SYNTHESIS OF THIENOINDOLES VIA THE VICARIOUS NUCLEOPHILIC SUBSTITUTION OF NITROBENZO[*b*]THIOPENES

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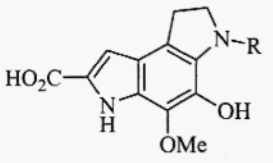
Abstract: The *8H*-thieno[3,2-*g*]indole (**12**) and *6H*-thieno[3,2-*e*]indole (**16**) were easily obtained by the reductive cyclisation of (5-amino-1-benzothien-4-yl)acetonitrile (**15**) and (7-amino-1-benzothien-6-yl)acetonitrile (**11**), the latter synthesised via cyanomethylation of 5- and 7-nitrobenzo[*b*]thiophenes.

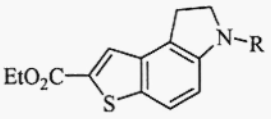
Background

The extremely potent, but with an unusual delayed lethality, antitumour antibiotic CC-1065 incorporates PDE-1 and PDE-11 **1** (Figure-1) in its structure.



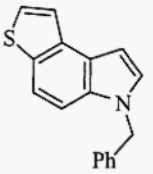
1

PDE-1 R = $CONH_2$
PDE-11 R = COMe



2

R = H, $CONH_2$, COMe



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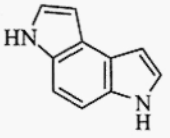

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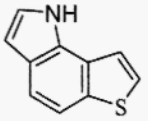


5

Figure 1

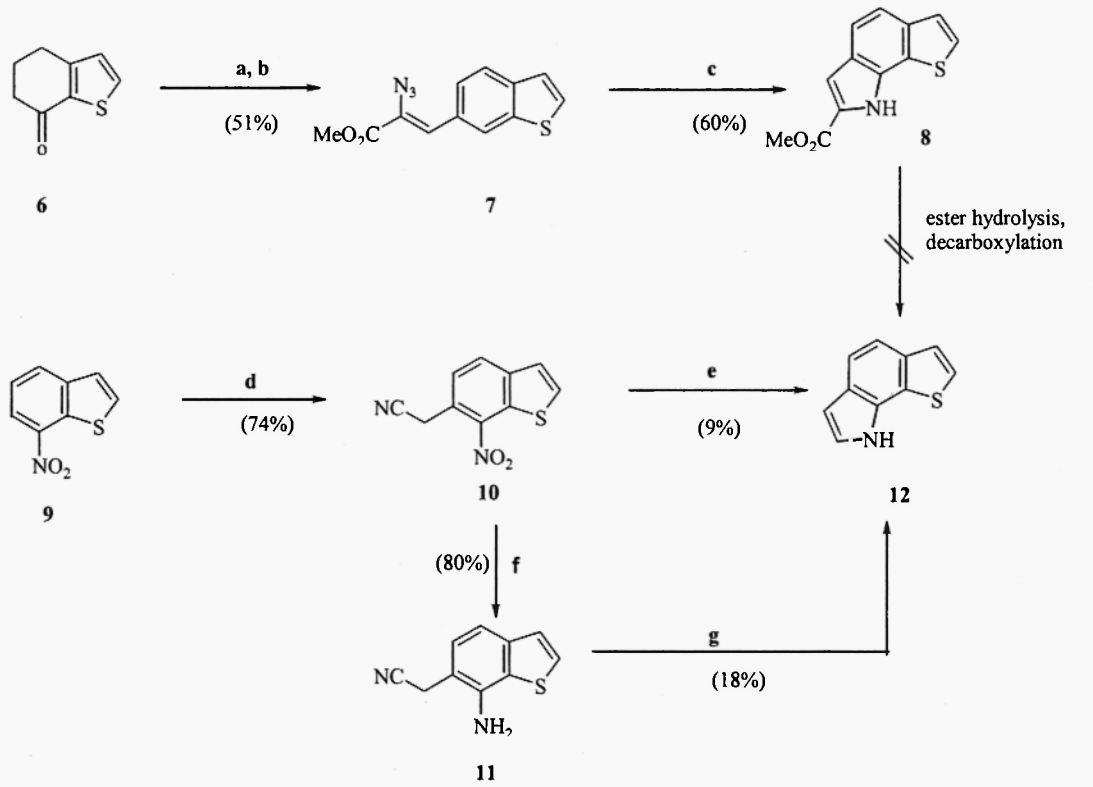
The synthesis of PDE-1 and PDE-11 based on palladium/carbon mediated photocyclisation of stilbenoid heterocycles have been reported by Cava *et al.*.[1] The same authors have synthesised, among others, compounds **2** and **3** as interesting analogues to the PDEs. Debenzylation of **3** would lead to the parent so far unreported compound **16**. In the CA the registry number of *6H*-thieno[3,2-*e*]indole (**16**) is 41775-39-7 and reference to the publication by Jacquignon[2] and co-workers for its preparation, is claimed. The paper though does not contain **16**, but its dione.

The pyrrolo[3,2-*e*]indole (**4**) viewed as a potential bioisostere of the 5-hydroxyindole component of serotonin, has been reported by Macor *et al.*.[3] It would be of biological interest to replace one of the pyrrole rings of compound **4** by a thiophene ring. By the same reasoning above, the tricyclic compound **16** could be seen as a potential bioisostere of the 5-hydroxyindole component of serotonin. 5-Substituted benzo[*b*]thiophenes have been reported to be biologically active.[4, 5] Syntheses of nitrobenzo[*b*]thiophenes [6,7] is extensively presented in the literature. Functionalised benzo[*b*]thiophenes, apart from being interesting for their bioactivity, *per se*, are important precursors to annelation compounds incorporating the fused thiophene ring. Such compounds have been investigated as potential carcinogens,[8] analogues to naturally occurring bio-active molecules,[1] or as heterohelicenes.[9]

Compound **5**[10] (no melting point is given although stated it was low and ^{1}H NMR assigns the same proton different shifts) was synthesised via an azidocinnamate in a way similar to that depicted in the first reaction sequence in Scheme 1. Methyl*8H*-thieno[3,2-*g*]indole-7-carboxylate (**8**) was synthesised by this strategy [11] a few years later. Subsequent hydrolysis and decarboxylation of this ester, that would lead to compound **12**, gave uncharacterisable polymeric materials as reported by these authors. Since this parent heterocycle is not mentioned anywhere in the literature, we decided to initiate its synthesis by a different methodology.

Cyanomethylation of nitrobenzenes, -pyridines and –quinolines [12,13] have proved to be useful, as the *ortho*-substituted nitroacetonitriles formed can be reductively cyclised to pyrrole ring systems. Since there is no report in the literature, to our knowledge, of cyanomethylation of nitrobenzo[b]thiophenes, we decided to explore this as an alternative approach to **12** and **16**. The unprecedented *8H*-thieno[3,2-*g*]indole (**12**) has now been prepared from 7-nitrobenzo[*b*]thiophene in three steps as shown in Scheme-1.

The study on this methodology, was extended to include the use of 5-nitrobenzo[*b*]thiophene in the preparation of the isomeric *6H*-thieno[3,2-*e*]indole (**16**) Scheme-2.



Reaction Conditions : (a) $CH(OEt)_3$, BF_3-EtO_2,$EtN(iso\text{-}Pr)_2$, $NaHCO_3$, CH_2Cl_2, −78 °C to −20 °C, NBS (b) N_3CH_2COOEt, NaOEt, EtOH, −15 °C (c) KOH, EtOH, reflux, 16 h (d) *p*-$ClPhOCH_2CN$, ^{t}BuOK, DMF, −10 °C (e) Fe, AcOH (100%), reflux (f) H_2, Pd/C, EtOH/Et_3N, 100 psi, rt (g) DibalH, Benzene, −15 °C, argon gas

Scheme-1

Results and Discussions

The Vicarious Nucleophilic Substitution of Hydrogen of nitroarenes has been extensively used by Mąkosza[12] and co-workers. Mąkosza and later others,[13] have then used this protocol to introduce the pyrrolo moiety to numerous compounds eligible to the methodology. Our search in the literature though revealed that nitrobenzo[*b*]thiophenes to date had not been cyanomethylated by this method or otherwise.

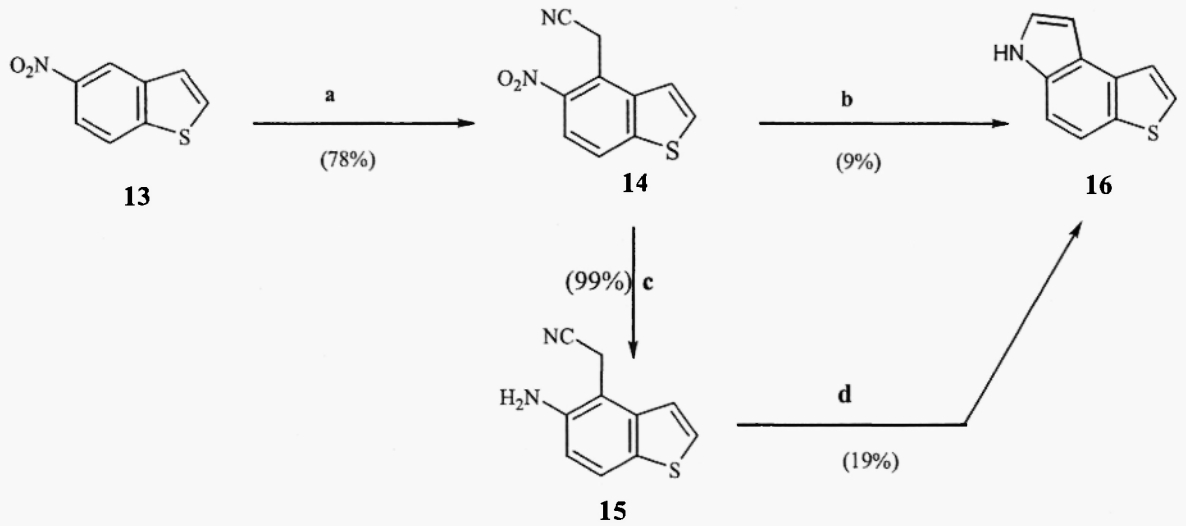
We initiated our investigations on the cyanomethylation of nitrobenzo[*b*]thiophenes on 7- and 5-nitrobenzo[*b*]thiophenes.

The 5-nitrobenzo[*b*]thiophene (**13**) and the 7-nitrobenzo[*b*]thiophene (**9**) used in these experiments were synthesised according to literature methods.[14, 15] Cyanomethylation of 5-and 7-nitrobenzo[*b*]thiophenes (**13**) and (**9**) gave (in good yields) the (5-nitro-1-benzothien-4-yl)acetonitrile (**14**) and the (7-nitro-1-benzothien-6-yl)acetonitrile (**10**) respectively.

In one approach **10** was treated with iron filings in glacial acetic acid giving only poor yields (8 %) of the expected *8H*-thieno[3,2-*g*]indole (**12**). However a mixture of products as indicated by tlc (dichloromethane:EtOAc 1/1) resulted when the reaction conditions used by Vlachou and co-workers,[13] namely hydrogenation in 10% Pd/C at 100 psi in HOAc/EtOH/H_2O, were applied. We then reduced the nitrile **10** to an amino derivative **11** using the Makosza[16] protocol (Scheme 2). Reductive cyclisation[17] of **11** gave the thienoindole **12** in a pure form, *albeit* still in poor yields (18 %). According to the tlc analysis all the starting material had been transformed to the one and only expected indole. However during the work-up there were some losses incurred, as the yield of the expected product was low.

The latter experiments were repeated with **13** leading consequently to the *6H*-thieno[3,2-*e*]indole (**16**) with almost identical results.

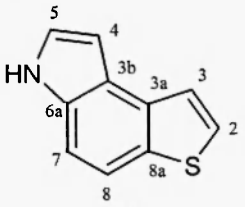
In conclusion we have, by applying the Vicarious Nucleophilic Substitution of Hydrogen on these nitrobenzo[*b*]thiophenes synthesised, *albeit* in poor yields, the new indoles **12** and **16** that are herein fully characterised (Table-1).



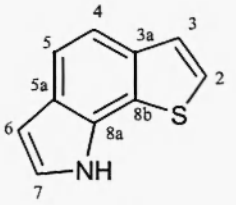
Reaction conditions: (a) *p*-ClPhOCH$_2$CN, ^{t}BuOK, DMF, −10 °C (b) Fe, AcOH (100%), reflux (c) H_2, Pd/C, EtOH/Et_3N, 100 psi, rt (d) DibalH, Benzene, −15 °C, argon gas.

Scheme-2

Table-1: Spectral data



16



12

Compound	Index	^{1}H δ(ppm)	^{13}C δ(ppm)	HMBC cross peaks
	2	7.45	125.21	$^{2}J_{H3-C2}$
12	3	7.41	121.93	$^{2}J_{H2-C3}$
	3a		124.81	$^{3}J_{H5-C3a}$
	4	7.58	118.05	$^{3}J_{H3-C5}$
	5	7.51	115.62	$^{3}J_{H6-C5}$
	5a		130.47	$^{3}J_{H4-C5a}$, $^{3}J_{H7-C5a}$
	6	6.60	103.12	$^{2}J_{H4-C6}$
	7	7.34	123.23	
	8a		123.45	$^{2}J_{H7-C8a}$
	8b		135.17	$^{3}J_{H2-C8b}$, $^{3}J_{H3-C8b}$, $^{3}J_{H4-C8b}$
	2	7.71	125.70	$^{2}J_{H3-C2}$
16	3	7.68	115.04	$^{3}J_{H8-C3}$, $^{2}J_{H5-C3}$
	3a		130.47	$^{3}J_{H8-C3a}$
	3b		132.83	$^{3}J_{NH-C3b}$, $^{3}J_{H5-C3b}$
	4	6.81	100.02	$^{2}J_{NH-C4}$
	5	7.39	124.12	$^{3}J_{H4-C5}$
	6a		122.20	$^{3}J_{H8-C6a}$, $^{3}J_{H2-C6a}$
	7	7.63	122.14	$^{3}J_{NH-C7}$
	8	7.47	110.16	$^{2}J_{H2-C8}$
	8a		132.12	$^{3}J_{H3-C8a}$
	NH	11.34		

Experimental

Analytical TLC was performed using aluminium plates precoated with silica gel 60 F254 (Merck) and visualized under UV light and the Van Urk's reagent. Melting points (uncorrected) were determined on a Büchi Melting Point B–545. All NMR spectra were recorded on a Bruker DPX 300 spectrometer at 25 °C. ^{1}H and ^{13}C–NMR signals were referenced to the solvent (DMSO-d_6 δ_H 2.50 and δ_C 39.5). Gradient HMBC and PENDANT experiments were used for the assignments. Coupling constants are given in Hz and without sign. The IR spectra were recorded on a Thermo Nicolet Avatar 330 FT–IR (neat) instrument.

Methyl5-nitrobenzo[*b*]thiophene-2-carboxylate

This product was obtained according to the literature. mp 212–214 °C (213–215 °C)[15]

The ^{1}HNMR in $CDCl_3$ (not reported earlier) is given below.

^{1}H ($CDCl_3$) δ 8.77 (1H, d, *J* 2.1), 8.29 (1H, dd, *J* 2.2, 9.0), 8.26 (1H, s,), 8.00 (1H, d, *J* 9.0), and 3.98 (3H, s, OCH_3).

5-Nitrobenzo[*b*]thiophene-2-carboxylic acid
The acid with the mp 234–237 °C (236–238 °C)[15] was obtained according to the literature.
We present the ^{1}H and ^{13}C-NMR in DMSO is given.
^{1}H δ 8.79 (1H, s), 8.14 (2H, dd, *J* 9.2) and 7.83 (1H, s).
^{13}C δ 163, 147.7, 146.8, 144.9, 139.5, 126.4, 123.9, 120.4 and 119.0.

7-Nitrobenzo[*b*]thiophene(9)
This compound was prepared according to the literature.[14]

(7-Nitro-1-benzothien-6-yl)acetonitrile (10)
This compound was prepared in an analogous procedure to the preparation of **14**. The yellow solid (74%) with a melting point of 196–199 °C was recovered. *Anal.* Calcd. for $C_{10}H_6N_2O_2S$: C, 55.04; H, 2.77; N, 12.84. Found C, 54.91; H, 2.90; N, 12.60.
^{1}H δ 8.32 (1H, d, *J* 8.84), 8.19 (1H, d, *J* 5.64), 8.06 (1H, d, *J* 8.84), 7.98 (1H, d, *J* 5.64) and 4.59 (2H, s, CH_2).
^{13}C δ 145.63 (C), 144.3 (C), 139.49 (C), 132.61 (CH), 123.92 (CH), 123.08 (CH), 121.08 (C), 120.12 (CH), 117.6 (C) and 18.72 (CH_2).
IR (neat) ν 3106, 2924, 2242, 1511, 1489, 1317 and 829 cm^{-1}.

(7-Amino-1-benzothien-6-yl)acetonitrile (11)
The yields of the amino-nitrile obtained by the reduction of **10** in similar reaction conditions as in the preparation of **15** were quite low 80% (*cf* 99% for **15**).The crystallised (EtOH) **11** had a melting point of 163–165 °C. *Anal.* Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88
Found C, 63.60; H, 4.39; N, 14.63.
^{1}H δ 7.65 (1H, d, *J* 5.35), 7.33 (1H, d, *J* 5.35), 7.17 (2H, s), 5.53 (2H,br s, NH_2) and 3.95 (2H, s, CH_2).
^{13}C δ 140.4 (C), 140.3 (C), 126.6 (CH), 126.5 (CH), 124.6 (CH), 119 (C), 112.1 (CH), 107.8 (C), 107.6 (C) and 18.8 (CH_2).
IR (neat) ν 3364, 3243, 3078, 2907, 2252, 1655, 1565, 1474, 1397 and 795 cm^{-1}.

***8H*-Thieno[3,2-*g*]indole (12)**
Compound **11** was reductively cyclised under the conditions given for the preparation of **16,** giving a grey solid (18%), m.p 96–98 °C.
The spectral analysis of this compound was done in 2 different solvents. In DMSO the signals were so near that assignment was impossible. However when the experiment was run in acetone-d_6, there was good separation but some information got lost as the NH proton exchanged with the solvent deuterium. The assignments given in Table 1 was done in acetone-d_6. *Anal.* Calcd. for $C_{10}H_7NS$: C, 69.33; H, 4.07; N, 8.09. Found C, 69.20; H, 4.18; N, 7.81.
^{1}H δ 11.7 (1H, br, s NH), 7.52 (4H, m), 7.34 (1H,m), 6.55 (1H, m)
^{13}C δ 135.4 (C8b), 129.9 (C5a), 125.1 (C2), 124.1 (C8a), 123.8 (C7), 123.1 (C3a), 122.5 (C3), 117.8 (C4), 115.3 (C5) and 102.6 (C6).
IR (neat) ν 3397, 3097, 3059, 1611, 1444, 1362, 1314, 805 and 713 cm^{-1}.

5-Nitrobenzo[*b*]thiophene (13)
The product with mp 142–146 °C (149–150 °C)[15] was obtained according to the literature method. No further purification was necessary for the next step. ^{1}H NMR was run in $CDCl_3$
^{1}H ($CDCl_3$) δ 8.74 (1H, d, *J* 2.0), 8.21 (1H, dd, *J* 2.06, 8.91), 8.01 (1H, d, *J* 8.87), 7.67 (1H, d, *J* 5.49) and7.52 (1H, d, *J* 5.48).

(5-Nitro-1-benzothien-4-yl)acetonitrile (14)
t-BuOK (4.48 g, 40.0 mmol) was dissolved in dry THF (20 mL) and stirred under argon gas at –10 °C. A solution of 5-nitrobenzo[b]thiophene (1.60 g, 10.1 mmol) and 4- chlorophenoxyacetonitrile (1.68 g, 10.1 mmol) in dry THF (20 mL) was added dropwise to the later upon which the solution immediately turned purple. After ca. 3 h stirring at this temperature tlc (hexane/EtOAc 3:1, R_f 0.2) analysis showed that the reaction had come to completion. The reaction mixture was poured to ice water (200 mL) and the yellow precipitate that formed collected by filtration using a water aspirator. The precipitated solid was washed with cold water (50 mL) and crystallized from dry ethanol giving 1.70 g (78%) as yellow crystals with the melting point of 212–214 °C. *Anal.* Calcd. for $C_{10}H_6N_2O_2S$: C, 55.04; H, 2.77; N, 12.84. Found C, 54.94; H, 2.85; N, 12.68.

^{1}H ($CDCl_3$) δ 8.12 (1H, d, *J* 8.8, 6-H), 8.04 (1H, d, *J* 8.9, 7-H), 7.83 (1H, d, *J* 5.6, 2-H), 7.67 (1H, d, *J* 5.6, 3-H) and 4.41 (2H, s, CH_2).
^{13}C ($CDCl_3$) δ 145.7 (C-5), 145.0 (C-7a), 139.5 (C-3a), 131.7 (C-2), 123.7 (C-7), 122.1 (C-3), 120.6 (C-6), 120.5 (C-4), 116.0 (CN) and 19.2 (CH_2).
IR (neat) ν 3112, 3089, 2971, 2259, 1585, 1509, 1336, 1153 and 738 cm^{-1}.

(5-Amino-1-benzothien-4-yl)acetonitrile (15)
o-Nitrobenzylcyanide **14** (0.34 g, 1.56 mmol) was dissolved in a mixture of dry ethanol (25 mL) and Et_3N (5 mL) and palladium in carbon 10% (0.22 g) was added to the mixture. Hydrogenation of the latter in Parr set up at 100 psi at rt was performed. After about 40 min tlc analysis showed all the starting material had been consumed. The mixture was filtered through a thin layer of celite and the latter washed with a little (20 mL) warm chloroform. The filtrate was then concentrated *in vacuo* giving a fine powder of amino compound **7** (0.289 g, 99% yield). mp 113–116 °C. *Anal.* Calcd. for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88. Found: C, 63.62; H, 4.35; N, 14.77.
^{1}H δ 7.69 (1H, d, *J* 5.5), 7.62 (1H, d, *J* 8.6), 7.43 (1H, d, *J* 5.2), 6.84 (1H, d, *J* 8.63), 5.3 (2H, br s, NH_2) and 4.10 (2H, s, CH_2).
^{13}C δ 143.7 (C), 139.7 (C), 127.9 (CH), 127.8 (C), 122.5 (CH), 121.3 (CH), 118.9 (C), 115.4, 105.9 (CH) and 15.7 (C).
IR (neat) ν 3459, 3373 3259, 2921, 2252, 1635, 1593, 1420, 806 and 705 cm^{-1}.

***6H*-Thieno[3,2-*e*]indole (16)**
A solution of (4.5 mL, 4.5 mmol) 1.0 M DibalH in toluene was added to 10 mL dry benzene and cooled to 0 °C. The amino-nitrile **15** (0.19 g, 1.0 mmol) was dissolved in benzene until the solution was homogenous (20 mL). The latter was then added to the cooled DibalH while maintaining the temperature at 0 °C and at the same time keeping foaming of the reaction mixture to a minimum. After 30 min, tlc (dichloromethane:EtOAc 1/1 R_f 0.7) analysis of the reaction mixture showed that all the starting material had been consumed. The reaction was quenched with ice-cold aqueous KF solution and the two layers stirred for 40 min before saturating the mixture with NaCl and then extracting it with equal volume (3 x) EtOAc. The combined extracts dried over Na_2SO_4, filtered and the filtrate concentrated *in vacuo* leaving a grey solid (19%). mp 208–210 °C. *Anal.* Calcd.for $C_{10}H_7NS$: C, 69.33; H, 4.07; N, 8.09 found C, 69.23; H, 4.12; N, 7.89.
^{1}H δ 11.3 (1H, br s, NH), 7.71 (2H, dd, *J* 5.8, 6.2), 7.63 (1H, d, *J* 8.7), 7.47 (1H, d, *J* 8.7), 7.4 (1H, t, *J* 2.8) and 6.81 (1H, m).^{13}C δ 132.85 (C3b), 132.14 (C8a), 130.98 (C3a), 125.76 (C2), 124.17 (C5), 122.25 (C6a), 122.18 (C7), 115.08 (C3), 110.20 (C8) and 100.06 (C4).
IR (neat) ν 3400, 2978, 1716, 1456, 1153, 1019 and 737 cm^{-1}.

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