Heteroaromatic annulation studies on 2-[bis(methylthio)methylene]-1-methyl-3-oxoindole: synthesis of novel heterocyclo[*b*] fused indoles

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Dedicated to Professor P. T. Narasimhan on his 75th birthday
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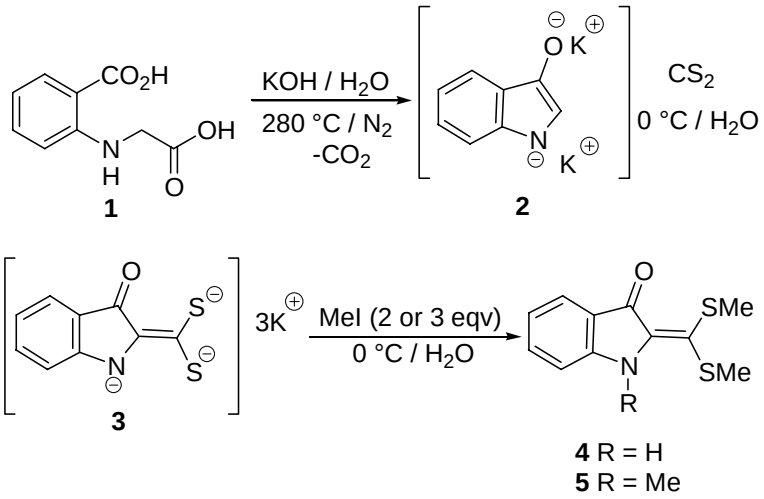
Abstract: Heteroannulation of 2-[Bis(methylthio)methylene]-1-methyl-3-oxoindole with *β*-substituted *β*-lithioaminoacrylonitrile, malononitrile and guanidine has been reported to yield novel substituted pyrido[3,2-*b*]indoles and pyrimido[5,4-*b*]indole derivatives in varying yields.

Keywords: Oxoindole, heterocyclization, *δ*-carbolines, pyrimido[5,4-*b*]indoles

Introduction

In the earlier work from this laboratory, we have described for the first time, the synthesis of 2-[bis(methylthio)methylene]-1*H*-3-oxoindole **4** and the corresponding *N*-methyl analog **5** by careful *in situ* trapping of the unstable dipotassium salt **2** of the indoxyl enolate (obtained by base induced intramolecular condensation of **1**) with carbon disulphide in an inert atmosphere and subsequent *in situ* methylation of the dithiolate salt **3** with either two or three equivalents of methyl iodide (Scheme 1).[1] We have further carried out aromatic and heteroaromatic annulation studies on the *N*-methyl analog **5** with various allyl Grignard reagents and the anions derived from aryl/heteroaryl acetonitriles and antipyrine yielding novel benzo[*c*]-, naphtho[1,2-*c*]- and heterocyclo- fused carbazoles in good yields.[1] Similarly, the heterocyclization studies on **5** with various 1,3-heterobinucleophilic species such as lithioacetonitrile, lithioaminocrotononitrile and 2- picolyllithium afforded the novel heterocyclo[*b*]- fused indoles such as pyrido[3,4-*b*]- or pyrido[3,2-*b*]indoles and the corresponding indolo[3,2-*b*]- quinolizinium salts in good yields.[1] In continuation of these studies and in view of the biological importance of indolo[*b*]- fused heterocycles,[2] we have now further investigated heterocyclization of ketene dithioacetal **5** with other bifunctional heterobinucleophiles such as *β*-substituted-*β*-lithioaminoacrylonitriles,

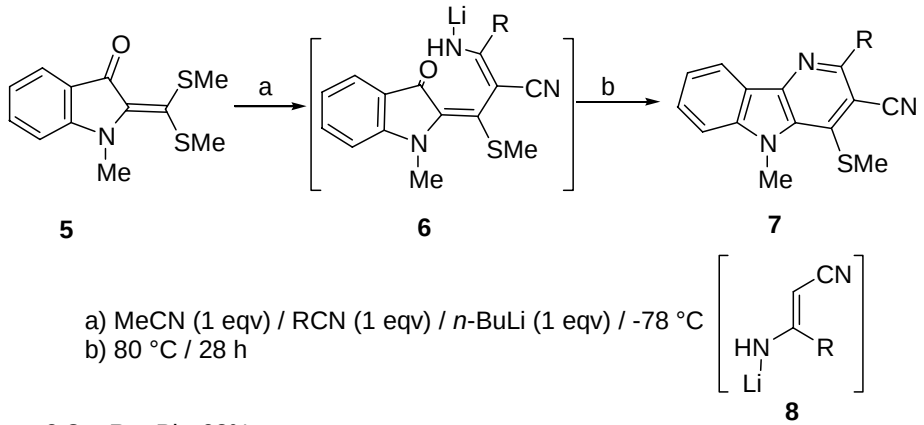
malononitriles and guanidine yielding novel pyrido- and pyrimido fused indolo[*b*]- heterocycles. The results of these studies have been reported in the present paper.



Scheme 1

Results and Discussion

We have earlier reported the reaction of *β*-lithioaminocrotononitrile generated *in situ* by treatment of one equivalent of *n*-butyllithium with two equivalents of acetonitrile at –78 °C with **5** affording the corresponding 3-cyano-2,5-dimethyl-4-(methylthio)pyrido[3,2-*b*]indole (*δ*-carboline) in good yield.[1,3] To further explore the scope of this reaction, we extended this method for the synthesis of various 2-substituted *δ*-carbolines by addition of the corresponding *β*-substituted *β*-lithioaminoacrylonitriles **8** generated *in situ* by addition of lithioacetonitrile to various aromatic and aliphatic nitriles as shown in Scheme 2.[3]

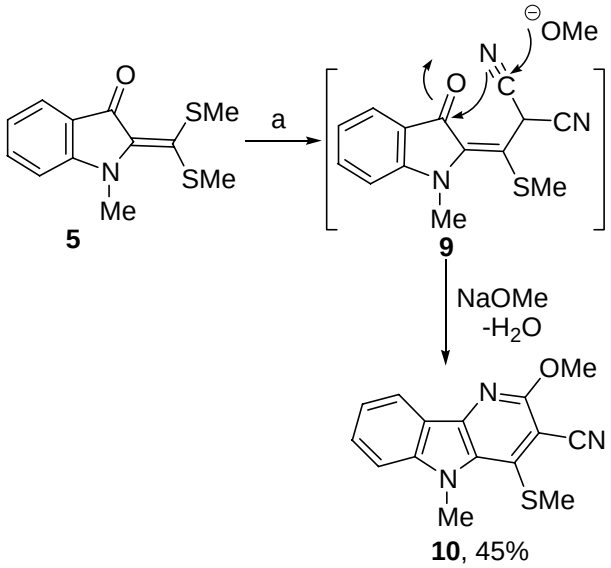


6-8a, R = Ph, 62%
b, R = 4-MeOC$_6$H$_4$, 63%
c, R = 2-thienyl, 58%
d, R= MeOCH$_2$, 64%

Scheme 2

Thus the 2-substituted 3-cyano-4-(methylthio)pyrido[3,2-*b*]- indoles **7a-d** were obtained in 58-64% overall yields through initial 1,4-conjugate addition of lithioaminoacrylonitriles **8a-d** followed by *in situ* heterocyclization of adducts **6a-d** as observed earlier. The present method thus provides an efficient three component route for substituted δ-carbolines. It should be noted that the reported methods for the synthesis of δ-carbolines are scant in the literature in comparison to those for β- or γ-carboline derivatives.[2g,4] The structures and regiochemistry of all newly synthesized δ- carbolines **7a-d** were confirmed with the help of spectral and analytical data.

In an another approach towards functionalized pyrido[3,2-*b*]indole frameworks, the ketene dithioacetal **5** was reacted with malononitrile in presence of sodium methoxide in refluxing methanol, when the reaction mixture after work-up yielded the corresponding 2-methoxy-3-cyano-5-methyl-4-(methylthio)pyrido[3,2-*b*]indole **10** in 45% yield (Scheme 3). This is again an interesting example of three component heterocyclization leading to a substituted pyrido[3,2-*b*]indole through attack of methoxy group on one of the nitrile groups in the intermediate conjugate adduct **5** followed by cyclodehydration.

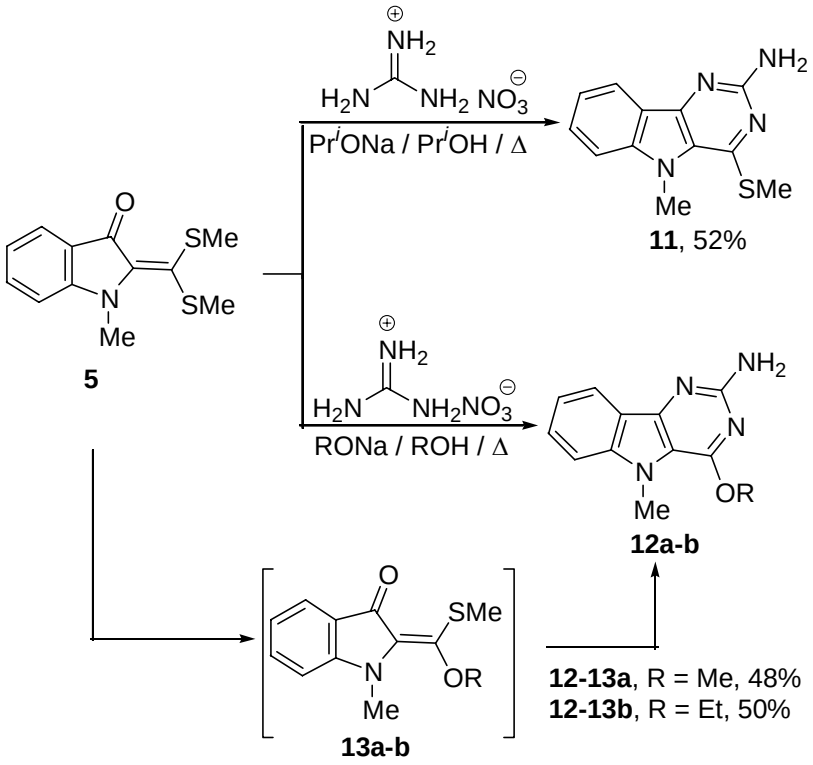


a) $CH_2(CN)_2$ / NaOMe, MeOH / Δ.

Scheme 3

We next investigated the heterocyclization of **1** with guanidine nitrate[5] with a view to synthesize the pyrimido[5,4-*b*]indole framework[6] as shown in Scheme 4. Thus when **5** was reacted with guanidine nitrate in the presence of sodium isopropoxide in refluxing isopropanol, the expected 2-amino-4-(methylthio)-5-methylpyrimido[5,4-*b*]indole **11** was obtained in 52% yield. On the other hand, when **5** was reacted with guanidine nitrate in the presence of sodium methoxide or sodium ethoxide in refluxing methanol (or ethanol), the corresponding 4-methoxy- and 4-ethoxypyrimido[5,4-*b*]indoles **12a-b** were obtained in 48% and 50% yields respectively.

Apparently the ketene dithioacetal **5** undergoes thiomethyl displacement to give the corresponding *O*,*S*-acetals **13a-b** which further reacted with guanidine nitrate to afford the observed fused pyrimidines **12a-b** (Scheme 4). The sodium isopropoxide being a hindered base does not undergo displacement with **5** under these conditions.



Scheme 4

In summary, heterocyclization studies on 2-[bis(methylthio)methylene]-2,3-dihydro-3-oxo-1-methylindole **5** with *β*-substituted-*β*-lithioaminoacrylonitriles, malononitrile and guanidine yield novel substituted pyrido[3,2-*b*]indole and pyrimido[5,4-*b*]indole derivatives in moderate to good yields.

Experimental Section

General Procedures. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ and TMS was used as an internal reference. Melting points are uncorrected. Chromatographic purification was conducted by column chromatography using 60-120 mesh silica gel obtained from Acme Synthetic Chemicals. THF was distilled over sodium/benzophenone prior to use. 4-Methoxybenzonitrile, 2-cyanothiophene, methoxyacetonitrile, malononitrile, guanidine nitrate, *n*-BuLi(1.6M in hexane) were purchased

from standard firms and used directly. The 2-bis(methylthio)methylene-1-methyl-3-oxoindole (**5**) was prepared according to the earlier reported procedure.[1]

General procedure for the generation of 2-substituted 2-lithioaminoacrylonitriles 8 and their reactions with 5: Synthesis of 2-substituted 3-cyano-4-(methylthio)pyrido[3,2-*b*]indoles 7a-d

To stirred solution of acetonitrile (0.4 mL, 7.6 mmol) in dry THF (25 mL), *n*-BuLi (7.5 mmol, 1.6M in hexane) was added under N_2 at –78 °C and the reaction mixture was stirred for 0.5 h at the same temperature. To the resulting white suspension of lithioacetonitrile, a solution of alkyl/aryl or heteroaryl nitrile (7.5 mmol) in dry THF (10 mL) was added dropwise and the reaction mixture was further stirred at the same temperature for 0.5 h to give a light reddish solution of 2-substituted 2-lithioaminoacrylonitriles. To these *in situ* generated 2-lithioaminoacrylonitriles, a solution of **5** (1.26 g, 5.0 mmol) in dry THF (25 mL) was added dropwise at –78 °C. The reaction mixture was brought to room temperature and refluxed with stirring for 40-48 h (monitored by TLC). It was then cooled, poured into saturated NH_4Cl solution, extracted with $CHCl_3$ (2 × 100 mL) and the combined organic layers were washed with water, dried (Na_2SO_4) and concentrated to give crude **7a-7d**, which were purified by column chromatography over silica gel using hexane-EtOAc (19:1) as eluent.

3-Cyano-5-*N*-methyl-4-(methylthio)-2-phenylpyrido[3,2-*b*]indole (7a). Colorless crystals (ether-hexane); mp 171-172 °C Yield 62%; IR (KBr): 2210, 1546, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.71 (s, 3H, SCH_3), 4.42 (s, 3H, NCH_3), 7.36-7.41 (m, 1H, ArH), 7.49-7.56 (m, 4H, ArH), 7.67-7.71 (m, 1H, ArH), 7.95-7.97 (m, 2H, ArH), 8.45 (d, *J* = 8.0 Hz, 1H, ArH); MS: (*m/z*, %): 329 (M^+, 100), 314 (31); Anal. Calcd. for $C_{20}H_{15}N_3S$ (329.43): C, 72.92; H, 4.59; N, 12.76%. Found: C, 73.19; H, 4.95; N, 12.59%.

3-Cyano-2-(4-methoxyphenyl)-5-*N*-methyl-4-(methylthio)pyrido[3,2-*b*]indole (7b). Colorless crystals (ether-hexane); mp 209-210 °C Yield 63%; IR (KBr): 2200, 1596, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H, SCH_3), 3.88 (s, 3H, OCH_3), 4.23 (s, 3H, NCH_3), 7.01 (d, *J* = 8.8 Hz, 2H, ArH), 7.05-7.09 (m, 1H, ArH), 7.31-7.33 (m, 2H, ArH), 7.77 (d, J = 8.0 Hz, 1H, ArH), 7.95 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 13.02, 32.95, 55.47, 108.32, 109.54, 114.45, 115.21, 117.63, 118.66, 119.61, 125.70, 128.61, 128.62, 137.94, 146.57, 150.30, 151.71, 161.13, 162.09; MS: (*m/z*, %): 359 (M^+, 100); Anal. Calcd. for $C_{21}H_{17}N_3OS$ (359.45): C, 70.17; H, 4.77; N, 11.69%. Found: C, 70.41; H, 4.68; N, 11.61%.

3-Cyano-5-*N*-methyl-4-methylthio-2-(thienyl)pyrido[3,2-*b*]indole (7c). Colorless crystals (ether-hexane); mp 228-229 °C Yield 58%; IR (KBr): 2202, 1550, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.64 (s, 3H, SCH_3), 4.18 (s, 3H, NCH_3), 7.04-7.16 (m, 2H, ArH), 7.26-7.34 (m, 2H, ArH), 7.50 (d, *J* = 5.12 Hz, 1H, ArH), 7.68 (d, *J* = 5.1 Hz, 1H, ArH), 7.76 (d, *J* = 7.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 13.02, 32.91, 106.86, 109.54, 112.10, 113.51, 117.23, 118.66, 119.66, 125.83, 127.19, 128.47, 129.82, 138.00, 138.52, 146.64, 160.64, 183.17; MS: (*m/z*, %): 335 (M^+, 100); Anal. Calcd. for $C_{18}H_{13}N_3S_2$ (335.45): C, 65.45; H, 3.91; N, 12.53%. Found: C, 65.69; H, 4.02; N, 12.41%.

3-Cyano-2-methoxymethyl-5-*N*-methyl-4-(methylthio)pyrido[3,2-b]indole (7d). Colorless crystals (ether-hexane); mp 180-181°C; Yield 64%; IR (KBr): 2202, 1600, 1541 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 3H, SCH_3), 3.62 (s, 3H, OCH_3), 4.37 (s, 3H, NCH_3), 4.91 (s, 2H, CH_2OCH_3), 7.38 (t, *J* = 7.9 Hz, 1H, ArH), 7.50 (d, *J* = 8.2 Hz, 1H, ArH), 7.65-7.69 (m, 1H, ArH), 8.42 (d, *J* = 7.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 20.64, 32.21, 59.20, 74.68, 109.50, 111.80, 116.60, 121.08, 121.22, 122.24, 130.13, 130.91, 132.76, 144.00, 144.45, 152.29; MS: (*m/z*, %): 297 (M^+, 24), 267 (100); Anal. Calcd. for $C_{16}H_{15}N_3OS$ (297.38): C, 64.62; H, 5.08; N, 14.13%. Found: C, 64.79; H, 5.22; N, 14.31%.

Procedure for cycloannulation of 5 with malononitrile

A solution of **5** (1.26 g, 5 mmol) in dry methanol was added to a solution of malononitrile (0.61 g, 5 mmol) and sodium methoxide (from 0.05 mole of sodium) in 50 mL of dry methanol and the reaction mixture was refluxed for 12 h. The solvent was removed under reduced pressure, the residue was diluted with cold water and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ layer was dried (Na_2SO_4) and concentrated to give crude product which was then purified by column chromatography over silica gel using hexane-EtOAc (6: 1) as eluent.

3-Cyano-2-methoxy-5-*N*-methyl-4-(methylthio)pyrido[3,2-*b*]indole (10). Colorless crystals (ether-hexane); mp 228-229 °C Yield 45%; IR (KBr): 2202, 1550, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 3.97 (s, 3H, NCH_3), 7.06 (t, J = 7.08 Hz, 1H, ArH), 7.24 (d, J = 8.32 Hz, 1H, ArH), 7.35-7.39 (m, 1H, ArH), 7.74 (d, *J* = 8.0 Hz, 1H, ArH); Anal. Calcd. for $C_{15}H_{13}N_3SO$ (283.45): C, 63.58; H, 4.62; N, 14.83%. Found: C, 63.69; H, 4.52; N, 14.74%.

Reaction of 5 with guanidine nitrate

(a) in the presence of sodium isopropoxide

A solution of **5** (1.26 g, 5.0 mmol) in dry isopropanol was added to a suspension of guanidine nitrate (0.61 g, 5.0 mmol) and sodium isopropoxide (0.05 mmol of sodium) in dry isopropanol (50 mL) and the reaction was refluxed for 12-14 h. The solvent was removed under reduced pressure, the residue diluted with cold water and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ layer was dried (Na_2SO_4) and concentrated to give crude product which was then purified by column chromatography over silica gel using hexane-EtOAc (6: 1) as the eluent.

2-Amino-5-*N*-methyl-4-(methylthio)pyrimido[5,4-*b*]indole (11). Light yellow crystals (methanol); mp 227-228 °C Yield 52%; IR (KBr): 3250, 3100, 1650, 1600, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.01 (s, 3H, SCH_3), 4.12 (s, 3H, NCH_3), 7.10-7.26 (m, 1H, ArH), 7.35-7.37 (m, 1H, ArH), 7.55-7.59 (m, 1H, ArH), 8.20 (d, *J* = 7.9 Hz, 1H, ArH); MS: (*m/z*, %): 244 (M^+, 100); Anal. Calcd. for $C_{12}H_{12}N_4S$ (244.32): C, 58.99; H, 4.95; N, 22.93%. Found: C, 58.79; H, 4.62; N, 22.81%.

(b) in methanol or ethanol

A solution of **5** (1.26 g, 5.0 mmol) in dry methanol/ethanol was added to a suspension of guanidine nitrate (0.61 g, 5.0 mmol) and sodium methoxide or ethoxide (from 0.05 mmol of

sodium) in 50 mL of the respective alcohol and the reaction mixture was refluxed for 12-14 h. The solvent was removed under reduced pressure, the residue was diluted with cold water and extracted with $CHCl_3$ (2 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated to give crude product which was then purified by column chromatography over silica gel using hexane-EtOAc (6:1) as eluent.

2-Amino-5-*N*-methyl-4-(methoxy)pyrimido[5,4-*b*]indole (12a). Colorless crystals (Ether-hexane); mp 145-146 °C Yield 48%; IR (KBr): 3466, 3295, 3161, 3100, 1650, 1600, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.86 (s, 3H, SCH_3), 3.99 (s, 3H, NCH_3), 4.92 (brs, 2H, NH_2), 7.17-7.21 (m, 1H, ArH), 7.33-7.35 (m, 1H, ArH), 7.50-7.53 (m, 1H, ArH), 8.14 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 31.64, 53.49, 109.45, 115.12, 119.18, 119.94, 121.26, 128.34, 141.85, 146.40, 156.82, 157.68; MS: (*m/z*, %): 228 (M^+, 100), 213 (56); Anal. Calcd. for $C_{12}H_{12}N_4S$ (228.25): C, 63.14; H, 5.30; N, 24.55%. Found: C, 63.39; H, 5.45; N, 24.32%.

2-Amino-5-*N*-methyl-4-(ethoxy)pyrimido[5,4-*b*]indole (12b). White crystals (ether-hexane); mp 225-226 °C Yield 50%; IR (KBr): 3479, 3287, 3151, 1650, 1600, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (t, J = 7.0 Hz, 3H, CH_3), 4.00 (s, 3H, NCH_3) 4.56 (q, J = 7.08, 2H, CH_2CH_3), 4.83 (brs, 2H, NH_2), 7.17-7.21 (m, 1H, ArH), 7.35 (d, J = 8.6 Hz, 1H, ArH), 7.49-7.53 (m, 1H, ArH), 8.14 (d, J = 7.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 14.57, 31.58, 62.18, 109.43, 115.23, 119.43, 120.04, 121.22, 128.26, 141.90, 146.21, 156.89, 157.43; MS: (*m/z*, %): 242 (M^+, 100), 227 (50); Anal. Calcd. for $C_{13}H_{14}N_4O$ (242.28): C, 64.45; H, 5.82; N, 23.13%. Found: C, 64.65; H, 5.60; N, 23.41%.

Acknowledgements

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