JOC Notes

A New, Stereoselective, Ring-Forming Reaction of 1,2-Ethanedithiol with *N*-Acylated Indoles

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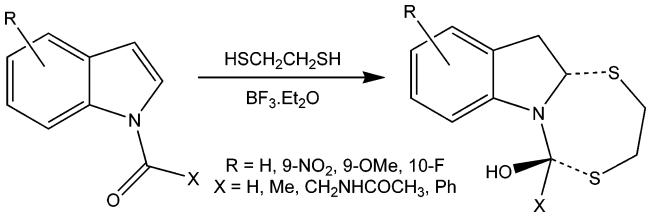
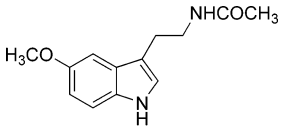


While attempting to prepare 2,5-dithiacyclopentyl derivatives from *N*-acyl 5-fluoroindole by reaction with 1,2-ethanedithiol we discovered that, instead of the expected product, annelation occurred to give a tricyclic compound containing a 3,6-dithiaazepine ring. This reaction is stereoselective and was found to be general for *N*-acylindoles, not being affected by substituents on the indole ring.

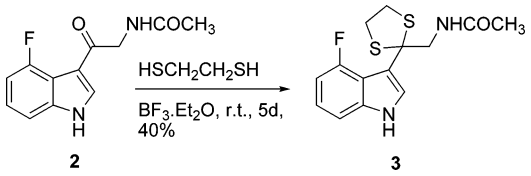
During studies on analogues of the pineal hormone melatonin (*N*-acetyl-5-methoxytryptamine, **1**)[1,2] we wished to prepare β-2,5-dithiacyclopentyl derivatives of melatonin as we had found that the corresponding β-cyclopentyl compounds had an interesting profile.[3]



Melatonin (1)

We prepared the 4-fluoroindole analogue **3** (Scheme 1) in 40% yield by standard treatment of the ketone **2** with 1,2-ethanedithiol and boron trifluoride etherate. Compound **3** was a modest melatonin antagonist (pIC_{50} = 4.96 nM)[4] with some selectivity (11-fold) for the MT_2 receptor.[5] In an attempt to improve potency and receptor site selectivity we decided to relocate the side chain from C3 to *N*1 (compound **8a,** Scheme 2). This would require starting from compound **7a** where, however, the reactive carbonyl group is of the amide rather than of the ketone type, making the synthesis of the dithiane unusual. Nevertheless, a very recent report demonstrates that in a reaction similar to ours, *N*-acylamides can add EtSH to give orthothioamides.[6]

SCHEME 1. Method of Preparation of the C3-β-Conformationally Constrained Melatoninergic Indolic



2 **3**

However, when we reacted amide **7a** with 1,2-ethanedithiol, the spectroscopic data obtained for the compound isolated were not in agreement with structure **8a**. The LC−MS showed a molecular mass of 328, in contrast to the expected value of 310. Clearly, ethanedithiol addition did take place, but this was not followed by water loss to give the dithiolane. ^{1}H NMR revealed that there were only three aromatic protons, with a coupling pattern compatible with the trisubstituted benzene moiety, and that addition to the pyrrole double bond and formation of an indolidine had occurred. More detailed chemical shift, *J*-coupling (COSY) and NOESY analysis (see ESI, Table 1) showed the product to correspond to the structure **9a**.

While the initial reaction, thiol addition to an *N*-acyl indole carbonyl, has been previously reported,[6] the subsequent C2−C3 addition of the thiol to the indole ring appears unprecedented in the literature. It is noteworthy that Belhadj and Goekjian report that the reaction of acylindole with EtSH in the presence of BF_3 leads only to the formation of orthothioamide, without the formation of the C2−C3 addition product, even at high temperature and after long reaction times; the effect of these more rigorous conditions is the cleavage of the C−N bond.[6] Clearly, the present *exo-trig* cyclization must be driven by a favorable substrate stereochemistry,[7a,b] as also has been recently observed in an analogous reaction reported by Clavé et al.[8]

The two addition reactions that take place more or less simultaneously at the carbonyl and at the pyrrole carbon pose a further problem concerning the relative stereochemistry of the newly formed stereogenic centers. GC data and the NMR spectra clearly indicated the formation of only one diastereomer.

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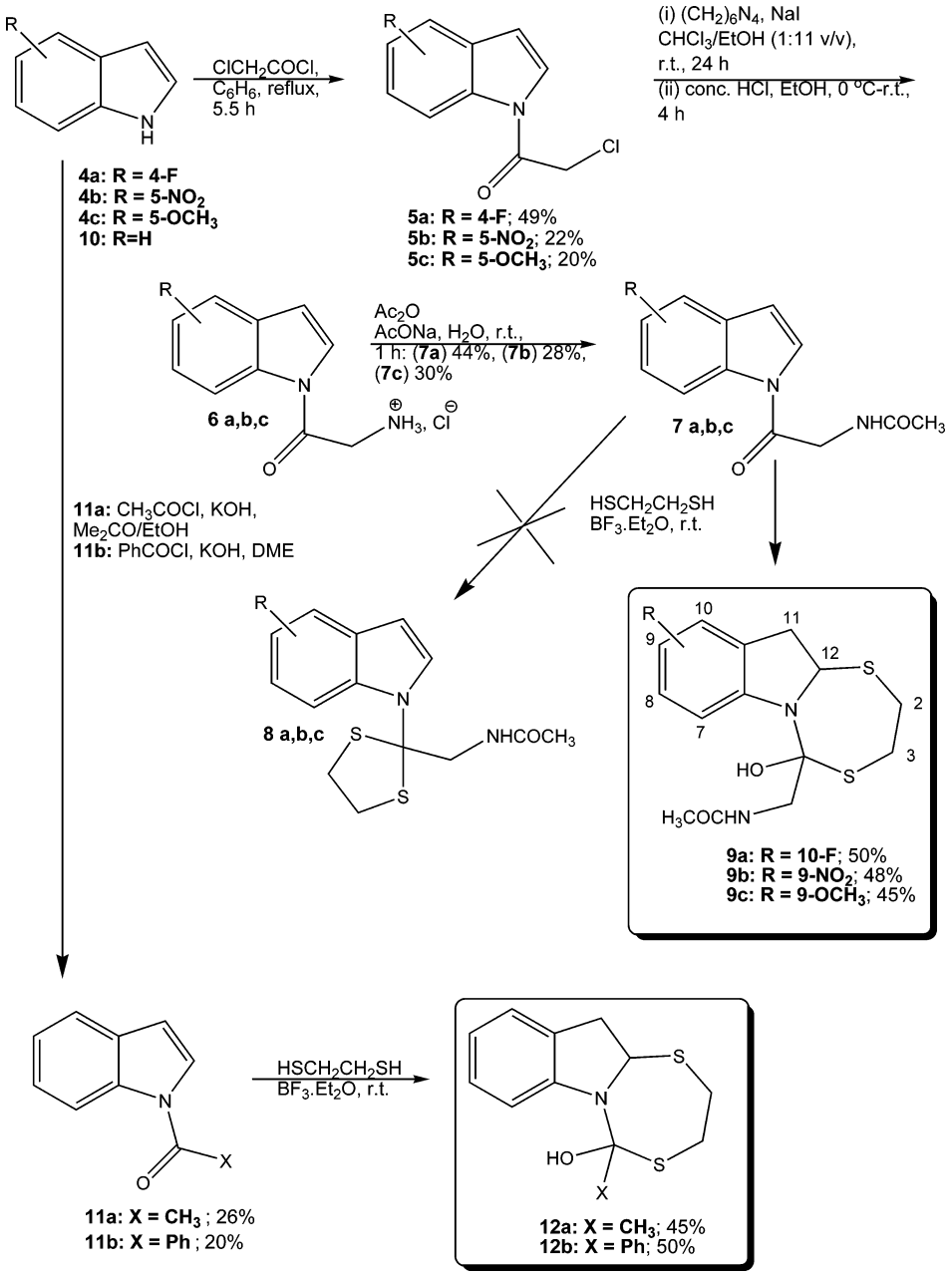
SCHEME 2. Preparation of the *x*-Substituted 5-(Alkanamidomethyl)-2,3,11,12-tetrahydro-5*H*-1,5,3-dithiazepino[3,2-*a*]indol-5-ol Derivatives 9a−c and Their Congeners 12a,b



To confirm the structure and to determine the relative stereochemistry of compound **9a**, we ran ROESY experiments at 600 MHz, in conjunction with molecular mechanics conformational searches (MMFF force field, Spartan '06, Wavefunction, Inc., Irvine, CA). The results of ROESY are pictorially summarized in Figure 1.

The ROE between the methylene protons at 3.87 ppm and the methine at 4.67 ppm is the first indication of their *cis* arrangement. Moreover, the rest of the ROE network is fully compatible with the low-energy MMFF conformations found for the (*R*,*R*)/(*S*,*S*) diastereomer, but in total disagreement with the (*R*,*S*)/(*S*,*R*) diastereomer. Thus, the signal at 3.87 ppm also exhibits a NOE with that for the aromatic proton at 7.29 ppm. The two simultaneous NOEs observed for the methylene signal are in accord with the lowest-energy MMFF structure for the (*R*,*R*)/(*S*,*S*) diastereomer (Figure 2), but with none of the low-energy MMFF structures for the (*R*,*S*)/(*S*,*R*) diastereomer (within 3 kcal/mol from the absolute minimum).

Wishing to establish the synthetic generality of this remarkably facile 7-*exo*-*trig* cyclization, we subjected a variety of 4- or 5-substituted 1-(alkanamidoacetyl) indoles (Scheme 2) to the same experimental protocol and found that, in each case, the annulation proceeded smoothly over 24 h at ambient temperature to produce their respective 9- or 10-substituted 5-(alkanamidomethyl)-2,3,11,12-tetrahydro-5*H*-1,5,3-dithiazepino[3,2-*a*]indol-5-ol derivatives **9b**,**c**[9] (Scheme 2). Analogous products were obtained (**12a** and **12b**[9]) when the X group in compounds **11a**

(9) Satisfactory analytical data and attributable NMR spectra were obtained for all new compounds.

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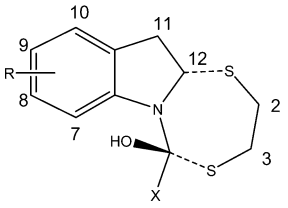
TABLE 1. ^{1}H NMR Chemical Shifts of Thioorthoamides Annulation Products



9a: R=10-F; X=$CH_2NHCOCH_3$

9b: R=9-NO_2; X=$CH_2NHCOCH_3$

12a: R=H; X=CH_3

12b: R=H; X=C_6H_5

cmpd	9a	9b	12a	12b
H12	4.67	4.78	4.70	4.77
H11a-b	3.08	3.19	3.04	3.09
H10	–	8.19	7.26	7.36
H9	7.01	–	7.11	7.22
H8	7.25	8.10	7.19	7.27
H7	7.29	7.92	7.31	7.30
H2–H3	3.18–3.27	3.18–3.27	3.20–3.22	3.14–3.25
OH	9.42	9.24	9.34	9.96
	3.87(CH_2)	3.95	2.2(CH_3)	7.95(2H, *o*)
X	8.28(NH)	8.29		7.53(2H, *m*)
	1.89(CH_3)	1.89		7.60(1H, *p*)

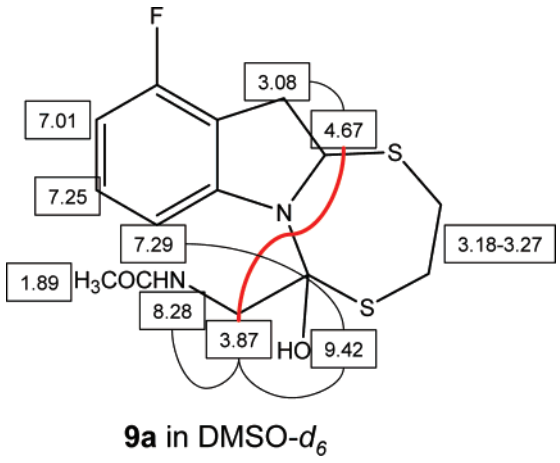


FIGURE 1. Compound **9a**: ROESY proton spatial interactions.

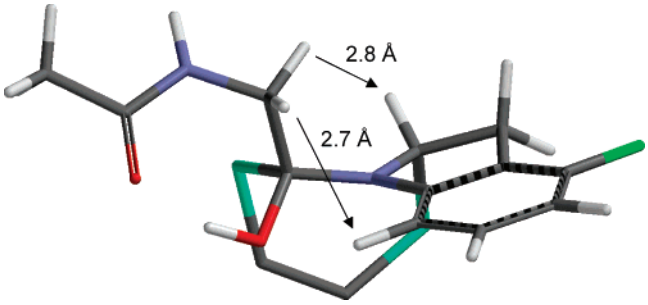
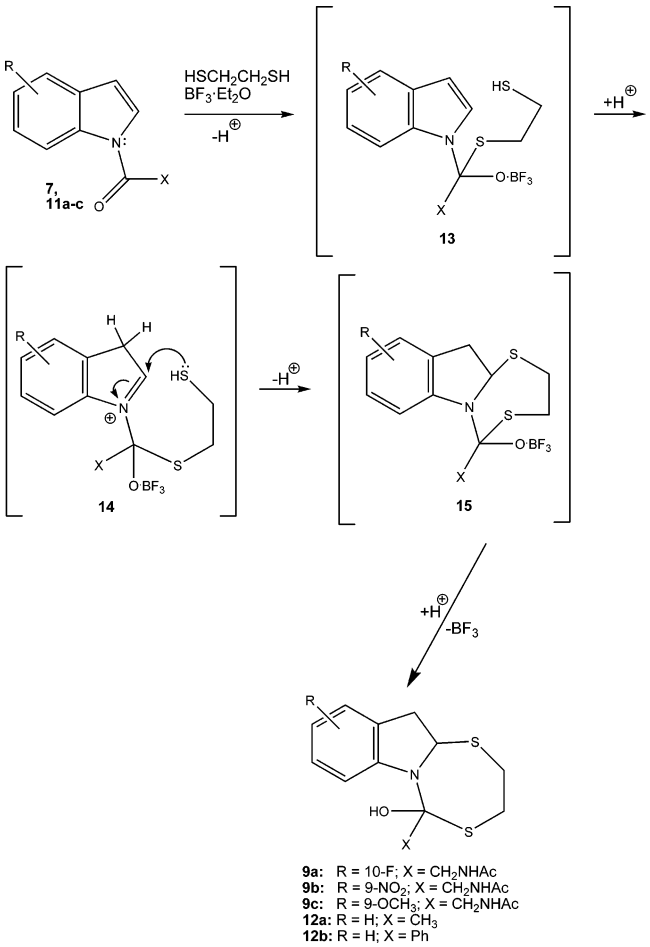


FIGURE 2. Lowest-energy MMFF structure computed for (*R*,*R*)-**9a** (some hydrogens have been removed for clarity).

and **11b** was methyl and phenyl, respectively (Scheme 2). It seems, therefore, that the proposed cyclization is not affected by the nature of the *N*-acylating group, nor by the electron-releasing or electron-withdrawing character and/or position of the indole substituent.

A plausible pathway for the conversion of analogues **7** and **11** into **9** and **12**, respectively, is outlined in Scheme 3. According to the proposed mechanism, the catalyst (BF_3·Et_2O) is complexed with **7** and **11** to form an electrophilic substrate for 1,2-ethanedithiol. The nucleophilic attack of the latter on

SCHEME 3. Proposed Mechanism for the Conversion of 7 and 11 into 9 and 12, Respectively



the amide carbon leads to the formation of the chiral semithioketal **13**. The second mercapto group of 1,2-ethanedithiol is added to the C2–C3 double bond of the indolic analogue **14** to give the indolino intermediate **15** and finally the new tricyclic nuclei **9a**,**b**,**c** and **12a**,**b**.

This new cyclization proceeds with very high stereoselective control to afford an *N*1-C2 annulated indoline as a single diastereomer. We are now examining the application of this reaction to other *N*-heterocycles and are investigating the reactions of these dithiazepines, which represents a relatively unknown system.[12,13] Their biological activity will be described elsewhere.

Experimental Section

Typical Experimental Procedure: Synthesis of 5-(Acetamidomethyl)-10-fluoro-2,3,11,11^a-tetrahydro-5*H*-1,5,3-dithiazepino-[3,2-*a*]indol-5-ol (9a). Chloroacetylchloride (3.3 mL, 41.4 mmol) was added dropwise to a solution of 4-fluoroindole (**4a**) (0.56 g, 4.11 mmol) in anhydrous benzene (15 mL). The mixture was heated at reflux for 5.5 h and then treated with 50 mL of aqueous NaOH (8%). The organic phase was separated, and the aqueous was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine, the solvent was removed in vacuo, and the

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brownish residue was purified by recrystallization from methanol to afford 0.40 g (49%) of pure 1-chloroacetyl-4-fluoroindole (**5a**). Mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (s, 2H, $COCH_2$-Cl), 6.80−6.81 (d, J = 4.0 Hz, 1H, H_{arom}), 6.97−7.01 (t, J = 8.9 Hz, 1H, H_{arom}), 7.28−7.34 (m, 1H, H_{arom}), 7.39−7.40 (d, J = 4.0 Hz, 1H, H_{arom}), 8.19−8.21 (d, J = 8.1 Hz, 1H, H_{arom}).

To a solution of α-chloroketone **5a** (0.40 g, 1.90 mmol) in chloroform (2.5 mL) was added dropwise a solution of hexamethylenetetramine (0.50 g, 3.57 mmol) in absolute ethanol (25 mL). The mixture was stirred at ambient temperature for 10 min and then treated with sodium iodide (0.32 g, 2.13 mmol). The resulting suspension was stirred for 24 h at room temperature and then chilled to 0 °C. The precipitate formed was filtered, washed with cold absolute ethanol, and dried in vacuo. The solid was then dissolved in absolute ethanol (18 mL) and treated dropwise with concd HCl (1.5 mL) at 0 °C. The mixture was then allowed to thaw, stirred at room temperature for 4 h and at reflux for 2 more hours. The resulting solid was filtered and washed with cold absolute ethanol to give **6a**, which was used as such in the next reaction.

To a stirred, chilled (0 °C) solution of **6a** in H_2O (4 mL) was sequentially added acetic anhydride (0.2 mL) and an aqueous solution (2 mL) of sodium acetate (0.32 g, 3.9 mmol). The resulting suspension was allowed to thaw, stirred at ambient temperature for 1 h, and acidified by the cautious addition of concd HCl. The mixture was then extracted with CH_2Cl_2 (3 × 25 mL), the combined organic phases were washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a beige solid. The solid was triturated with EtOAc (1 mL) to afford pure 1-(acetamidoacetyl)-4-fluoroindole (**7a**) as a white solid (yield 45 mg, 44%). Mp 66−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H, $COCH_3$), 4.66−4.67 (d, J = 3.3 Hz, 2H, CH_2NH), 6.50 (bs, 1H, NHCO), 6.78−6.80 (d, J = 2.9 Hz, 1H, H_{arom}), 6.93−7.02 (t, J = 8.4 Hz, 1H, H_{arom}), 7.27−7.31 (m, 1H, H_{arom}), 7.37−7.38 (d, J = 2.6 Hz, 1H, H_{arom}), 8.13−8.17 (d, J = 8.4 Hz, 1H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 43.1, 106.3, 109.6, 110.0, 112.4, 123.1, 126.5, 126.6, 153.2, 167.1, 170.3. Anal. calcd for $C_{12}H_{11}FN_2O_2$ (%) C, 61.53; H, 4.73; N, 11.96; found (%) C, 61.47; H, 4.65; N, 11.85.

To a solution of **7a** (30.0 mg, 0.14 mmol) in 1,2-ethanedithiol (1.5 mL) a catalytic quantity of freshly distilled BF_3·Et_2O (10 drops) was added dropwise at room temperature, and the mixture was stirred for 24 h. The crude product was dissolved in EtOAc (50 mL) and washed with a saturated aqueous solution of sodium bicarbonate and brine. The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure to give a residue, which was purified by flash column chromatography (silica gel; eluent 5% MeOH/EtOAc) to afford 5-(acetamidomethyl)-10-fluoro-2,3,-11,11*a*-tetrahydro-5*H*-1,5,3-dithiazepino[3,2-*a*]indol-5-ol (**9a**) (yield 20 mg, 44%) as a white solid. Mp 118−120 °C (ethanol); ^{1}H NMR (600 MHz, DMSO, data referred to the residual solvent shift at δ 2.49 ppm) δ 1.89 (s, 3H, CH_3), 3.08 (d, J = 7.9 Hz, 2H, H11), 3.18−3.27 (m, 4H, H2−H3) 3.87 (d, J = 4.9 Hz, CH_2), 4.67 (t, J = 7.9 Hz, H12), 7.01 (t, J = 8.5 Hz, H9), 7.25 (t, J = 7.3 Hz, H8), 7.29 (d, J = 7.3 Hz, H7), 8.28 (bt, J = 4.2 Hz, NH) 9.42 (s, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 23.3, 31.5, 34.6, 43.6, 52.9, 60.6, 112.7, 113.2, 122.4, 128.8, 138.5, 169.3, 170.8. MS: M^+ = 328. Anal. calcd for $C_{14}H_{17}FN_2O_2S_2$ (%) C, 51.20; H, 5.22; N, 8.53; found (%) C, 51.16; H, 5.19; N, 8.49.

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Supporting Information Available: NMR spectra and spectral data for selected compounds and elemental analysis data for key target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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