlorohydrin leads to the formation of the oxazolo[3,2-*a*]indole skeleton. Some chemical properties of this tricyclic system were investigated. Its reaction with secondary amines unexpectedly proceeds with the opening of the oxazole ring.

1. Introduction

It is known that indole, 2-phenylindole, and 4-hydroxy-1*H*-indole-3-carbaldehyde undergo alkylation with epichlorohydrin to form 1-(oxiran-2-ylmethyl) derivatives.[1,2] Similar compounds react with amines to produce derivatives having the 3-amino-2-hydroxypropyl chain at the 1-position of the indole ring, and are used as HIV-1 protease inhibitors[3] and antitumor compounds.[4] Reactions of 1-(oxiran-2-ylmethyl) indoles with phenols give alcohols, which are inhibitors of human cytosolic phospholipase $A_2\alpha$.[5]

2. Results and discussion

With the aim of obtaining 2-chloro-1-(oxiran-2-ylmethyl)-1*H*-indole-3-carbaldehyde we investigated the reaction of 2-chloroindole-3-carbaldehyde **1** with epihalogenohydrins. We found that the structure of the product depends on the kind of halogenohydrin. The reaction of compound **1** with epibromohydrin leads to desired compound **2**. However, the analogous reaction with epichlorohydrin leads to a derivative of the [1,3]oxazolo[3,2-*a*]indole ring system **4** and occurs as a tandem oxirane-opening—1,3-oxazole-closure process. It is obvious that this reaction proceeds by N-alkylation by the methylene group of oxirane ring with the formation of open-chain intermediate **3**. Similar intermediates were earlier observed in reactions of epichlorohydrin with other heterocyclic compounds.[6] Next, nucleophilic substitution of the chlorine atom in the intermediate **3** leads to the formation of tricyclic system 4 (Scheme 1). Data about some other compounds having the oxazolo[3,2-*a*]indole skeleton, which may be employed in the manufacture of 5-HT_4 receptor antagonists, were published.[7]

The ^{1}H NMR spectrum of product **2** shows that the signals of the methylene protons of the epoxide fragment are unequivalent due to the presence of the chiral center. Therefore, the signals of the protons of the OCH_2-group appear at 2.52–2.54 and 2.79–2.82 ppm as two multiplets. The multiplet of the proton at the chiral carbon atom is at 3.23–3.28 ppm. The signals of the protons of the NCH_2-group are characterized as two doublets of doublets at 4.22 and 4.53 ppm. The assignment of all protons in the ^{1}H NMR spectrum of substances **2** and **4** were carried out on the basis of two-dimensional heteronuclear correlation spectroscopy NMR {^{1}H, ^{13}C} using HSQC and HMBC experiments.

In the ^{1}H NMR spectrum of compound **4** the hydrogen atoms of the two methylene groups are magnetically unequivalent due to the presence of a chiral center and each of them is observed as a separate signal. The signals of the NCH_2-protons appear as two

* Corresponding author. Fax: +7 (863) 243 47 00; e-mail addresses: konsuz@gmail.com (K.F. Suzdalev), sofia1984@inbox.ru (S.V. Den'kina).

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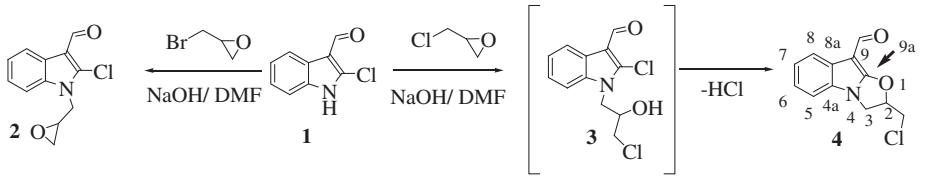


Scheme 1. Interaction of compound **1** with epihalogenohydrins.

doublets of doublets at 4.21 and 4.37 ppm. Evidence of the assignment of these signals as the NCH_2-protons is the presence of the two cross-peaks in the two-dimensional spectrum {^{1}H, ^{15}N} with coordinates 4.21, 132.61, and 4.36, 132.61 ppm, showing the interaction of each proton with the nitrogen atom. The signal of protons of the $ClCH_2$-group is at 3.91–3.97 ppm. For them, the correlation between {^{1}H, ^{15}N} is absent. This data show that the $ClCH_2$-group is out of cycle. In the two-dimensional {^{1}H, ^{13}C} HMBC spectrum, interaction between the proton at C-2 and the carbon atom C(9a) (cross-peak with coordinates ^{1}H, ^{13}C at 5.58, 162.5 ppm) is observed. Interaction of the protons of the NCH_2-group with the carbon atom C(9a) is observed as two cross-peaks with coordinates ^{1}H, ^{13}C at 4.21, 162.5 and at 4.37, 162.5 ppm, respectively.

Finally the structure of compound **4** was determined on the basis of X-ray analysis (Fig. 1). Cyclic atoms N(4), C(4a)–C9(a) are in one plane accurate within 0.05 Å. Atom C(2) and O(2) are over this plane at 0.145 Å and 0.264 Å, respectively. Atom Cl(1) is under the plane of the indole ring at 0.313 Å. The torsion angle C(3)–C(2)–C(10)–Cl(1) is 47.1°. The torsion angle C(8a)–C(9)–C(11)–O(2) is 1.6°.

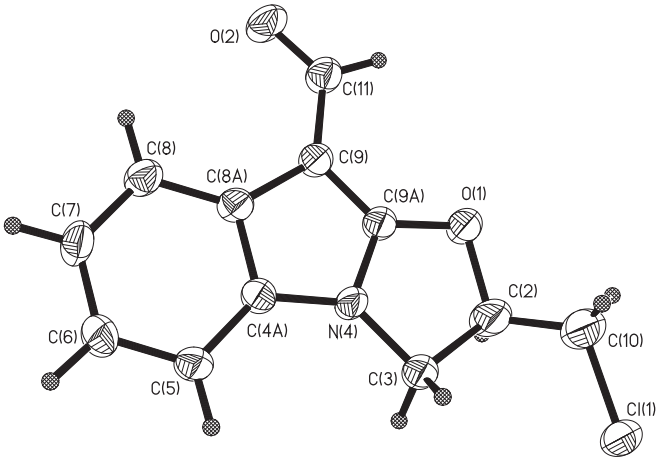
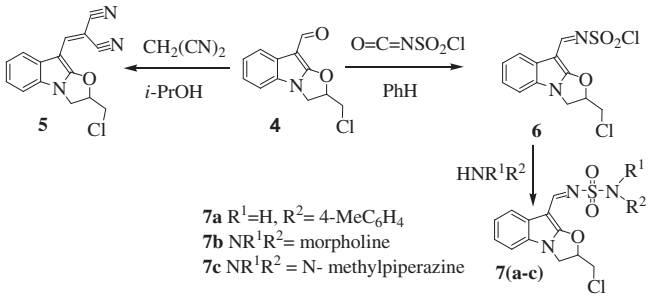


Fig. 1. Molecular structure of compound **4** (thermal ellipsoids are drawn at the 30% probability level).

We have investigated some chemical properties of compound **4**. Its reaction with malononitrile gives Knoevenagel condensation product **5**. Reaction with chlorosulfonyl isocyanate at the carbonyl group with the extrusion of CO_2,[8] forms unstable product **6**, which may be isolated and reacted with amines to give sulfonamides **7**(**a**–**c**) (Scheme 2).

In the ^{1}H NMR spectra of products **5**, **6**, **7**(**a**–**c**), the view and the location of signals of the aliphatic protons do not change in comparison with the initial spectrum of compound **4**.

The structure of compound **5** was determined by X-ray analysis (Fig. 2). Atoms of the indole ring N(4), C(4a)–C9(a) and atoms O(1) and C(2) are in one plane accurate within 0.04 Å. Atom C(3) goes out of plane at 0.073 Å. The torsion angle C(3)–C(2)–C(10)–Cl(1) is 56.8°. In contrast to compound **4**, atom Cl(1) goes out of indole plane at 2.66 Å; the dihedral angle between planes O(1)–C(2)–C(3) and C(2)–C(10)–Cl(1) is practically right (87.6°).



Scheme 2. Reactions of compound **4** with malononitrile and chlorosulfonyl isocyanate.

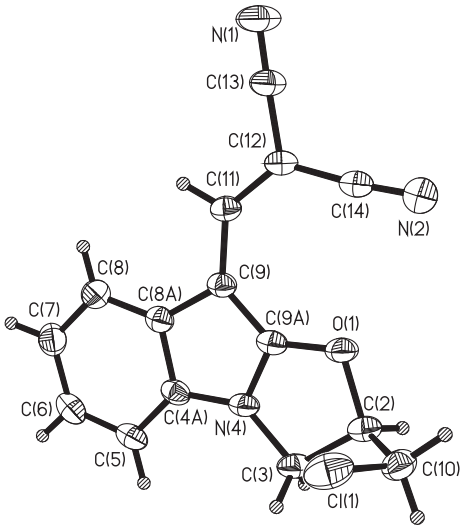
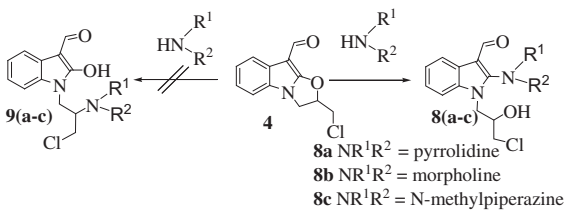


Fig. 2. Molecular structure of compound **5** (thermal ellipsoids are drawn at the 30% probability level).

In order to realize nucleophilic substitution of the chlorine atom, we explored the reaction of compound **4** with secondary amines. Unexpectedly we isolated another kind of compounds having a chlorine atom, according to data elemental and mass-spectral analyses. In the ^{1}H NMR spectra of these products we observed changes in the character of signals of the aliphatic protons in comparison with initial compound **4**, as well as observing the CHO-group intact. Therefore we suggest the ring-opening process is taking place with the formation of either **8**(**a**–**c**) or **9**(**a**–**c**), having a chloropropyl chain at the indole nitrogen (Scheme 3).



Scheme 3. Interaction of compound **4** with secondary amines.

It was impossible to make distinguish between structures **8** or **9** only on the basis of NMR and IR spectra. The ultimate proof of structure of substances **8**(**a**–**c**) was made by X-ray analysis of product **8a** (Fig. 3).

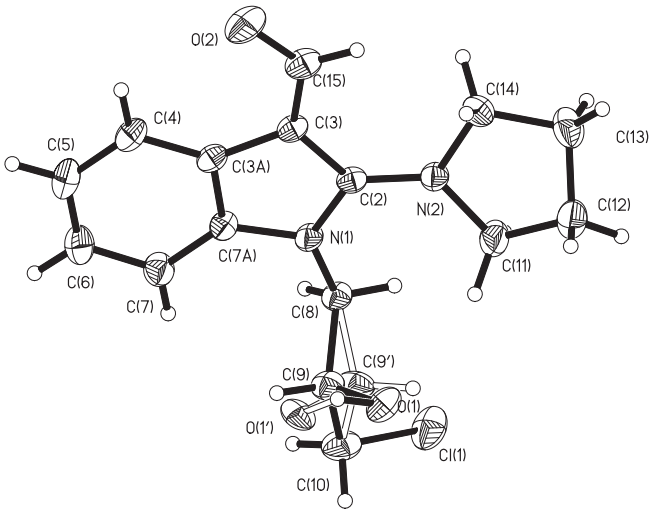
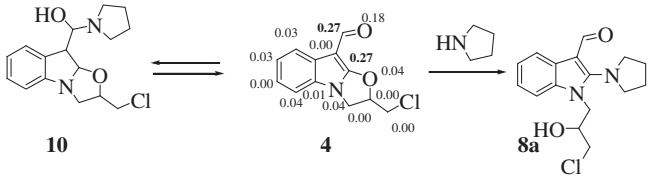


Fig. 3. Molecular structure of compound **8a** (thermal ellipsoids are drawn at the 30% probability level).

Due to the presence of a chiral center [C(9) or C(9′)] the X-ray crystal structure of molecule **8a** (Fig. 3) displays several interesting structural features. Both enantiomers have the composition of a monocrystal. In the unit cell, one quarter of atoms C(9′), H(9′), and O(1′) are situated in positions (unshaded lines), which differ from other molecules. In residual molecules, the fragment C(9), H(9), O(1) is located inversely (drawn by shaded lines). It is noteworthy that atom H(1) is common for both oxygen atoms O(1) and O(1′). The carbon atoms of the indole ring are in one plane accurate within 0.005 Å, nitrogen atoms N(1) and N(2) go out of plane in different directions at 0.018 Å, atoms C(15) and O(2) move aside at 0.092 Å as N(2). In the pyrrolidine ring, atoms C(12) and C(13) go out of plane N(2)C(11)C(14) at 0.39 and −0.24 Å. Torsion angles O(2)–C(15)–C(3)–C(2)=179.1, C(15)–C(3)–C(2)–N(2)=4.5, C(3)–C(2)–N(2)–C(14)=4.3°. The sum of angles at N(1)=359.5 and at N(2)=359.7°. The fact that the indole and pyrrolidine rings are situated near one plane indicate the presence of n-π conjugation between a lone pair of N(2) and the aromatic π-system. In the unit cell, the indole and pyrrolidine rings are located in a 'head to tail' manner with an intermolecular hydrogen bond between the O(2) atoms of one molecule and the hydrogen atom of the OH-group of another one.

2.1. Results of quantum-chemical calculations

According to the calculation of Fukui indices f^+, compound **4** has two reaction centers—the carbon atom of the aldehyde group and atom C(9a) (Scheme 4).[9]



Scheme 4. Fukui indices f^+ of compound **4** and its reactions with pyrrolidine.

Reaction of compound **4** with malononitrile proceeds at the carbon atom of the carbonyl group to give the Knoevenagel condensation product **5**. However, interaction of starting material **4** with secondary amines proceeds at C(9a). In order to explain experimental facts and compare the stability of reaction product **8a** and hypothetical molecule **10**, obtained by two alternative pathways, quantum-chemical calculations for reaction of compound **4** with pyrrolidine were carried out. Results, shown in Table 1, indicate that the energy of compound **10** is higher than the starting reaction point energy by15.1 kJ mol^{-1}. This result demonstrates endothermic character of the attack at the aldehyde group of **4** by the pyrrolidine molecule. At the same time the addition of pirrolidine leads to the formation of compound **8a**, which is more preferable by 28.9 kJ mol^{-1}.

Table 1
Total (E) and relative (ΔE) energies calculated in the gas phase by the B3LYP/6-311 G(d) method

Structure	E, a.u	ΔE, kJ mol^{-1}
4+Pyrrolidine	−1341.26388	0.0
8a	−1341.27488	−28.9
10	−1341.25815	+15.1

3. Experimental section

3.1. General

All commercially available compounds were used without further purification. 2-Chloroindole-3-carbaldehyde was obtained by the known protocol.[10] IR spectra were taken on Varian 3100 FT-IR, Excalibur Series instrument by means of Attenuated Total Reflectance (ATR) method. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-250 instrument. Two-dimensional heteronuclear correlation NMR spectra {^{1}H, ^{13}C} and {^{1}H, ^{15}N} using HSQC and HMBC experiments for compounds **2** and **4** were recorded on an Avance-600 (Bruker 600 MHz) spectrometer. Mass-spectra were obtained on a Varian MAT-44 spectrometer.

The X-ray data sets for **4** and **5** were collected on a Bruker APEX II diffractometer equipped with a CCD camera (Mo K_α, λ=0.71073 Å).[11] The X-ray diffraction study of **8a** was carried out on a Bruker P4 diffractometer (Mo K_α, λ=0.71073 Å). For compound **5** semiempirical absorption correction was applied.[12] The structures were solved by direct methods and using Fourier techniques and were refined by the full-matrix least squares against F^2 with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were positioned geometrically and refined using the riding model. All calculations were carried out with the use of the SHELX97 program package.[13]

3.2. 2-Chloro-1-(oxiran-2-ylmethyl)-1*H*-indole-3-carbaldehyde (2)

To 2-chloroindole-3-carbaldehyde (1.8 g, 0.01 mol) in DMF (10 mL) was added sodium hydroxide (0.5 g, 0.01 mol) in water (1 mL). The reaction mixture was stirred for 1 h. To this solution was added epibromohydrin (2.5 mL, 0.03 mol). The reaction mixture was stirred for 30 min and then slowly heated up to 50 °C. The mixture was poured into water (300 mL) and retained overnight. The crude product was filtered off and dried, then dissolved in benzene and passed through a filter funnel, containing Al_2O_3 (20 g). The solvent was evaporated to volume (10–15 mL). The formed precipitate was filtered off to give the *title compound* **2** (705 mg, 30%) as a white powder, mp 114–118 °C; [Found: C, 60.92; H, 4.26; Cl, 15.04; N, 5.94. $C_{12}H_{10}ClNO_2$ requires C, 61.16; H, 4.28; Cl, 15.04;

N, 5.93%]; ν_{max} 1648, 1613, 1581, 1512 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 2.52–2.54 (1H, m, OCH_2), 2.79–2.82 (1H, m, OCH_2), 3.23–3.28 (1H, m, CH), 4.22 (1H, dd, *J* 15.6, 5.3 Hz, NCH_2), 4.53 (1H, dd, *J* 15.6, 3.3 Hz, NCH_2), 7.26–7.37 (3H, m, H-5,6,7), 8.21–8.27 (1H, m, H-4), 10.07 (1H, s, CH=O); δ_C (150 MHz, $CDCl_3$) 45.0(C-10), 45.1(C-8), 49.7(C-9), 109.9(C-7), 113.2(C-3), 121.1(C-4), 123.5(C-5), 124.1(C-3a), 124.2(C-6), 135.8(C-7a), 136.1(C-2), 183.8 (C-11);*m*/*z* (M^+) 235 (100), 192 (63%).

3.3. 2-(Chloromethyl)-2,3-dihydro[1,3]oxazolo[3,2-*a*]indole-9-carbaldehyde (4)

To 2-chloroindole-3-carbaldehyde (23.5 g, 0.13 mol) in DMF (40 mL) was added sodium hydroxide (5.24 g, 0.131 mol) in water (5 mL). The reaction mixture was stirred for 1 h. To this solution was added epichlorohydrin (30.50 mL, 0.39 mol). The reaction mixture was stirred for 3 h and then slowly heated up to 50 °C. The mixture was poured into water (500 mL) and retained overnight. The crude product was filtered off and dried, then dissolved in benzene and passed through a filter funnel, containing Al_2O_3 (50 g). The solvent was evaporated to volume (15–20 mL). The formed precipitate was filtered off to give the crude product (15.0 g, 49%). Substance **4** was recrystallized from propan-2-ol to give the *title compound* **4** (8 g, 26%) as a white powder, mp 161–165 °C; [Found: C, 61.40; H, 4.30; Cl, 15.10; N, 5.96. $C_{12}H_{10}ClNO_2$ requires C, 61.16; H, 4.28; Cl, 15.04; N, 5.93%]; ν_{max} 1635, 1614, 1562, 1562 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 3.91–3.96 (2H, m, OCH_2), 4.21 (1H, dd, *J* 9.5, 6.4 Hz, NCH_2), 4.37 (1H, dd, *J* 9.5, 8.4 Hz, NCH_2), 5.67–5.71 (1H, m, CH), 7.06–7.37 (3H, m, H-5,6,7), 8.11 (1H, d, *J* 7.7 Hz, H-8), 9.88 (1H, s, CH=O); δ_C (150 MHz, $CDCl_3$) 43.9(C-10), 45.0(C-3), 87.7(C-2), 94.0(C-9), 109.0(C-5), 121.5(C-8), 122.4(C-6), 123.2(C-7), 128.7(C-8a), 128.8(C-4a), 162.3(C-9a), 180.6(C-11); *m*/*z* (M^+) 235 (100), 200 (50), 172 (30), 144 (68), 117 (35%). The crystallographic parameters for **4** at *T*=296(2) K are as follows: $C_{12}H_{10}ClNO_2$, *fw*=235.66, triclinic system, space group *P*−1, *a*=7.795(9) Å, *b*=8.067(9) Å, *c*=8.250(10) Å, *α*=94.236(19)°, *β*=92.663(17)°, *γ*=93.488(19)°, *V*=515.7(10) $Å^3$, *Z*=2, ρ_{calcd}=1.518 g cm^{-3}, *μ*=3.52 cm^{-1}, 3054 measured reflections, 976 reflections with $I>2.0\sigma(I)$, R_{int}=0.1222, GooF=0.974, R_1 ($I>2\sigma(I)$)=0.0727, wR_2 ($I>2\sigma(I)$)=0.1788. CCDC 831061.

3.4. {[2-(Chloromethyl)-2,3-dihydro[1,3]oxazolo[3,2-*a*]indol-9-yl]methylene}malononitrile (5)

To compound **4** (235 mg, 0.001 mol) in propan-2-ol (2 mL) and triethylamine (0.14 mL, 0.001 mol) was added malononitrile (100 mg). The reaction mixture was refluxed for 2 h. The yellow precipitate was filtered off and dried to give the crude product (100 mg, 35%), which was recrystallized from propan-2-ol to give the *title compound* **5** (80 mg, 28%) as a yellow powder, mp 180–182 °C; [Found: C, 63.75; H, 3.56; Cl, 12.55; N, 14.87. $C_{15}H_{10}ClN_3O$ requires C, 63.50; H, 3.55; Cl, 12.50; N, 14.81%]; ν_{max} 2211, 1617, 1588, 1529, 1468 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.90–4.05 (2H, m, CH_2Cl), 4.28–4.40 (1H, m, NCH_2), 4.43–4.54 (1H, m, NCH_2), 5.75–5.88 (1H, m, CH), 7.07–7.33 (3H, m, H-5,6,7), 7.64 (1H, s, CH=), 7.70–7.80 (1H, m, H-8); δ_C (60 MHz, $CDCl_3$) 45.3, 45.8, 67.9, 89.7, 89.8, 110.7, 116.0, 117.6, 121.1, 123.6, 123.8, 129.1, 130.3, 148.4, 162.3; *m*/*z* (M^+) 283 (25), 75 (73), 39 (100%). The crystallographic parameters for **5** at *T*=296(2) K are as follows: $C_{15}H_{10}ClN_3O$, *fw*=283.71, monoclinic system, space group $P2_1/n$, *a*=8.711(5) Å, *b*=10.988(7) Å, *c*=14.230(9) Å, *β*=103.854(10)°, *V*=1322.5(14) $Å^3$, *Z*=4, ρ_{calcd}=1.425 g cm^{-3}, *μ*=2.87 cm^{-1}, 11,510 measured reflections, 2166 reflections with $I>2.0\sigma(I)$, R_{int}=0.031, GooF=0.968, R_1 ($I>2\sigma(I)$)=0.0446, wR_2 ($I>2\sigma(I)$)=0.1389, $T_{min/max}$=0.9719/0.9830. CCDC 831062.

3.5. {(1*Z*)-[2-(Chloromethyl)-2,3-dihydro[1,3]oxazolo[3,2-*a*]indol-9-yl]methylene}sulfamoyl chloride (6)

To compound **4** (904 mg, 0.004 mol) in dry benzene (10 mL) was added dropwise chlorosulfonyl isocyanate (0.35 mL, 0.004 mol). This was retained at room temperature for 10–15 min. The formed precipitate was filtered off, washed with diethyl ether and dried to give crude product **6** (1 g, 75%). It was recrystallized from a mixture of benzene and acetonitrile (1:1) to give the *title compound* **6** (360 mg, 27%) as a light yellow powder, mp 165–168 °C; [Found: C, 43.43; H, 3.04; Cl, 21.37; N, 8.45; S, 9.66. $C_{12}H_{10}Cl_2N_2O_3S$ requires C, 43.26; H, 3.03; Cl, 21.28; N, 8.41; S, 9.62%]; ν_{max} 1619, 1576, 1539, 1525, 1475 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 4.23–4.38 (3H, m, CH_2Cl, NCH_2), 4.59–4.73 (1H, m, NCH_2), 6.06–6.25 (1H, m, CH), 7.11–7.55 (3H, m, H-5,6,7), 8.25–8.53 (2H, m, H-4, CH=).

3.6. *N*-{(1*Z*)-[2-(Chloromethyl)-2,3-dihydro[1,3]oxazolo[3,2-*a*]indol-9-yl]methylene}-*N*′-(4-methylphenyl)sulfamide(7a)

To 4-methylaniline (107 mg, 0.001 mol) in dry acetonitrile (3 mL) and triethylamine (0.14 mL, 0.001 mol) was added compound **6** (333 mg, 0.001 mol). To the precipitate of triethylamine hydrochloride was added water (20 mL). The remaining precipitate was filtered off and dried to give the crude product **7a** (400 mg, 99%). It was recrystallized from butan-1-ol (3 mL) to give the *title compound* **7a** (100 mg, 25%) as a white powder, mp 235–238 °C; [Found: C, 56.72; H, 4.51; Cl, 8.82; N, 10.44; S, 7.97. $C_{19}H_{18}ClN_3O_3S$ requires C, 56.50; H, 4.49; Cl, 8.78; N, 10.40; S, 7.94%]; ν_{max} 3245, 1615, 1576, 1513, 1475 cm^{-1}; δ_H (250 MHz, $CDCl_3$+0.1 mL DMSO-d_6) 1.83 (3H, s, Me), 3.51–3.74 (2H, m, CH_2Cl), 3.79–3.91 (1H, m, NCH_2), 4.03–4.18 (1H, m, NCH_2), 5.40–5.54 (1H, m, CH), 6.51–6.88 (7H, m, ArH), 7.51–7.63 (1H, m, H-8), 8.37 (1H, s, NH), 8.84 (1H, s, CH=); δ_C (60 MHz, DMSO-d_6); 21.2, 46.0, 46.3, 88.1, 91.0, 111.4, 120.6 (2C), 122.1, 123.7, 123.8, 128.5, 130.3 (2C), 130.6, 133.1, 137.1, 158.2, 165.4.

3.7. *N*-{(1*Z*)-[2-(Chloromethyl)-2,3-dihydro[1,3]oxazolo[3,2-*a*]indol-9-yl]methylene}morpholine-4-sulfonamide (7b)

To morpholine (0.1 mL, 0.001 mol) in dry acetonitrile (3 mL) and triethylamine (0.14 mL, 0.001 mol) was added compound **6** (333 mg, 0.001 mol). To the precipitate of triethylamine hydrochloride was added water (20 mL). The remaining precipitate was filtered off and dried to give the crude product **7b** (258 mg, 67%). It was recrystallized from butan-1-ol (3 mL) to give the *title compound* **7b** (112 mg, 29%) as a white powder, mp 195–198 °C; [Found: C, 49.87; H, 4.71; Cl, 9.20; N, 10.91; S, 8.32. $C_{16}H_{18}ClN_3O_4S$ requires C, 50.07; H, 4.73; Cl, 9.24; N, 10.95; S, 8.35%]; ν_{max} 1620, 1577, 1510, 1475 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 3.14–3.26 (4H, m, $N(CH_2)_{2morpholine}$), 3.68–3.83 (4H, m, $O(CH_2)_{2morpholine}$), 3.87–4.02 (2H, m, CH_2Cl), 4.22–4.34 (1H, m, NCH_2), 4.41–4.52 (1H, m, NCH_2), 5.69–5.83 (1H, m, CH), 7.05–7.32 (3H, m, H-5,6,7), 8.00–8.15 (1H, m, H-8), 8.83 (1H, s, CH=); δ_C (60 MHz, DMSO-d_6); 46.2, 46.3, 47.2 (2C), 66.1 (2C), 88.7, 91.2, 111.5, 122.4, 123.9, 124.0, 128.5, 130.8, 159.4, 165.6.

3.8. *N*-{(1*Z*)-[2-(Chloromethyl)-2,3-dihydro[1,3]oxazolo[3,2-*a*]indol-9-yl]methylene}-4-methylpiperazine-1-sulfonamide (7c)

To *N*-methylpiperazine (0.12 mL, 0.00106 mol) in dry acetonitrile (3 mL) and triethylamine (0.15 mL, 0.00106 mol) was added compound **6** (354 mg, 0.00106 mol). To the precipitate of triethylamine hydrochloride was added water (20 mL). The remaining precipitate was filtered off and dried to give the crude product **7c** (308 mg, 73%). It was recrystallized from butan-1-ol (3 mL) to give the *title compound* **7c** (170 mg, 40%) as a white powder, mp 131–135 °C; [Found: C, 51.24; H, 5.30; Cl, 8.89; N, 14.06; S, 8.05. $C_{17}H_{21}ClN_4O_3S$ requires 51.45; H, 5.33; Cl, 8.93; N, 14.12; S, 8.08%];

ν_{max} 1620, 1575, 1507, 1475 cm^{-1}; δ_H (250 MHz, $CDC1_3$) 2.28 (3H, s, Me), 2.42–2.61 (4H, m, $N(CH_2)_{2piperazine}$), 3.17–3.32 (4H, m, $N(CH_2)_{2piperazine}$), 3.85–4.02 (2H, m, CH_2Cl), 4.19–4.30 (1H, m, NCH_2), 4.37–4.50 (1H, m, NCH_2), 5.67–5.82 (1H, m, CH), 7.02–7.30 (3H, m, H-5,6,7), 8.00–8.13 (1H, m, H-8), 8.79 (1H, s, CH=); δ_C (60 MHz, $CDCl_3$); 44.4, 45.7, 46.2, 46.9 (2C), 54.5 (2C), 88.6, 89.2, 109.8, 123.3, 123.5, 123.9, 128.8, 129.9, 160.3, 164.2.

3.9. 1-(3-Chloro-2-hydroxypropyl)-2-pyrrolidin-1-yl-1*H*-indole-3-carbaldehyde (8a)

To compound **4** (235 g, 0.001 mol) in propan-2-ol (2 L) was added pyrrolidine (0.1 mL, 0.0013 mol) and triethylamine (0.14 L, 0.001 mol) and the reaction mixture was refluxed for 1 h. The precipitate was filtered off and dried to give the crude product (90 mg, 29%). The precipitate was recrystallized from benzene to give the *title compound* **8a** (52 mg, 17%) as a white powder, mp 125–128 °C; [Found: C, 62.89; H, 6.26; Cl, 11.61; N, 9.17. $C_{16}H_{19}ClN_2O_2$ requires C, 62.64; H, 6.24; Cl, 11.56; N, 9.13%]; ν_{max} 3237, 1597, 1581, 1533 cm^{-1}; δ_H (250 MHz, $CDC1_3$) 1.98–2.18 (4H, m, $(CH_2)_{2pyrrolidine}$), 3.42–3.72 (6H, m, CH_2Cl, NCH_2, CH, OH), 4.18–4.47 (4H, m, $N(CH_2)_{2pyrrolidine}$), 7.16–7.40 (3H, m, H-5,6,7), 8.13–8.25 (1H, m, H-4), 9.75 (1H, s, CH=O); δ_C (60 MHz, $CDCl_3$) 26.5 (2C), 47.2, 48.0, 54.5 (2C), 69.7, 107.3, 110.0, 121.0, 123.0, 123.1, 126.9, 135.7, 155.4, 183.1. The crystallographic parameters for **8a** at T=296(2) K are as follows: $C_{16}H_{19}ClN_2O_2$, fw=306.78, triclinic system, space group $P-1$, a=7.799(2) Å, b=9.829(2) Å, c=10.526(2) Å, α=67.500(10)°, β=81.63(2)°, γ=81.18(2)°, V=733.3(3) $Å^3$, Z=2, ρ_{calcd}=1.389 g cm^{-3}, μ=2.67 cm^{-1}, 3143 measured reflections, 1969 reflections with $I>2.0\sigma(I)$, R_{int}=0.0303, GooF=1.053, R_1 ($I>2\sigma(I)$)=0.0478, wR_2 ($I>2\sigma(I)$)=0.1252. CCDC 831063.

3.10. 1-(3-Chloro-2-hydroxypropyl)-2-morpholin-4-yl-1*H*-indole-3-carbaldehyde (8b)

To compound **4** (470 mg, 0.002 mol) in propan-2-ol (3 mL) was added morpholine (0.18 mL, 0.002 mol) and the reaction mixture was refluxed for 2 h. The precipitate was filtered off and recrystallized from benzene with charcoal to give the *title compound* **8b** (60 mg, 9%) as a white powder, mp 125–127 °C; [Found: C, 59.30; H, 5.91; Cl, 10.94; N, 8.65. $C_{16}H_{19}ClN_2O_3$ requires C, 59.54; H, 5.93; Cl, 10.98; N, 8.68%]; ν_{max} 3350, 1620, 1582, 1534, 1461 cm^{-1}; δ_H (250 MHz, $CDC1_3$) 2.67–2.79 (1H, m, OH), 3.20–3.51 (4H, $N(CH_2)_{2morpholine}$), 3.52–3.75 (2H, m, CH_2Cl), 3.77–4.08 (4H, m, $O(CH_2)_{2morpholine}$), 4.18–4.53 (3H, m, NCH_2, CH), 7.26–7.40 (3H, m, H-5,6,7), 8.13–8.33 (1H, m, H-4), 10.33 (1H, s, CH=O); δ_C (60 MHz, $CDCl_3$) 46.8, 47.3, 53.6 (2C), 67.8 (2C), 69.9, 88.4, 109.6, 110.9, 121.9, 123.0, 123.6, 124.2, 125.5, 181.1; m/z (M^+) 322 (64), 305 (82), 130 (78), 89 (70), 43 (100%).

3.11. 1-(3-Chloro-2-hydroxypropyl)-2-(4-methylpiperazin-1-yl)-1*H*-indole-3-carbaldehyde (8c)

To compound **4** (235 mg, 0.001 mol) in propan-2-ol (2 mL) were added *N*-methylpiperazine (0.11 mL, 0.001 mol) and triethylamine (0.14 mL, 0.001 mol) and the reaction mixture was refluxed for 2 h. The precipitate was filtered off and dried to give the crude product **8c** (186 mg, 55%). It was recrystallized from mixture benzene with acetonitrile (10:1) to give the *title compound* **8c** (70 mg, 21%) as a white powder, mp 160–164 °C; [Found: 60.56; H, 6.57; Cl, 10.52; N, 12.46. $C_{17}H_{22}ClN_3O_2$ requires C, 60. 80; H, 6.60; Cl, 10.56; N, 12.51%]; ν_{max} 3059, 1659, 1610, 1524, 1506, 1456 cm^{-1}; δ_H (250 MHz, $CDC1_3$) 2.35 (3H, s, Me), 2.46–2.67 (4H, m, $N(CH_2)_{2piperazine}$), 3.06–3.52 (5H, m, $N(CH_2)_{2piperazine}$, OH), 3.52–3.74 (2H, m, CH_2Cl), 4.11–4.42 (3H, NCH_2, CH), 7.18–7.38 (3H, m, H-5,6,7), 8.16–8.33 (1H, m, H-4), 10.26 (1H, s, CH=O); δ_C (60 MHz, $CDCl_3$); 46.2, 46.8, 47.5 (2C), 52.9 (2C), 55.7, 69.8, 110.7, 110.9, 121.9, 123.5, 124.1, 125.5, 134.6, 156.1, 184.2.

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